Towards a patient-driven approach to adverse events of targeted agents in oncology

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01 | General introduction

Targeted anticancer therapies are increasingly used in oncology care as single agents or in combination with other classes of oncology care. Like other treatment options, targeted therapies are associated with adverse events (AEs) which may cause treatment adjustments and deterioration of quality of life (QoL). Targeted therapies may induce AE burden, with or without significant clinical evidence of tissue damage, (1, 2) while having far reaching consequences for patient adherence with care and therefore cancer treatment outcomes. To be able to complete treatment as planned and to maintain QoL, AEs need to be addressed according to the patient's needs. Therefore, the patient's view is a critical component of an integral approach to AEs of targeted agents. In the future perspectives part of this dissertation a newly developed co-care model of approach to AEs is presented.

Targeted therapy refers to treatment with drugs that have been developed to "target" differences in characteristics of malignant cells compared to normal cells. Unlike cytotoxic chemotherapy, targeted therapy drugs have a primary effect on the cancer cell. Scientists had expected that targeted agents would cause less AEs than cytotoxic chemotherapy because cancer cells are more dependent on the targets than are normal cells. However, targeted agents can have substantial AEs.(3)

Due to the inflammatory processes,(4) the AEs of targeted therapies are generally distinct from those associated with cytotoxic chemotherapy and radiation therapy, and often require different management.(3) AEs are an adverse effect of the drug that is not its intended effect.(5) Targeted cancer therapies can have substantial AEs including mucocutaneous AEs,(6) high blood pressure, and hepatitis.(3)

Certain AEs of some targeted agents have been linked to better patient outcomes. For example, patients who develop a papulopustular rash while being treated with epidermal growth factor receptor inhibitors (EGFRIs) may have a better cancer outcome to these agents than patients who do not develop the rash.(7) Similarly, patients who develop high blood pressure while being treated with an angiogenesis inhibitor may have better cancer outcomes, i.e. longer survival.(8)

This dissertation focuses on mucocutaneous AEs involving skin and mucosal changes. Skin and mucosal AEs are the primary AEs associated with many targeted agents and can occur in up to 90% of people undergoing treatment with targeted agents.(6) Examples of skin AEs are a maculopapular or papulopustular eruption (or 'rash'), hand-foot skin reaction (HFSR), xerosis (abnormally dry skin), pruritus (itchiness), edema (skin swelling), hair alterations, nailfold infection (paronychia), and eyelid reactions. A mucous membrane is a membrane that produces mucus that covers delicate parts of the body such as in the nasal cavity,(9) the oral cavity, eyes, esophagus, intestines, anus, and genitals. Mucocutaneous symptoms can be very burdensome for patients,

even when the treatment is effective in combating the cancer. These AEs can lead to decreased QoL, delay in treatment, dose modification or early cessation of the antineoplastic therapy, which may affect cancer outcomes.(10) It is thought that most mucocutaneous AEs - when approached systematically and at an early stage - can be controlled, often with simple, inexpensive and over the counter products. This would reduce the cost of care, enhance adherence to anticancer regimes, and lead to a more favourable clinical outcome.(11) However, healthcare providers (HCPs) sometimes find it difficult to successfully manage mucocutaneous AEs. If the symptoms persist, the AEs should be thoroughly evaluated before treatment modification. Choosing the most appropriate treatment is made easier in collaboration with an adverse event expert and the patient.(12)

Patients are now more active in their treatment as they have access to their electronic medical files and disease related information. Also they are more involved in assessment of AE and treatment.(13) Policy makers and clinicians increasingly aim to take the patient's perspective into account in medical decision making.(14-17) Patients may respond better to treatment and comply better to guidelines when they are involved in decision making and satisfied with their care and treatment setting.(18-20) However, this approach is not patient-driven. Patient-driven means, the patient is truly in center while patient-centric implies clinicians are in charge, even if the patient is at the center.(13, 21-23) Characteristics of patient-driven approach to AEs of targeted agents include:

1. The patient and his/her social support use accurate terminology of an AE. In this way the patient actively contributes to determining the correct diagnosis of the AE.
2. Assessing both symptoms and signs of an AE by the patient and the impact of such an event on his/her health related quality of life (HRQoL).
3. Collecting and reporting the characteristics of an AE by the patient for more in-depth information about the AE.
4. Grading the severity of an AE by the patient.
5. Evaluation of the taken measures; reconfirmation of general measures and education about the AE treatment to be initiated.
6. Institute most appropriate and effective AE treatment strategies according to best evidence and the patient needs.

To decrease the chance that patients develop potentially severe AEs that might lead to treatment adjustments, the patient needs to be educated about prophylactic measures at the initiation of treatment.(24-27) Education may take place in the outpatient setting, because many targeted agents are available to outpatients. Education about AEs includes informing the patient about AEs during therapy decision, before starting the therapy, during treatment, when AEs occur, and at initiating of AE treatment.(28) Education should include discussing preventive measures, the nature, recognition, and severity of common and potentially severe AEs associated with the

agents provided. If the patient is trained to report these AE details correctly, unintended treatment delays or interruptions may be avoided. It is also important to encourage patients themselves decide how to integrate the daily care of skin and mucosa into their daily routine. For example, if a patient takes long, hot showers every day, it is important to be aware that the skin may become stressed, allowing deciding to then opt for intensive skin care after the shower or for taking a shorter shower and/or adjusting the water temperature.(12) When, despite preventive measures, an AE develops, it is even more important that skin and mucosa are healthy, as interventions using, for example, application of topical corticosteroids or keratolytics, may be too stressful for the skin or mucosa.

The first critical step in a patient-driven AE approach when AEs occur, is using accurate terminology of AEs. Terminology is about labelling or designating concepts in the right context.(29) Several AE names may be used interchangeably, even though they do not actually mean the same thing. For example, the terms “side effects and adverse events”, “reaction and toxicity”, “oral mucositis and stomatitis”, “diarrhea and loose stool”, and “hand-foot syndrome and hand-foot skin reaction” may be used interchangeably. Promoting consistency of the appropriate terminology of the AEs is important for documenting and comparing treatment. When terms such as targeted therapy-associated non-toxic reaction and chemo- and radiation therapy-associated toxic reaction (toxicities) are used consistently, it will be more likely to define the appropriate treatment option. For example: While the targeted therapy-associated hand-foot skin reaction (HFSR) and the chemotherapy-associated hand-foot syndrome (HFS) have similarities, HFSR and HFS also differ. They both have erythema, blisters, scaling of the skin, tenderness, pain in the hand palms and foot soles, and resolution of the AE upon discontinuation of the drug in common, but the patterns are different. While HFSR lesions commonly appear on the friction/pressure points, HFS often covers the entire palms and soles.(30) Because of this different mechanism of action, the treatment of a HFSR is quite straight forward, while the treatment of a HFS remains challenging.(12)

The second critical step in the patient-driven AE approach, is the self-assessment of symptoms and signs of AEs by the patient and the influence of the AEs on HRQoL. In oncology healthcare it is common to register signs of AEs by observable measurements assessed by clinician rated outcomes (CROs). However, in order to gain a deeper understanding of the patient’s experiences of an AE, there is also a need for patient reported outcome (PRO) assessments. PROs are “*any aspect of an individual’s health status that comes directly from the individual without amendment or interpretation of the patient’s response by a clinician or anyone else*”.(31, 32) PROs give valuable subjective information in addition to observable HCP assessments. This reflection of patient experience and the ability to capture the patient’s voice through PROs should be a central component of all clinical trials and regular clinical care.(33) PROs can be assessed by e.g. interviews and diaries or by questionnaires.(34-37)

Publications by Basch et al. (38, 39) demonstrated that systematic collection of patient-reported symptoms and telephone-based symptom management resulted in both higher QoL and survival improvement that rivaled the positive effects of many novel oncologic agents entering the market in 2016. Their studies show that current care delivery systems fall short in identifying symptoms since AEs are mainly reported by HCP's. This finding is consistent with previous research showing that, compared with patients, physicians often underreport AEs.(40) In addition, the burden of AEs for patients who are adherent but experience unaddressed symptoms cannot be underestimated.(33) To fully harness the potential of real-time patient data, PROs should be included within the medical record,(41, 42) where oncologists and nurses can view responses and take action to meet patient needs. Since existing evidence clearly shows that patients and clinicians differ in their assessments and grading of the severity of AEs, ideally, a system that captures both patient and clinician assessments is appropriate.(43) Patient-reported symptoms not only cause patients to enter the medical system, they also may affect subsequent use and the costs of medical care.(1) To overcome the issue of the rare patient voice, the next generation of patient-driven studies should provide deeper insights into how the risk and impact of AEs is perceived by both patients and physicians. Such insights might especially highlight the balance between AEs and efficacy that needs to be achieved for a cancer drug to be perceived as valuable by patients and physicians.(28)

Patient-driven AE approach requires self-report of the symptoms and impact. Patient self-report facilitates follow up since AE characteristics help to identify, differentiate, and more precisely describe a feature of the AEs.(44) For example, when reporting papules the following should be recorded by the patient: onset, site, location, severity, and associated signs such as shape and color (brown, purple, pink or red) and if scales are present. It is precisely this detailed reporting which is necessary to support the clinical decisions in treatment and follow up. In addition, clinical photographs, biopsies, and swabs by the HCP support the integral reporting of characteristics of AEs. Therefore, reporting AEs by characteristics by the patient as well as by the HCP, supplemented by appropriate testing (when needed) supports a precise and detailed AE recording.(12)

Another requirement in a patient-driven AE approach is severity grading. Targeted therapy-associated mucocutaneous AEs for instance include important subjective patient tolerability and discomfort. In general, patients are able to accurately grade AEs themselves.(45, 46) A prerequisite is that the grading instruments contain clear language since patients may find it difficult to define their AEs in terms of 'grade 0', 'grade 1', etc. Using an equivalent of this categorization, such as 'none', 'mild', 'moderate' or 'severe', makes it easier to grade the AE.

A vital next step in a patient-driven AE approach is the evaluation of the applied AE measures. Even if patients are aware of the importance of applying the intervention as

prescribed, the patient may nevertheless at times apply it incorrectly while believing otherwise. For example, when a patient with itchy and dry skin is advised to apply a greasy cream at least three times a day, but uses a lotion instead. What the patient may not know is that a watery lotion does not have the same effect as a greasy cream on a dry and itchy skin. When seen at follow-up the patient may report no improvement. The limited or lack of effect may be due to not following correct treatment. Therefore it is important to evaluate if the AE interventions have resulted in the desired outcomes and to ascertain the reasons it may not have been effective. This evaluation should already take place after 48 hours of initiation of AE treatment since when no response occurred within this timeframe, poor response can be expected after 48 hours and adjustment of AE treatment should be considered before targeted anticancer treatment adjustment.(47)

A fundamental step in approaching AEs is the treatment recommended. The patient plays a key role in all treatment processes and possibly even more in the treatment of AEs. Many treatment interventions involve skin care in general use of creams, antiseptic soaks, oral rinses, or other topical applications in the oral cavity. These interventions are stand-alone or may be given in combination with systemic treatments, such as steroids and antibiotics. In order to encourage adherence to the treatment recommended it is important that patients have sufficient information about the intervention(s). The patient should understand the reasons for both treatment and treatment outcome expectations, and be aware of the consequences if recommendations are not followed. The patient must also know which product to apply where, which a simple drawing can help achieve.(12)

Within the research line that the author has been active in, two clinical trials regarding treatment options for skin and oral complaints have been performed: the BeCet and the COMTT study.(48) The outcomes of these AE treatment trials lay beyond the scope of this dissertation, but the instruments generated specifically for these trials in order to be able to assess, report and grade skin and oral AEs contain questions that evaluate the outcomes of the AE treatment. These instruments are discussed throughout the dissertation.

Chapter 2 provides an overview of the prevalence and appearance of oral AEs with tyrosine kinase inhibitor (TKI) and mammalian target of rapamycin inhibitor (mTORI) treatment and the current assessment instruments commonly used in clinical trials in oncology.

Chapter 3 provides a review of the clinical presentation, terminology, pathogenesis, assessment, and management of mTORI-associated oral AEs.

Chapter 4 presents updates from the chemo-, radiation-, and targeted therapy-associated mucosal reactions guideline.

Chapter 5 presents a sub-analysis of the BeCet study. The current study studies the impact of the skin AEs on patients HRQoL, while the main study analyses the appearance and severity of skin AEs.

Chapter 6 provides the process of translation and linguistic validation of the FACT-EGFRI-18 questionnaire from English into Dutch.

Chapter 7 identifies how the FACT-EGFRI-18 reveals the difficulties regarding the assessment of the mucocutaneous AEs from the patients' point of view.

A general discussion, summary, and future perspectives are presented in **chapter 8** and a Summary in Dutch is given in **chapter 9**.

References

1. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273(1):59-65.
2. Ferrari V, Sgotti D, Amoroso V, Valcamonico F, Grisanti S, Consoli F, et al. Oral mucositis a side effect in Tyrosin-Kinase Inhibitor Therapy (Sunitinib): the role of assessment of symptoms in evaluation of toxicity. Eur J Cancer Supp. 2009;7(2):195-6.
3. National Cancer Institute. Targeted Cancer Therapies. 2018 [updated July 26, 2018]. Available from: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.
4. Pastore S, Mascia F, Mariani V, Girolomoni G. The epidermal growth factor receptor system in skin repair and inflammation. J Invest Dermatol. 2008;128(6):1365-74.
5. Walshe K. Adverse events in health care: issues in measurement. Qual Health Care. 2000;9(1):47-52.
6. Boers-Doets CB, Lacouture ME, Langenhoff JM, van Zuuren EJ, Stijnen T, Ouwerkerk J, et al. Interventions for skin reactions associated with targeted anticancer treatments (Protocol). Cochrane Database Syst Rev. 2011(7):Art. No.: CD009236. DOI: 10.1002/14651858.CD009236.
7. Petrelli F, Borgonovo K, Cabiddu M, Lonati V, Barni S. Relationship between skin rash and outcome in non-small-cell lung cancer patients treated with anti-EGFR tyrosine kinase inhibitors: a literature-based meta-analysis of 24 trials. Lung Cancer. 2012;78(1):8-15.
8. Cai J, Ma H, Huang F, Zhu D, Bi J, Ke Y, et al. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. World J Surg Oncol. 2013;11(306):1-8.
9. COBUILD Advanced English Dictionary. Mucous membrane: HarperCollins Publishers; 2018 [Available from: https://www.collinsdictionary.com/dictionary/english/mucous-membrane.
10. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol. 2009;161(5):1045-51.
11. Boers-Doets CB. The TARGET System: Six practical steps from diagnosis to management of adverse events of targeted therapy. Abstracts of the 2015 International MASCC/ISOO Symposium. Support Care Cancer. 2015;23 (Suppl 1):S1–S388(1):70-1.
12. Boers-Doets CB. The Target System - Approach to assessment, grading, and management of dermatological & mucosal side effects of targeted anticancer therapies. Wormer: Impaqtt; 2014.

13. Swan M. Emerging Patient-Driven Health Care Models: An Examination of Health Social Networks, Consumer Personalized Medicine and Quantified Self-Tracking. Int J Environ Res Public Health. 2009;6(2):492-525.
14. Harnett PJ, Bowles N, Coughlan A. Refocusing acute psychiatry, performance management, standards and accountability, a new context for mental health nursing. J Psychiatr Ment Health Nurs. 2009;16(5):434-9.
15. Durif-Bruckert C, Roux P, Morelle M, Mignotte H, Faure C, Moumjid-Ferdjaoui N. Shared decision-making in medical encounters regarding breast cancer treatment: the contribution of methodological triangulation. Eur J Cancer Care (Engl). 2015;24(4):461-72.
16. Obeidat RF, Homish GG, Lally RM. Shared decision making among individuals with cancer in non-Western cultures: a literature review. Oncol Nurs Forum. 2013;40(5):454-63.
17. Kashaf MS, McGill E. Does Shared Decision Making in Cancer Treatment Improve Quality of Life? A Systematic Literature Review. Med Decis Making. 2015;35(8):1037-48.
18. Jackson S, Hafemeister TL. Impact of parental consent and notification policies on the decisions of adolescents to be tested for HIV. J Adolesc Health. 2001;29(2):81-93.
19. Kizer KW. Patient centred care: essential but probably not sufficient. Qual Saf Health Care. 2002;11(2):117-8.
20. Worthington DL. Plaintiff life-taking: the effect of mock juror attitudes toward suicide on assignment of negligence and damages in a civil suit. Behav Sci Law. 2004;22(5):715-30.
21. Tefferi A, Kantarjian H, Rajkumar SV, Baker LH, Abkowitz JL, Adamson JW, et al. In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs. Mayo Clin Proc. 2015;90(8):996-1000.
22. Nikolajsen C, Dinesen B, editors. Patient-driven Health Care Models: The Future Patient using Self-tracking Technologies. Int J Integr Care; 2015;15(7): ETC Conf Suppl; URN:NBN:NL:UI:10-1-117181.
23. Norquist G. Patient-Driven Research Will Lead To Better Health: Health Affairs; 2016 [cited 2016 May 19, 2016]. Available from: https://www.healthaffairs.org/do/10.1377/hblog20160519.054923/full/.
24. Kav S, Johnson J, Rittenberg C, Fernadez-Ortega P, Suominen T, Olsen PR, et al. Role of the nurse in patient education and follow-up of people receiving oral chemotherapy treatment: an international survey. Support Care Cancer. 2008;16(9):1075-83.
25. Kav S, Schulmeister L, Nirenberg A, Barber L, Johnson J, Rittenberg C. Development of the MASCC Teaching Tool for Patients Receiving Oral Agents for Cancer. Support Care Cancer. 2010;18(5):583-90.
26. Boucher J, Lucca J, Hooper C, Pedulla L, Berry DL. A Structured Nursing Intervention to Address Oral Chemotherapy Adherence in Patients With Non-Small Cell Lung Cancer. Oncol Nurs Forum. 2015;42(4):383-9.

27. Rittenberg C. Meeting Educational Needs and Enhancing Adherence of Patients Receiving Oral Cancer Agents Through Use of the MASCC Oral Agent Teaching Tool©. Eur Oncol Haematol. 2012;8(2):97–100.
28. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. Support Care Cancer. 2017;25(2):651-60.
29. Temmerman R. Towards New Ways of Terminology Description. The sociocognitive approach. Amsterdam/Philadelphia: John Benjamins Publishing Company; 2000.
30. Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol. 2008;144(7):886-92.
31. Lipscomb J, Reeve BB, Clauser SB, Abrams JS, Bruner DW, Burke LB, et al. Patient-reported outcomes assessment in cancer trials: taking stock, moving forward. J Clin Oncol. 2007;25(32):5133-40.
32. US Food and Drug Administration. Guidance for industry: Patient-reported outcomes measure: Use in medical product development to support labeling claims. 2009 [updated 12/2009. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
33. Rocque G. What Is the Role of Symptom Management and Patient-Reported Outcomes in Adherence to Aromatase Inhibitors? J Clin Oncol. 2018;36(4):308-9.
34. Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 1: why evaluate health-related quality of life? J Clin Pharm Ther. 2003;28(6):513-21.
35. Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 2: methodological considerations for the assessment of health-related quality of life in clinical trials. J Clin Pharm Ther. 2004;29(1):85-94.
36. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr. 2007(37):16-21.
37. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin Trials. 2004;25(6):535-52.
38. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol. 2016;34(6):557-65.
39. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA. 2017;318(2):197-8.
40. Di Maio M, Gallo C, Leighl NB, Piccirillo MC, Daniele G, Nuzzo F, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol. 2015;33(8):910-5.

41. Zhang B, Lloyd W, Jahanzeb M, Hassett MJ. Use of Patient-Reported Outcome Measures in Quality Oncology Practice Initiative-Registered Practices: Results of a National Survey. J Oncol Pract. 2018;14(10):e602-e11.
42. Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of Patient-Reported Outcomes in Routine Medical Care. Am Soc Clin Oncol Educ Book. 2018(38):122-34.
43. Boers-Doets CB, Lacouture ME. Dermatologic Events in Oncology: How to Measure the Impact of Dermatologic and Mucosal AEs on Symptom Burden and Quality of Life. ASCO Post. 2013;4(20):70-1.
44. The Free Dictionary. Characteristics 2014 [updated 2014. Available from: http://www.thefreedictionary.com/Characteristics.
45. National Cancer Institute. Patient-Reported Outcomes version of the CTCAE 2013 [Available from: https://healthcaredelivery.cancer.gov/pro-ctcae/.
46. Hay JL, Atkinson TM, Reeve BB, Mitchell SA, Mendoza TR, Willis G, et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res. 2014;23(1):257-69.
47. Boers-Doets CB. Oral Drugs: Challenges for the Oncology Nurse. The Breast. 2017;36:S24.
48. Boers-Doets CB, Kaptein AA, Brakenhoff JA, Nortier JW, Gelderblom H. Doelgerichte therapie geassocieerde mucocutane bijwerkingen - de BeCet en de COMTT studie [Targeted therapy associated mucocutaneous reactions - the BeCet and the COMTT study]. Ned Tijd Oncol. 2013;10(8):343-7.

02 | Oral Adverse Events Associated With Tyrosine Kinase and Mammalian Target of Rapamycin Inhibitors in Renal Cell Carcinoma: A Structured Literature Review.

Oncologist 2011;17(1):135-44.

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ABSTRACT

Background. Oral adverse events (OAEs) associated with multitargeted tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORIs) are underestimated but frequent and novel presentations of mucosal manifestations. Because optimal antitumor activity requires maintaining the optimal dose, it is essential to avoid unintended treatment delays or interruptions.

Methods. We review the reported prevalence and appearance of OAEs with TKIs and mTORIs and the current oral assessment tools commonly used in clinical trials. We discuss the correlations between OAEs and hand–foot skin reaction (HFSR) and rash.

Results. The reported prevalence of oral mucositis/stomatitis of any grade is 4% for pazopanib, 28% for sorafenib, 38% for sunitinib, 41% for temsirolimus, and 44% for everolimus. Oral lesions associated with these agents have been reported to more closely resemble aphthous stomatitis than OM caused by conventional agents. In addition, these agents may result in symptoms such as oral mucosal pain, dysgeusia, and dysphagia, in the absence of clinical lesions. Because of these factors, OAEs secondary to targeted agents may be underreported. In addition, a correlation between OAEs and HFSR was identified.

Conclusions. OAEs caused by TKIs and mTORIs may represent dose-limiting toxicities, especially considering the fact that even low grades of OAEs may be troubling to the patient. We discuss how these novel AEs can be assessed because current mucositis assessment tools have limitations. Prospective studies investigating the pathogenesis, risk factors, and management of OAEs are needed in order to minimize the impact on patient's health-related quality of life.

INTRODUCTION

As a result of the introduction of targeted anticancer therapy for advanced renal cell carcinoma (RCC) and metastatic RCC (mRCC), the overall survival time of patients with this disease has increased dramatically. Currently, six U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved targeted agents are available for treating RCC: sunitinib malate (Sutent®; Pfizer, New York), sorafenib tosylate (Nexavar/Nexxava®; Bayer HealthCare, Leverkusen, Germany), pazopanib (Votrient®; GlaxoSmithKline, Greenford, U.K.), temsirolimus (Torisel®; Wyeth Pharmaceuticals, Philadelphia), everolimus (Afinitor®; Novartis Pharmaceuticals, East Hanover, NJ), and bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) plus interferon-®2a. These agents are indicated as first- and second-line therapies. Bevacizumab differs from the other agents reported here in that it blocks vascular endothelial growth factor, whereas the other agents block multiple receptors and intracellular pathways (Table 1).

With longer survival times, it has become even more important to optimize health-related quality of life (HRQoL) during treatment. These agents have a spectrum of mucocutaneous adverse events (AEs) with oral adverse events (OAEs), hand–foot skin reaction (HFSR) (for sunitinib, sorafenib, pazopanib, and everolimus), and rash as disabling and dose-limiting AEs. There are no evidence-based management options to prevent and treat these AEs.

Treatment of mRCC with Targeted Anticancer Agents

Targeted anticancer therapy is a general term that refers to drugs that target pathways in the growth and development of a tumor cell. Targeted therapies such as (multitargeted) tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORIs) for RCC demonstrate a high level of efficacy with acceptable tolerability [1]. Targeted therapies may be continuously administered for their long-term ability to inhibit tumor growth, progression, cell proliferation, and angiogenesis.

In a short span of 4 years, the oral (multitargeted) TKIs sunitinib, sorafenib, and pazopanib, the i.v. mTORI temsirolimus, and the oral mTORI everolimus were approved by the FDA and EMA. Sorafenib received FDA and EMA approval in 2005 [2], sunitinib received approval in 2006 [3], temsirolimus received approval in 2007 [4], everolimus received approval in early 2009 [5], and pazopanib received approval in late 2009 [6]. Sunitinib also received FDA and EMA approval in 2006 for the treatment of gastrointestinal stromal tumor (GIST) [3], and sorafenib received approval in 2007 for the treatment of unresectable hepatocellular carcinoma (HCC) [2].

Treatment Delay, Dose Modifications, and Early Cessation

Optimal antitumor activity requires maintaining the optimal dose in individual patients. In order to improve HRQoL and adherence, AEs should be prevented if possible and treated if necessary. Current oral formulations of targeted agents consist of various schedules (e.g., continuous administration or 4 weeks on and 2 weeks off for sunitinib only) to optimize the risk– benefit profile.

Impaired HRQoL may have a negative impact on patient treatment adherence. Treatment over- or underadherence can have a significant impact on efficacy and the severity of treatment-related AEs [7]. Poor adherence may affect the therapeutic alliance, create skepticism in both the therapist and patient, induce resistance, worsen the disease or the prognosis attributed to missed doses, and increase health care costs [8]. Adherence to anticancer treatment is particularly important when prescribing self-administered oral therapies [9]. Because sorafenib, sunitinib, pazopanib, and everolimus are taken in the outpatient setting, patient education on the correct treatment dosing, usage, and the nature, recognition, and severity of AEs is essential to avoid unintended treatment delays or interruptions.

CONVENTIONAL CYTOTOXIC CHEMOTHERAPY- AND RADIOTHERAPY-INDUCED OAES

There are a number of cancer treatment–related, clinically important AEs that disrupt the function and integrity of the mouth. These AEs include OAEs characterized by redness, swelling, and ulceration; xerostomia (subjective dry mouth); and dysgeusia/ageusia (altered taste/taste loss). OAEs can result in significant clinical consequences, including oral sensitivity and pain, and can affect function, such as with difficulty in chewing and swallowing food, potentially leading to nutrient and caloric deficits, difficulty taking oral medications, and a higher risk for local and systemic infections [9, 10].

Stomatitis is a general term that includes inflammation and ulceration of the mucosal lining of the mouth resulting from any cause. Oral mucositis (OM) is the more specific term that is used to describe oral mucosal inflammation and ulceration induced by cancer therapies [11]. Conventional cytotoxic chemotherapy- or radiotherapy-induced OM is inflammatory mediated damage of the mucosal membranes, most commonly involving nonkeratinized mucosa, that line the oral cavity; the ulcerative phase of development presents clinically with irregular and often confluent ulceration that is typically preceded by regional erythema. Whereas the first phases of mucositis involve the submucosal connective tissue, the epithelial cells of these mucosal tissues have a high turnover rate, which may make them susceptible to the effects of cancer chemotherapy and radiotherapy on the connective tissue and epithelium [12]. It is now recognized that it is not just the epithelium that is affected by cytotoxic treatment, but also the underlying connective tissue. OM develops almost exclusively on nonkeratinized mucosal surfaces (e.g., the buccal and labial mucosa, lateral tongue, floor of mouth, and soft palate).

The management of OAEs includes assessment, diagnosis, teaching oral care, administering interventions aimed at prevention and palliation of symptoms, and supporting patients in coping with symptom distress [9].

Table 1. Targeted agents for advanced RCC and dermatological AEs

Agent	Brand name	Mode of action	FDA and EMA approved indications	Any cutaneous AE (%)
Sunitinib	Sutent®	TKI	Advanced RCC, imatinib-resistant GIST	81[a], NR
Sorafenib	Nexxava®/Nexavar®	TKI	Advanced RCC, unresectable HCC	74[a], NR
Pazopanib	Votrient®	TKI	Advanced RCC	NR
Temsirolimus	Torisel®	mTORI	Advanced RCC	NR
Everolimus	Afinitor®	mTORI	Advanced RCC after failure of sunitinib or sorafenib	NR

All severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

[a]From Lee et al. (2009) [13].

Abbreviations: AE, adverse event; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumor; mTORI, mammalian target of rapamycin inhibitor; NR, not reported; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

TKI- AND MTORI-INDUCED MUCOCUTANEOUS AES

Targeted therapy–related AEs, such as rash, xerosis, pruritus, mucosal, and hair abnormalities, occur in up to 81% of patients during treatment with TKIs or mTORIs [13]. Recognizing the fact that head-to-head comparisons are lacking and interpretation and scoring of AEs may not be univocal, Lee et al. [13] found that cutaneous reactions were more diverse in patients treated with sunitinib than in those treated with sorafenib. HFSR and OAEs were the most common mucocutaneous AEs (Tables 2 and 3).

TKI- and mTORI-Induced OAEs

To date, information on the pathobiology of the OAEs induced by targeted therapies is limited. In addition, there is no consensus on terminology, and in the literature on OAEs associated with targeted therapies, the terms mucositis and stomatitis are used interchangeably. This makes comparison of OAE data from different authors difficult.

An analysis of the appearance, course, and toxicity associations of mTORI-associated OAEs demonstrated that the condition is distinct from conventional mucositis and more closely resembles the presentation of aphthous stomatitis [14]. OAEs appeared within 5 days of deforolimus administration and were discrete, circular or ovoid, superficial, well demarcated, and surrounded by an erythematous halo primarily involving nonkeratinized mucosa. Their clinical appearance and distribution were similar to that of aphthous stomatitis but inconsistent with conventional mucositis. The lack of other gastrointestinal involvement but the presence of a higher prevalence of concomitant cutaneous AEs provided additional evidence to suggest a distinction between mTORI-associated OAEs and conventional cytotoxic therapy–induced OM [14].

In the study of Sonis et al. [14] of 78 solid tumor patients treated with deforolimus, OAEs, reported as mucositis, were dose-limiting toxicities for this new class of agents. OAEs were reported in 66% of the 78 study participants.

In a study of 30 mRCC patients treated with sunitinib, no correlation was found between the intensity of oral symptoms and clinical evidence of mucosal damage [15]. Patients were examined according to three standard assessments—the World Health Organization (WHO) Oral Toxicity Scale [16], National Cancer Institute Common Toxicity Criteria (NCI-CTC) [17], and Oral Mucositis Assessment Scale (OMAS) [16]—and according to an experimental assessment (EA) [15]. The EA consisted of an assessment of a number of symptoms using a visual analog scale (VAS) (range, 0–10) of dysgeusia, (subjective) dysphagia, odynophagia, and oral mucosal pain, which are subjective parameters, and objective mucosal erythema and ulceration. Whereas at the end of treatment the WHO Oral Toxicity Scale, NCI-CTC, and OMAS assessment were grade 0 in 62% of patients and grade 1 in 38% of patients, in the EA they observed no mucosal ulceration but 63% of patients experienced intense dysgeusia (VAS score, 7–10). Ten percent had intense (VAS score, 7–10) and 13% had moderate (VAS score, 4–6) odynophagia. Thirteen percent of the patients had acute pain (VAS score, 7–10) and 40% had intermediate pain (VAS score, 4–6). Three percent had moderate and 3% had severe dysphagia. Moderate erythema was observed in 40% of patients.

TKI- and mTORI-Induced HFSR

HFSR usually manifests as bilateral palmoplantar lesions, especially in areas of trauma or friction, such as over the interphalangeal joints, distal phalanges, or heels [18], and significantly affects patients' QoL [13]. Although most commonly associated with sorafenib and sunitinib, it is also reported with pazopanib and everolimus [19, 20].

HFSR is associated with symptoms that are seen with OAEs too. Patients can develop localized, tender lesions that appear as blisters or hyperkeratosis, which in some cases can be surrounded by an erythematous halo (Fig. 1). Pain, dysesthesia, erythema, and edema [21, 22] are common symptoms on mechanically strained regions and can even appear without obvious skin alterations [23].

In a meta-analysis by Chu et al. [24] on the incidence of and potential relationship between tumor type and sorafenib-associated HFSR, in total, 4,883 patients with metastatic tumors from 11 trials were included for analysis. They found that, among 3,252 patients with RCC, the prevalence of all-grade HFSR was 42.0% (95% confidence interval [CI], 24.9%–61.3%) and that of high-grade HFSR was 8.9% (95% CI, 6.3%–12.3%), whereas for 545 patients with malignancies other than RCC, the prevalence of all-grade HFSR was 27.6% (95% CI, 20.2%–36.4%) and the incidence of high grade HFSR was 9.1% (95% CI, 7.2%–11.3%). There was a significant difference detected between patients with RCC and those with cancers other than RCC in terms of the prevalence of sorafenib-associated all-grade HFSR (relative risk [RR], 1.52; 95% CI, 1.32–1.75; p<.001). However, there was no significant difference between patients with RCC and those with cancers other than RCC in terms of the prevalence of high-grade HFSR (RR, 0.98; 95% CI, 0.76 –1.26; p<.86) [24].

Table 2. Prevalence and severity of OAEs

Oral AEs any grade(%)	Sunitinib for RCC	Sunitinib for GIST	Sorafenib for RCC	Sorafenib for HCC	Pazopanib	Temsirolimus	Everolimus
OM/S	38[b]	29[c]	28[a]	25[a]	4[e]	41[f]	44[g]
OM/S grade 3/4	0[b]	NR	NR	NR	0[e]	3[f]	5[g]
oral pain	53[b]	6[c]	NR	NR	NR	NR	NR
(Aphthous like) ulcers	33[a]	43[a]	NR	NR	<1[e]	NR	NR
Dysphagia (difficulty swallowing)	7[b]	NR	NR	NR	NR	NR	4[g]
Difficulty oral intake	NR	NR	NR	NR	NR	NR	NR
Dry mouth	12[i]	6[d]	NR	NR	NR	NR	8[g]
Dysgeusia	63[b]	21[c]	NR	NR	16[e]	20[f]	10[g]
Other oral AEs	Odynophagia 23[b]	Mucosal inflammation 12[d], glosso-dynia 6[d]	NR	Hoarseness 6[h]	NR	NR	Mucosal inflam-mation 19[g]
Onset	1st -15th week[a]; Before 4th week in 81% of pts[a]		1st-8th week[a]; Before 4th week in 90% of pts[a]		NR	NR	NR
Dose interruption caused by oral AEs	9[a]		7[a]		NR	NR	NR
Dose reduction caused by oral AEs	26[a]		18[h]		NR	NR	NR
Treatment discontinuation caused by oral AEs	0[a]		NR[a]		NR	NR	NR

All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

[a]Lee et al. (2009) [13].

[b]Ferrari et al. (2009) [15].

[c]Adams and Leggas (2007) [43].

[d]Theou-Anton et al. (2009) [44].

[e]European Medicines Agency (2010) [45].

[f]Kwitkowski et al. (2010) [46].

[g]Novartis (2010) [48].

[h]Llovet et al. (2008) [29].

[i]Motzer et al. (2009) [26].

Abbreviations: AE, adverse event; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; NR, not reported; OAE, oral adverse event; OM/S, oral mucositis/stomatitis; RCC, renal cell carcinoma.

In a meta-analysis of HFSR with pazopanib [25], the overall incidences of all-grade and high-grade HFSR were 4.5% (95% CI, 2.5%–7.9%) and 1.5% (95% CI, 0.7%–3.1%), respectively. The RRs for all-grade and high-grade HFSR with pazopanib monotherapy in comparison with controls were greater, reaching statistical significance for all-grade (RR, 6.05; 95% CI, 1.11–33.12; p=.038) but not for high-grade (RR, 2.51; 95% CI, 0.12–51.9; p=.55) HFSR. We did not identify reports of HFSR caused by temsirolimus.

Because of the high prevalence of HFSR associated with TKI use (Table 3), early detection and timely treatment are vital in managing patients during their drug courses to allow continued treatment [13].

Table 3. Prevalence and severity of HFSR

HFSR	Sunitinib for RCC	Sunitinib for GIST	Sorafenib for RCC	Sorafenib for HCC	Pazopanib	Temsirolimus	Everolimus
Any grade (%)	33[a]	43[a]	59[4]	49[a]	7[f]	NR	5[g]
Grade 3/4 (%)	9[b]	4[c]	11[4]	8[e]	1[f]	NR	NR
Onset, days	5-82 (median 32.4)[a]		3-56 (median 18.4)[a]		NR	NR	NR
Transient dose interruption	30[a]		29[a]		NR	NR	NR
Temporary dose reduction	44[a]		40[a]		NR	NR	NR
Treatment discontinuation caused by severe HFSR	19[a]		17[a]		NR	NR	NR

All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[a]Lee et al. (2009) [13].
[b]Motzer et al. (2009) [26].
[c]Adams and Leggas (2007) [43].
[d]Szczylik et al. (2007) [47].
[e]Llovet et al. (2008) [29].
[f]European Medicines Agency (2010) [45].
[g]Novartis (2010) [48].
Abbreviations: GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HFSR, hand–foot skin reaction; NR, not reported; RCC, renal cell carcinoma.

OBJECTIVE

The aim of this study is to provide an overview of the prevalence and appearance of OAEs with TKI and mTORI treatment and the current oral assessment tools commonly used in clinical trials. We also wanted to find out if there is a correlation among OAEs, HFSR, and rash.

METHODS

Search Strategy

We designed a search strategy to identify relevant literature that described OAEs resulting from targeted anticancer therapy among RCC patients in each database as outlined below. We performed our search in the electronic databases PubMed, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for literature published from 1980 through January 7, 2011, linking the subject search headings with text word, MESH terms, and substance name. We linked the key words “mucositis,” “stomatitis,” “ulcer,” “aphthous,” “oral pain,” “deglutition disorders,”

"swallowing," "dry mouth," and "altered taste" to the generic agents and classes of drug. We didn't make language restrictions. OAEs in patients with cancer types other than RCC, GIST, or HCC were not appropriate. Because of the paucity of OAE studies on TKIs and mTORIs at the time of the search, all publication types were considered.

Selection Criteria

We were primarily interested in the clinical presentation of OAEs caused by TKIs and mTORIs. To be included, a paper had to be focused on OAEs, including assessment as (one of) the primary or secondary outcomes, and focusing on TKIs or mTORIs. Papers that only described the appearance of OAEs as a safety issue were excluded.

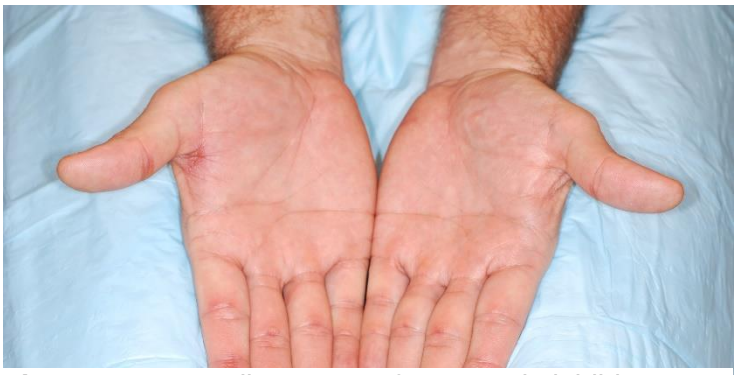

Figure 1. Mammalian target of rapamycin inhibitor (mTORI)- induced hand–foot skin reaction (HFSR). HFSR caused by temsirolimus, an mTORI. HFSR is associated with symptoms that are seen with oral adverse events too. As shown in this picture, patients can develop localized, tender lesions that appear as blisters or hyperkeratosis, which in some cases can be surrounded by an erythematous halo.

RESULTS

Initial searching found a total of 630 citations; 239 hits in PubMed, 376 in Embase, and 15 in CINAHL. After removing duplicates, 501 citations remained; 472 were discarded based on title or abstract because they did not meet the inclusion criteria and 29 citations were included for review.

TKI- and mTORI-Induced AE Profiles

Although some targeted agents share a common mode of action, it should not be assumed that their AE profiles are comparable. Indeed, evidence indicates clinically relevant differences among the toxicity profiles of targeted therapies, including between agents with the same mode of action. For example, sorafenib and sunitinib are both multitargeted TKIs, but in patients with RCC, HFSR appears to occur more frequently with sorafenib (30%) than with sunitinib (19%) [13], whereas leukopenia, neutropenia, and anemia are common with sunitinib (78%, 77%, and 79%) but not with sorafenib. Febrile neutropenia or grade 4 thrombocytopenia did not occur with sorafenib. Grade 3 or 4 anemia occurred in 3% of patients and grade 3 or 4 lymphopenia occurred in 13% of patients [26–28]. It should also be noted that the AE profile for a targeted agent may differ among tumor types. For example, HFSR may occur less frequently with sorafenib in patients with HCC than in patients with RCC (Table 3) [27, 29]. In a meta-analysis performed by Chu et al. [30], it was found that patients with RCC had a significantly greater risk for all-grade HFSR than patients with a malignancy other than RCC, 42% (95% CI, 24.9%–63.3%) and 27.6% (95% CI, 20.2%–36.4%), respectively.

TKI- and mTORI-Induced OAEs

OAEs are associated with many targeted agents. The oral burden can be very difficult for patients, even when the treatment is effective in combating the cancer. These circumstances can lead to lower HRQoL, delay in treatment, dose modification, or early cessation of critical antineoplastic therapy [13].

Clinical Presentation of TKI and mTORI OAEs

A variety of oral signs and symptoms have been described in association with the use of TKIs and mTORIs. For example, sunitinib treatment has been associated with oral mucosal hypersensitivity, oral ulcers, cheilitis, and taste alterations [23, 31]. Oral lesions associated with mTORIs have been described as discrete, oval, superficial ulcers with an erythematous halo (Fig. 2), an appearance similar to that of aphthous stomatitis and unlike that of OM secondary to conventional chemotherapeutic agents [14]. Interestingly, and also unlike oral mucosal toxicity associated with conventional chemotherapy, patients on such targeted agents may sometimes present with oral complaints such as mouth pain, dysgeusia, and dysphagia in the absence of any clinically apparent lesion [14, 21, 32]. Such symptoms have been reported to rapidly improve during treatment- free intervals [23] and may occur again with additional dosing of the targeted agent.

Prevalence of TKI- and mTORI-Induced OAEs

Current data on the frequency of the OAEs associated with each of the different targeted agents are highlighted in Table 2. OAEs are early symptoms, generally observed in sunitinib and sorafenib patients 1–15 weeks after initiation of treatment. As outlined in Table 2, many OAEs are not separately reported. The highest score of any-grade OM or stomatitis is reported with everolimus (44%) and the lowest score is reported with pazopanib (4%). OAEs generally appear 1–15 weeks after initiation of treatment; symptoms began before the fourth week of treatment in 81% and 90%, respectively, of sunitinib- and sorafenib-treated patients. The presence of OAEs required dose reduction in 26% of the sunitinib-treated patients and in 18% of the sorafenib treated patients. No patient permanently discontinued treatment as a result of severe OAEs.

With mTORIs, oral lesions have a rapid onset (usually within 5 days) and are usually of mild to moderate severity (NCI-CTCAE grade 1–2). Lesions are usually found on the mucosa of the lips, lateral tongue, buccal mucosa, and soft palate. Unlike viral-induced ulcers, they are not commonly seen on the hard palate

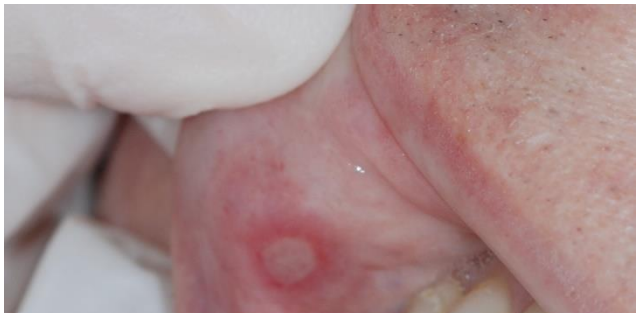

Figure 2. Mammalian target of rapamycin inhibitor (mTORI)-induced oral adverse events. Aphthous stomatitis caused by temsirolimus, an mTORI. As shown in this picture, patients can develop localized, tender lesions that appear as aphthous stomatitis and that can be surrounded by an erythematous halo.

or outer aspects of the lip. They often present as individual ulcers, similar to aphthous ulcers (canker sores): distinct round-oval lesions with grayish-white necrotic centers surrounded by a ring of erythema. Unlike radiation- and chemotherapy-associated mucositis, there is no pseudomembrane formation (Fig. 2). Occasionally they are severe (grade 3), but generally they are reversible by withholding treatment. In many cases mucositis improves or resolves spontaneously despite treatment continuation [33].

Assessment of TKI- and mTORI-Induced OAEs

Numerous OM grading scales have been developed over the years to grade conventional mucositis [34]. The complexity and detail of these scales vary significantly and selection of a mucositis scale is influenced by the reason for assessing mucositis for either clinical care or OM research [35].

Targeted therapy may induce subjective symptoms of oral burden without significant clinical evidence [15]. No validated targeted therapy–specific grading scales are currently available. The frequently used OM scales like the WHO Oral Toxicity Scale, NCI-CTCAE, and OMAS are not designed to evaluate OAEs caused by TKIs and mTORIs and may result in underreporting and poor grading of OAEs in patients treated with these agents (Table 4). For example, the OMAS focuses on objective ulceration and redness, whereas the WHO Oral Toxicity Scale is mainly driven by the patient's ability to eat and drink. The EA suggested by Ferrari et al. [15] may be more adequate for scoring TKI- and mTORI-induced OAEs. The Vanderbilt Head and Neck Symptom Survey (VHNSS), version 2.0, is a tool developed for head and neck cancer patients treated with chemoradiation. It assesses patient-reported symptom burden in the head and neck area and function loss within symptom subscales, including nutrition, taste, pain, voice, swallow, and mucous/dry mouth [36]. The Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group proposed a grading system for the most common epidermal growth factor receptor inhibitor (EGFRI)-induced mucocutaneous AEs [37]. That scale is consistent with the grading principles and language of the CTCAE, version 4.0, and may be formally integrated into future CTCAE versions.

Management of OAEs

For the prevention of conventional OM, most recommendations begin with the use of oral care plans coupled with patient education [38]. A range of products is currently in development for the prevention and management of OAEs that fall into four main categories— cell resistance modifiers, mechanism specific inhibitors, damage control agents, and healing accelerators. However, to date, proven approaches for the prevention and treatment of OAEs are limited [38, 39]. No trials have assessed the management of TKI- and mTORI-induced OAEs. Sonis et al. [14] suggested that mTORI-induced OAEs were distinct entities from conventional OM.

Table 4. Selected tools and their potential to assess OAEs caused by TKIs and TORIs

Scale	**NCI-CTCv3.0[a][51]**	**WHO Oral Toxicity Scale [16]**	**OMAS [16]**	**VHNSS2.0 [36]**
Developed for	Toxicities associated with conventional CT, RT, HSCT	OM following conventional CT, RT, and HSCT	OM due to HSCT	H&N toxicities of (C)RT for HNSCC
Scale description	Clinician rated, objective, subjective, and functional parameters; 0-5 point scale	Clinician rated, combined, objective, subjective, and functional parameters; 0-4 point scale	Clinician rated, objective tissue scale; 1 total score	PRO; subjective and functional parameters; includes Likert scale for each item
Main driver of scale	Severity of AE; impact on ADL	Ulceration and ability to eat and drink	Cumulative surface of ulcerations, and severity of redness	PRO; severity of toxicities associated with HNSCC treatment and functional impact
Oral sites evaluated	Depends on toxicity; (non-keratinized) anatomical sites typically at risk for conventional OM	(Non-keratinized) anatomical sites typically at risk for conventional OM	(Non-keratinized) anatomical sites typically at risk for conventional OM	Symptoms associated with complications in the head and neck area
Potential for use for TKI or mTORI-induced oral lesions	+ Can be modified for this purpose	+/- Inclusion of keratinized/specialized oral sites Moderate risk for underscoring of subjective mucosal alterations	+/- Inclusion of keratinized/specialized oral sites High risk for underscoring of subjective mucosal alterations	+ When extended with questions for oral ulcerations. Should be combined with objective evaluation
Potential for use for TKI/mTORI oAEs	+ Can be modified for this purpose	-	-	+ Should be combined with objective evaluation
Potential for use for mucocutaneous AEs	+ Can be modified for this purpose	-	-	-

[a]CTCAEv3.0, because within CTCAEv4.0 oral ulcerations are not addressed.
Abbreviations: ADL, activities of daily living; AE, adverse event; CT, chemotherapy; HNSCC, head and neck squamous cell carcinoma; HSCT, hematopoietic stem cell transplantation; mTORI, mammalian target of rapamycin inhibitor; NCICTCAEv3.0, National Cancer Institute-Common Terminology Criteria for Adverse Events, version 3.0; OAE, oral adverse event; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; PRO, patient-reported outcome measure; QoL, quality of life; RT, radiation therapy; TKI, tyrosine kinase inhibitor; VHNSS2.0, Vanderbilt Head and Neck Symptom Survey, version 2.0; WHO, World Health Organization.

The exact etiology of aphthous stomatitis has not been fully determined, but it is considered to involve immune mechanisms such as antibody-dependent cell-mediated

cytotoxicity and immune complex formation; this is different from what is considered to occur with conventional OM [40]. Interventions for persistent TKI- or mTORI-related OAEs, therefore, may include the use of various agents such as topical corticosteroids and anti-inflammatory agents as well as supportive treatments such as local anesthetics and antimicrobials [40]. It is important, however, to avoid unfavorable drug interactions with TKI and mTORI drugs.

Table 5. Prevalence and severity of rash

Rash	Sunitinib for RCC	sunitinib for GIST	sorafenib for RCC	sorafenib for HCC	pazopanib	temsirolimus	everolimus
Any grade (%)	24[a]	14[b]	41[c]	19[d]	9[e]	47[f]	29[g]
Grade 3 or 4 (%)	2[a]	1[b]	6[c]	1[d]	<1[e]	5[f]	1[g]

All severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
[a]Motzer et al. (2009) [26].
[b]Adams and Leggas (2007) [43].
[c]Szczylik et al. (2007) [47].
[d]Bayer HealthCare (2009) [49].
[e]European Medicines Agency (2010) [45].
[f]Pfizer [50].
[g]Novartis (2010) [48].
Abbreviations: GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

Correlation of OAEs with Dermatological AEs

Correlation Between OAEs and HFSR

Lee at al. [13] found a strong correlation between OAEs and HFSR in the patients they studied, who were treated with sunitinib and sorafenib. A significant correlation was found between the occurrence of stomatitis and severity of HFSR ($p<.01$, χ^2 test for trend). OAEs were observed in 72% of patients with grade 3 HFSR and in 47% of patients with grade 2 HFSR. OAEs were more likely to occur in patients with severe HFSR than in those with mild HFSR. There was a significant relationship between the occurrence of stomatitis and severity of HFSR ($p=.004$, χ^2 test for trend), although no significant correlation was found between HFSR severity and response to treatment [13].

Correlation Between OAEs and Rash

Rash caused by TKIs or mTORIs can affect 9%–47% of patients (Table 5). Because there was a significant relationship found between the occurrence of OAEs and severity of HFSR in sunitinib- and sorafenib-treated patients, it is interesting to assess the potential for OAEs occurring with rash. As far as we know, there is no literature addressing this possible correlation.

DISCUSSION

TKI- and mTORI-related OAEs are underrecognized although they may represent a dose-limiting toxicity for this new class of agents, especially considering the fact that even low grades of OAEs with chronic daily dosing may result in morbidity that may lead to dose reductions [14]. With the longer survival times for RCC patients, it has become even more important to optimize HRQoL during treatment.

The prevalence of OAEs of any grade in renal cancer patients is 38% for sunitinib, 28% for sorafenib, 4% for pazopanib, 41% for temsirolimus, and 44% for everolimus. Interestingly, targeted therapy may induce subjective symptoms of oral burden without objective clinical evidence (e.g., mucosal sensitivity and pain, odynophagia, xerostomia, and taste alterations). Because of these symptoms and aphthouslike ulcerations being distinct from conventional ulcerative OM, current tools are of limited value for OAE assessment. The EA from Ferrari et al. [15] and a modified version of the VHNSS, version 2.0, are potentially useful to grade OAEs. There is a gap in the current literature related to assessing OAEs, HFSR, and rash resulting from therapy with TKIs and mTORIs. Therefore, development of a comprehensive grading system for TKI- and mTORI-associated mucocutaneous AEs similar to the MASCC EGFRI mucocutaneous AE–specific scale seems appropriate.

It is feasible that TKIs and mTORIs are associated with other less frequent or not yet investigated oral complications. For example, a case of jaw osteonecrosis associated with sunitinib has been reported [41], salivary gland function may be affected, resulting in hyposalivation and qualitative salivary alterations, and patients taking mTORIs may be at risk for periodontitis because these drugs induce immunosuppression and affect collagen synthesis.

A strong correlation was found between severe OAEs and HFSR. The results of the current review suggest that OAEs induced by TKIs and mTORIs are distinct from conventional chemotherapy- and radiotherapy-induced OM. More studies are necessary into the pathobiology of OAEs induced by TKIs and mTORIs. In addition, studies of individual patient characteristics predisposing for toxicities are promising, because these may lead to optimal treatment strategies. For example, a recent study indicated that polymorphisms in genes encoding metabolizing enzymes, efflux transporters, and drug targets are associated with sunitinib-related toxicities [42].

Targeted agents have mucocutaneous AEs in common, with OAEs, HFSR, and rash as the most disabling AEs. Evidence-based management guidelines to prevent and treat these complications are required; presently they are lacking.

Additional studies of management strategies may therefore be important for dose adherence to TKI and mTORI therapy and for the overall acceptance of this therapy for patients.

Educating patients on the importance of reporting all AEs and on compliance with the prescribed dose may increase early recognition and ensure adherence to treatment, allowing the most effective treatment strategy for the patient. There is currently only limited evidence for the prevention and management of OAEs caused

by targeted agents, which indicates the need for more evidence derived from well-designed prospective clinical studies in order to improve management.

AUTHOR CONTRIBUTIONS

Conception/Design: Christine B. Boers-Doets, Joel B. Epstein
Provision of study material or patients: Christine B. Boers-Doets
Collection and/or assembly of data: Christine B. Boers-Doets, Richard M. Logan
Data analysis and interpretation: Christine B. Boers-Doets, Joel B. Epstein, Judith E. Raber-Durlacher, Jan Ouwerkerk, Richard M. Logan, Jan A. Brakenhoff, Mario E. Lacouture, Hans Gelderblom
Manuscript writing: Christine B. Boers-Doets, Joel B. Epstein, Judith E. Raber-Durlacher, Jan Ouwerkerk, Richard M. Logan, Jan A. Brakenhoff, Mario E. Lacouture, Hans Gelderblom
Final approval of manuscript: Christine B. Boers-Doets, Joel B. Epstein, Judith E. Raber-Durlacher, Jan Ouwerkerk, Jan A. Brakenhoff, Mario E. Lacouture, Hans Gelderblom

REFERENCES

1. Bukowski RM. Systemic therapy for metastatic renal cell carcinoma in treatment naïve patients: A risk-based approach. Expert Opin Pharmacother 2010;11:2351–2362.
2. National Cancer Institute. FDA Approval for Sorafenib Tosylate, November 19, 2007. Available at http://www.cancer.gov/cancertopics/druginfo/fda-sorafenib-tosylate#Anchor-Live-50484, accessed October 20, 2010.
3. National Cancer Institute. FDA Approval for Sunitinib Malate, February 5, 2007. Available at http://www.cancer.gov/cancertopics/druginfo/fdasunitinib-malate#kidney, accessed October 20, 2010.
4. National Cancer Institute. FDA Approval for Temsirolimus, June 1, 2007. Available at http://www.cancer.gov/cancertopics/druginfo/fdatemsirolimus, accessed October 20, 2010.
5. U.S. Food and Drug Administration. Everolimus, January 11, 2010. Available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm127799.htm, accessed October 20, 2010.
6. National Cancer Institute. FDA Approval for Pazopanib Hydrochloride, October 29, 2009. Available at http://www.cancer.gov/cancertopics/druginfo/fda-pazopanibhydrochloride, accessed October 20, 2010.
7. Partridge AH, Avorn J, Wang PS et al. Adherence to therapy with oral antineoplastic agents. J Natl Cancer Inst 2002;94:652– 661.
8. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–497.

9. Harris DJ, Eilers J, Harriman A et al. Putting evidence into practice: Evidence-based interventions for the management of oral mucositis. Clin J Oncol Nurs 2008;12:141–152.
10. Wood LS. Managing the side effects of sorafenib and sunitinib. Commun Oncol 2006;3:558–562.
11. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent Clin North Am 2008;52:61–77, viii.
12. Rubenstein EB, Peterson DE, Schubert M et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100(9suppl):2026 –2046.
13. Lee WJ, Lee JL, Chang SE et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol 2009;161:1045–1051.
14. Sonis S, Treister N, Chawla S et al. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 2010;116:210 –215.
15. Ferrari V, Sgotti D, AmorosoVet al. Oral mucositis a side effect in tyrosine-kinase inhibitor therapy (sunitinib): The role of assessment of symptoms in evaluation of toxicity [abstract]. Eur J Cancer 2009;2(suppl 7):195.
16. Sonis ST, Eilers JP, Epstein JB et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer 1999;85:2103–2113.
17. National Cancer Institute. Common Toxicity Criteria (CTC), Version 2.0. 30–4-1999. Available at www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf, accessed November 9, 2009.
18. Lacouture ME, Reilly LM, Gerami P et al. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. Ann Oncol 2008;19:1951–1966.
19. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol 2010;28:1061–1068.
20. Novartis Pharmaceuticals Corporation. Afinitor® (everolimus) tablets [prescribing information]. Available at http://www.afinitor.com/index.jsp, accessed November 12, 2010.
21. Porta C, Paglino C, Imarisio I et al. Uncovering Pandora's vase: The growing problem of new toxicities from novel anticancer agents. The case of sorafenib and sunitinib. Clin Exp Med 2007;7:127–134.
22. Autier J, Escudier B, Wechsler J et al. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 2008;144:886–892.
23. Kollmannsberger C, Soulieres D, Wong R et al. Sunitinib therapy for metastatic renal cell carcinoma: Recommendations for management of side effects. Can Urol Assoc J 2007;1(2 suppl):S41–S54.

24. Chu D, Lacouture ME, Fillos T et al. Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis. Acta Oncol 2008;47: 176–186.
25. Balagula Y, Wu S, Su X et al. The risk of hand foot skin reaction to pazopanib, a novel multikinase inhibitor: A systematic review of literature and meta-analysis. Invest New Drugs 2011 Mar 11 [Epub ahead of print]. DOI: 10.1007/s10637– 011-9652–2.
26. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–3590.
27. Escudier B, Eisen T, Stadler WM et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312–3318.
28. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–134.
29. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378 –390.
30. Chu D, Lacouture ME, Weiner E et al. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: A meta-analysis. Clin Genitourin Cancer 2009;7:11–19.
31. Gru¨nwald V, Soltau J, Ivanyi P et al. Molecular targeted therapies for solid tumors: Management of side effects. Onkologie 2009;32:129 –138.
32. Ivanyi P, Winkler T, Ganser A et al. Novel therapies in advanced renal cell carcinoma: Management of adverse events of sorafenib and sunitinib. Dtsch Arztebl Int 2008;105:232–237. In German.
33. Sankhala K, Mita A, Kelly K et al. The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. Target Oncol 2009;4:135–142.
34. Sonis ST, Elting LS, Keefe D et al. Perspectives on cancer therapy-induced mucosal injury: Pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004;100(9suppl):1995–2025.
35. Brennan MT, von Bu¨ltzingslöwen I, Schubert MM et al. Alimentary mucositis: Putting the guidelines into practice. Support Care Cancer 2006;14:573–579.
36. Cooperstein E, Epstein JB, Murphy BA et al. Vanderbilt Head and Neck Symptom Survey Version 2.0 (VHNSS 2.0): A tool for the study of longterm oral health consequences of therapy for head and neck cancer (HNC) [abstract]. J Clin Oncol 2010;28(15 suppl):9055.
37. Lacouture ME, Maitland ML, Segaert S. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer 2010;18:509 –522.
38. Keefe DM, Schubert MM, Elting LS et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007;109:820–831.
39. Al-Dasooqi N, Gibson RJ, Bowen JM et al. Matrix metalloproteinases: Key regulators in the pathogenesis of chemotherapy-induced mucositis? Cancer Chemother Pharmacol 2009;64:1–9.

40. Messadi DV, Younai F. Aphthous ulcers. Dermatol Ther 2010;23:281–290.
41. Koch FP, Walter C, Hansen T et al. Osteonecrosis of the jaw related to sunitinib. Oral Maxillofac Surg 2011;15:63– 66.
42. van Erp NP, Eechoute K, van der Veldt AA et al. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol 2009;27:4406–4412.
43. Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clin Ther 2007;29: 1338–1353.
44. Theou-Anton N, Faivre S, Dreyer C et al. Benefit-risk assessment of sunitinib in gastrointestinal stromal tumours and renal cancer. Drug Saf 2009; 32:717–734.
45. European Medicines Agency. Summary of Product Characteristics: Pazopanib (Votrient®), 2010. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001141/WC500094272.pdf , accessed November 17, 2010.
46. Kwitkowski VE, Prowell TM, IbrahimAet al. FDA approval summary: Temsirolimus as treatment for advanced renal cell carcinoma. The Oncologist 2010;15:428–435.
47. Szczylik C, Demkow T, Staehler M et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: Final results [abstract]. J Clin Oncol 2007;25(18 suppl):5025.
48. Novartis. Afinitor® (everolimus) [prescribing information], 2010. Available at http://www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf, accessed November 15, 2010.
49. Bayer HealthCare Pharmaceuticals Inc. Nexavar® (sorafenib [prescribing information], 2009. Available at http://www.nexavar.com/html/download/Nexavar_PI.pdf, accessed November 12, 2010.
50. Pfizer. Torisel® (temsirolimus) [prescribing information], 2010. Available at http://www.pfizerpro.com/content/showlabeling.asp?id=490, accessed November 12, 2010.
51. National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 9 – 8-2006. Available at www.eortc.be/services/doc/ctc/ctcaev3.pdf, accessed November 9, 2009.

03 | Mammalian target of rapamycin inhibitor-associated stomatitis.

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ABSTRACT

With the recent introduction of inhibitors of mammalian target of rapamycin (mTOR) in oncology, distinct cutaneous and oral adverse events have been identified. In fact, stomatitis and rash are documented as the most frequent and potentially dose-limiting side effects. Clinically, mTOR inhibitor-associated stomatitis (mIAS) more closely resembles aphthous stomatitis than oral mucositis due to conventional anticancer therapies. While most cases of mIAS are mild to moderate and self-limiting, more severe and persistent mIAS can become a dose-limiting toxicity. Small ulcerations may cause significant pain and mucosal sensitivity may occur in the absence of clinical changes. Use of clinical assessment tools that are primarily driven by ulceration size may underestimate mIAS, and assessment should include patient-reported outcomes. This article provides an up-to-date review of the clinical presentation, terminology, pathogenesis, assessment and management of mIAS and other mTOR inhibitor-associated oral adverse events. In addition, areas of future research are considered.

Mammalian target of rapamycin (mTOR) is a serine/tyrosine protein kinase that acts as a master switch for protein synthesis, cell proliferation, cell cycle progression and cell survival, integrating signals from growth stimuli to cell cycle progression [1]. Dysregulation of the PI3K/AKT/mTOR signaling pathway has been identified in several human malignancies, and investigation of this signaling network has led to the development of targeted cancer therapies [2]. One of the primary pharmacologic targets has been mTOR, which occurs in two multiprotein complexes, mTORC1 and mTORC2. mTOR inhibitors that are currently in clinical use inhibit mTORC1 through allosteric binding and demonstrate efficacy with acceptable tolerability [2]. These agents are associated with sustained, durable clinical responses in several cancer types, including, for example, advanced renal cell carcinoma and neuroendocrine pancreatic cancers [3].

The first mTOR inhibitor developed was sirolimus (Rapamune®; Wyeth-Ayerst, NJ, USA), which is used as an antirejection medication in solid and stem cell transplantation. For the treatment of cancer, two mTOR inhibitors are currently available: temsirolimus (Torisel®; Pfizer, NY, USA) and everolimus (Afinitor®; Novartis Pharmaceuticals, NJ, USA). Temsirolimus is intravenously administered and is approved for the treatment of advanced renal cell carcinoma [101]. Everolimus is an oral mTOR inhibitor that is US FDA approved for the second-line treatment of advanced renal cell carcinoma [102], neuroendocrine pancreatic cancers, and aromatase inhibitor-resistant hormone receptor-positive, HER2-/neu-negative advanced breast cancers and for tuberous sclerosis complex related renal angiomyolipomas. In addition, everolimus was recently approved for nonresectable subependymal giant cell astrocytoma [103]. A third mTOR inhibitor, ridaforolimus (deforolimus, Jenzyl® [EU], Taltorvic® [US]; Merck & Co. Inc, NJ, USA) continues to be under clinical investigation for a range of cancers [104].

This new class of oncology drugs has a spectrum of adverse events (AEs) that are unique as compared with conventional anticancer chemotherapy. AEs include hyperglycemia, hyperlipidemia, hypophosphatemia, hematologic toxicities and mucocutaneous eruptions. In particular, stomatitis and skin rash are documented as the most frequent and potentially dose-limiting side effects [4,5]. When mTOR inhibitors are used for immunosuppression, they are often given in combination with other immunosuppressant agents, including corticosteroids that may actually diminish and/or prevent mouth and skin AEs. Moreover, the prevalence of mouth and skin toxicity could also be decreased owing to a significant lower dose applied in transplantation medicine.

In the majority of cancer patients treated with mTOR inhibitors, stomatitis is reported as mild to moderate. However, even small lesions can be painful and invalidating since patients are treated continuously, rather than in cycles of determined length as in conventional chemotherapy [105,106]. As a consequence, even mild-to-moderate oral AEs may have a negative impact on health related quality of life, leading to unplanned treatment delays or interruptions, dose reductions or ultimately to cessation of therapy [6,7]. Therefore, minimizing and managing oral AEs is important.

This article reviews the clinical presentation, terminology, pathogenesis, assessment and management of mTOR inhibitor-associated stomatitis (mIAS). In addition, other reported oral AEs that have been associated with mTOR inhibitors will be described.

Terminology

The terminology and classification of oral AEs associated with mTOR inhibitors has been inconsistent throughout different clinical trials. For example, in a review article by Bellmunt et al. on the AEs of temsirolimus for the treatment of renal cell carcinoma, the frequencies of mucositis, stomatitis, aphthous stomatitis and mouth ulceration were reported as distinct categories [8]. Moreover, mucosal inflammation and tongue ulceration were reported as distinct oral AEs [107,Merck, Pers. Comm.]. The terms oral mucositis and stomatitis are often used interchangeably, but they do not reflect identical processes. Oral mucositis is a Medical Subject Headings term that describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation. It typically manifests as erythema or ulcerations and may be exacerbated by local factors, such as secondary infections and trauma. Stomatitis is a less specific term that refers more generally to any inflammatory condition of oral tissues [9,108].

In a seminal paper describing the unique clinical features of oral ulcerations associated with mTOR inhibitors, Sonis et al. proposed the term mIAS in order to provide clarity and delineation from oral mucositis due to conventional cytotoxic chemotherapy and radiation [7]. Other authors also emphasized the importance of using consistent terminology [4,5,10,11]. Among oral medicine specialists managing patients with oral mucosal lesions associated with mTOR inhibitors, there is consensus that the term mIAS is preferable to the term oral mucositis.

Clinical presentation & prevalence of mIAS & other oral complications

The clinical presentation of mIAS typically involves solitary or multiple ulcerations resembling aphthous stomatitis, characterized as distinct, ovoid ulcers with a central gray area surrounded by a ring of erythema (Figure 1). Typically, ulcerations are small (<0.5 cm), whereas oral ulcerations caused by traditional cytotoxic chemotherapy agents (e.g., 5-fluorouracil) are typically larger, more irregular in shape, with or without surrounding erythema and without elevated borders [5,7].

Similar to conventional mucositis and aphthous stomatitis, mIAS almost exclusively affects the nonkeratinized, movable oral surfaces, including the buccal and labial mucosa, lateral tongue, soft palate and floor of mouth. Ulcerations affecting the keratinized oral mucosa (gingiva, tongue dorsum and hard palate) are more likely to have an infectious, particularly viral etiology [12]. Although mTOR inhibitors are immunosuppressive, it is not clear whether this puts patients at risk for oral infections.

mIAS lesions typically present with a rapid onset (usually within 5 days), most frequently in the first cycle of mTOR inhibitor therapy. Most often mIAS is graded as mild to moderate in severity grades 1–2, according to the oral mucositis scale of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) [13]. Most cases improve or resolve spontaneously despite continuing mTOR inhibitor treatment [11]. However, even small ulcerations can be very painful and can interfere with a patient's ability to chew and swallow and as a result may compromise nutritional status. In some patients mIAS may persist over an extended period. A study characterizing toxicity in patients enrolled in the Phase III RECORD-1 trial, which evaluated everolimus for the treatment of metastatic renal cell carcinoma, indicated that 42% of the patients developed stomatitis, of which 39% experienced mild-to-moderate stomatitis that resolved within 3 days [14]. However, nearly 10% required a dosage modification or treatment interruption, while nearly half required supportive therapies for symptom control. In a recent systematic review evaluating 44 studies of mTOR inhibitors, mIAS was identified as the most frequent AE overall (73.4%), the third most frequent severe AE (20.7%), accounting for 27.3% of dose reductions, and 13.1% of discontinuations, and was the most frequent dose-limiting toxicity (52.5%) [15]. In patients enrolled in ridaforolimus trials, there was a notably higher frequency of severe mIAS and related dose modifications and discontinuations compared with the other mTOR inhibitors, most likely related to the intensity of therapy [16–18,Merck, Pers. Comm.].

Mucositis induced by chemotherapy and radiotherapy to the head and neck area often leads to difficulties with swallowing (dysphagia) and need for a liquid diet. Pharyngitis and dysphagia have also been reported with ridaforolimus, but seem to occur less frequently than in conventional cancer treatments [11,14]. Throat pain has been reported in association with oral ulcerations [7,107,Merck, Pers. Comm.]. In addition, other clinically important AEs that disrupt oral function have been described relating to the use of mTOR inhibitors. These include altered taste/taste loss (dysgeusia/ageusia), oral sensitivity and pain without the presence of clinical oral lesions, and xerostomia [19,107,Merck, Pers. Comm.]. Compared with mIAS, less attention has been paid to these AEs and they have not been well described.

Pathobiology

While significant progress has been made in obtaining insight into the pathobiologic mechanisms of mucositis due to cytotoxic drugs and/or ionizing radiation, mIAS is a recently recognized phenomenon and its pathogenesis is not well understood [7]. Although it is not clear what mechanisms are involved in the development of mIAS, it is probable that these differ from what occurs in conventional oral mucositis based on differences in clinical presentation. The association with concomitant cutaneous AEs provides additional evidence to suggest a distinction between mIAS and oral mucositis induced by conventional cancer therapies [7,10]. The clinical resemblance of mIAS to

aphthous stomatitis may indicate common pathobiological pathways, but also the pathobiology of aphthous stomatitis is not well understood. The etiology of recurrent aphthous stomatitis is believed to be multifactorial, including genetic, environmental, hormonal and emotional factors, in addition to trauma and irritating food and drink. Immune dysregulation is thought to play a role and several potential mechanisms have been described, including antibody-dependent cell-mediated cytotoxicity [20]. Moreover, loss of peripheral tolerance resulting in autoimmune reactions may occur and cross-reactions between a microbial antigen and a peptide within the oral epithelium may play a role [21]. Recently, it has been suggested that CD4+CD25+ Tregs are decreased and function improperly in patients suffering from recurrent aphthous stomatitis. Tregs are vital for the maintenance of peripheral tolerance throughout life and when the generation and expansion of these cells are decreased, this may result in loss of control over autoreactive T cells and consequently lead to loss of peripheral tolerance of the oral mucosa [22].

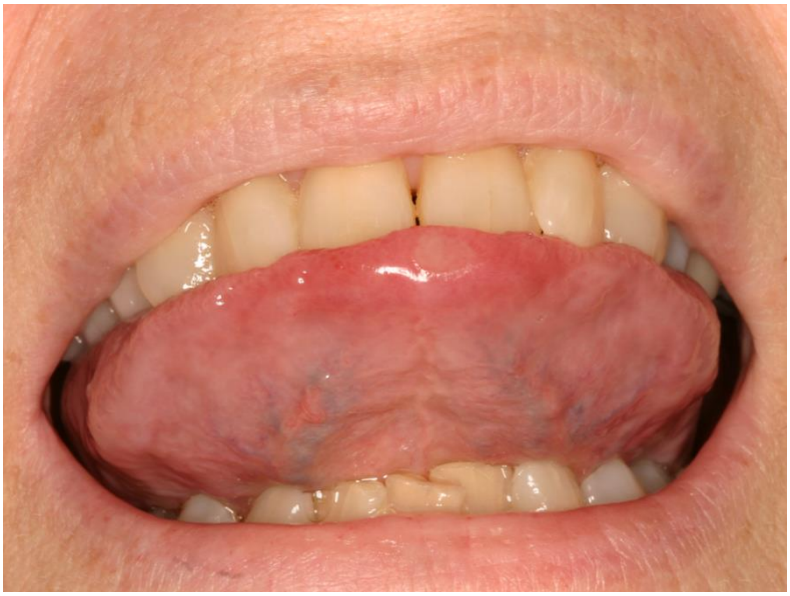

Figure 1. Typical mammalian target of rapamycin inhibitor-associated stomatitis with ulceration and an erythematous halo clinically resembling aphthous stomatitis in a patient treated with temsirolimus.

By contrast, several in vitro studies suggest that mTOR inhibitors increase stimulation of Tregs leading to increased peripheral tolerance, but mechanisms of action of rapamycin and its analogs are multifaceted and can exert both immunosuppressive and immunostimulatory effects [23]. Of interest is the hypothesis that in patients with mTOR inhibitor-induced interstitial pneumonitis, mTOR inhibitors may bind directly to tissue proteins evoking an autoimmune-like inflammatory response, mediated by conventional CD4 cells in the absence of infection [24]. Consistent with this observation, proinflammatory properties of mTOR inhibitors have also been described in various experimental models [25] and similar mechanisms may be involved in the development of mIAS.

Moreover, impaired wound healing has been suggested to play a pathobiological role in aphthous ulceration and may also be involved in the pathogenesis of mIAS. It is known that angiogenesis and vascular cell proliferation are important for wound repair, and both processes may be impeded by mTOR inhibitors [26]. Furthermore, mTOR inhibitors may induce glucose levels to increase in patients with pre-existing

diabetes mellitus and in nondiabetic patients, which may also have a negative impact on wound healing.

With respect to the non-mIAS oral AEs as a response to mTOR inhibiting therapy, the potential mechanisms are even less clear. Greater characterization of these AEs and their relationship with the presence or absence of mIAS is necessary before mechanisms can be elucidated.

Assessment scales

Numerous oral mucositis grading scales have been developed over the years to grade conventional mucositis [27]. The complexity and detail of these scales varies significantly and the selection of a mucositis scale is often influenced by the reason for assessing mucositis (clinical care or research) [28]. Frequently used scales for conventional oral mucositis assessment, such as the WHO Oral Toxicity Scale and the Oral Mucositis Assessment Scale [29], were not developed to evaluate mIAS ulcerations and mIAS-associated complaints. In clinical trials of mTOR inhibitors, AEs, including mIAS, have been described primarily according to NCI-CTCAE versions 2.0 and 3.0 [19,109]. The mucositis scales of these prior versions of the NCI-CTCAE include grading of objective signs as well as subjective symptoms. However, such scales, which depend on ulceration size and extent, may underestimate the morbidity of mIAS, since even small localized ulcerations can be extremely painful and affect compliance. In this manner, the WHO scale may be a reasonable instrument for assessing mIAS. The mucositis component of the NCI-CTCAE version 4.0 is purely symptom and function driven [110]. However, this scale as well as the WHO scale emphasizes the impact of oral lesions on the subject's diet (e.g., WHO grade 3 is given when only a liquid diet can be tolerated). Since mIAS typically does not impact patients' diet to the same extent as conventional mucositis, such scales may not be sensitive enough to measure the impact of mIAS. In summary, scales developed for oral mucositis secondary to conventional chemotherapy and radiation therapy have several limitations when applied to mIAS.

The primary variables determining the morbidity of mIAS are the pain experienced by the subject and the duration of the lesions. It is important that these factors be carefully assessed in scoring mIAS. An accurate assessment of the morbidity of the toxicity will allow for informed decisions on dose modification and interruption, which have far reaching consequences. Therefore, a new scale has been developed for mIAS. This scale has a subjective component measuring pain and an objective component measuring duration of lesions. The subjective grading criteria range from 0 for no pain to 3 for a pain score of 6 or higher on a 0–10 scale. The objective grading criteria range from 0 for no visible lesion to 3 for lesion(s) persisting for more than 7 days. It is suggested that dose modification be considered

Table 1. Selected tools and their potential to assess mammalian target of rapamycin inhibitor-associated stomatitis.

Scale	Developed for	Scale description	Main driver of scale	Evaluation includes	Suitable for use in mIAS	Suitable for use for other mTOR inhibitor-associated oral complaints	Suitable for use for nonoral mucocutaneous adverse events	Ref.
WHO Oral Toxicity Scale	OM induced by conventional CT, RT, HSCT	Clinician- rated, combined, objective, subjective, and functional parameters; 0-4 point scale	Ulceration and ability to eat and drink	Anatomical oral sites typical at risk for conventional OM and mIAS	+/- High risk for underscoring of subjective mucosal alterations	-	-	[29]
OMAS	OM due to HSCT	Clinician-rated, objective tissue scale; yes/no score	Cumulative surface of ulcerations, and severity of redness	Anatomical oral sites typical at risk for conventional OM and mIAS	+/- High risk for underscoring of objective mucosal alterations, no subjective measurement	-	-	[29]
NCI-CTCAE vs3.0	AEs associated with conventional CT, RT, HSCT	Clinician-rated, objective, subjective, and functional parameters; 0–5 point scale	Severity of AE; need for interventions, impact on ADL	Anatomical sites typically at risk for conventional OM and mIAS	+	+	+	[109]
NCI-CTCAE v4.0	AEs associated with conventional CT, RT, HSCT	Clinician rated, objective, subjective, and functional parameters; 0–5 point scale	Severity of AE; need for interventions, impact on ADL	Oral and oropharyngeal symptoms and dietary limitation associated with conventional OM	+/- High risk for underscoring of morbidity of mIAS	+/-	+/-	[110]
VHNSS2.0	Head and neck AEs of CRT/RT for HNSCC	PRO; subjective and functional parameters; includes Likert scale for each item	Severity of AEs associated with HNSCC treatment and functional impact	Measures symptoms associated with complications in the head and neck area, no objective assessment of oral ulcers	+ No objective assessment of oral ulcers	+ Should be combined with objective evaluation	-	[31]
mIAS scale	mIAS	Clinician-rated objective component and patient-rated subjective component; 0–4 point scale	Duration of ulceration(s) attributed to mIAS and severity of associated pain	Persistence of lesions and pain	++ Specifically developed for mIAS	-	-	[30]

++: Highly suitable to assess mIAS; +: Suitable to assess mIAS; +/-: Somewhat suitable to assess mIAS; -: Not suitable to assess mIAS; ADL: Activities of daily living; AE: Adverse event; CRT: Chemoradiotherapy; CT: Chemotherapy; HNSCC: Head and neck squamous cell carcinoma; HSCT: Hematopoietic stem cell transplantation; mIAS: mTOR inhibitor-associated stomatitis; mTOR: Mammalian target of rapamycin; NCI-CTCAEv3.0: National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0; NCI-CTCAEv4.0: National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0; OM: Oral mucositis; OMAS: Oral Mucositis Assessment Scale; PRO: Patient-reported outcome measure; RT: Radiation therapy; VHNSS2.0: Vanderbilt Head and Neck Symptom Survey version 2.0.

only when both subjective and objective grades are 3, representing persistent lesions with significant pain, despite analgesic use [30]. These parameters (duration and pain of the lesions) have an effect upon oral and pharyngeal function.

In addition, detailed assessment of other oral and oropharyngeal AEs that may be associated with mTOR inhibitors use (e.g., swallowing problems, sensitive mucosa, dysgeusia and xerostomia) is warranted to obtain an insight of the prevalence and severity of these complaints and to assess whether these complaints are associated with mIAS or may also develop independently of clinically assessable oral ulceration. The Vanderbilt Head and Neck Symptom Survey version 2.0 measures patient-reported treatment-related symptom burden and oral health outcomes in the head and neck area and function loss within symptom subscales, including nutrition, taste, pain, voice, swallowing and mucus/dry mouth [31]. This scale may be adapted to assess such other mTOR inhibitor-associated oral complaints and their impact on patients' health-related quality of life (Table 1).

Prevention & treatment implications

Prevention and treatment of mTOR inhibitor-associated oral complications can be critical in order to maintain regimen adherence and reduce the need for dose interruptions or reductions. To date, interventions aimed at managing mTOR inhibitor-associated oral complaints are mainly based on expert opinion and show similarities with basic oral care measures aimed at the prevention and treatment of conventional oral mucositis as well as management strategies for aphthous stomatitis (Table 2).

Management begins with assessment and patient education on oral hygiene measures, diet modifications and pain management [4,8,20,32]. In most cases pain can be controlled with mouthwashes or locally applied products containing lidocaine or doxepin and mucosal coating agents [33–35]. Additionally, over the counter non-narcotic analgesics may play a role, whereas prescription of opioids is seldom necessary [10,20,36]. Most often mIAS is self-limiting, but in persistent cases treatment with local or systemic corticosteroids may be considered. This is on the premise that mIAS resembles aphthous stomatitis, in which management protocols include the use of corticosteroids. Topical high-potency corticosteroid gels were reported to be effective in mIAS in a series of reports from both the solid organ transplantation and oncology literature [14,20,36]. In addition, intralesional administration of corticosteroids has been reported to be an effective treatment option [5]. In more severe and refractory cases, or when painful esophageal ulcers are present, pulsed high-dose systemic corticosteroid therapy may be indicated [10,20,36]. In severe and persistent cases, dose reductions may be considered [5], and specific strategies for dosage reduction have been described [14,37]. Dose modifications or permanent discontinuation of mTOR inhibitors should only be considered when palliative management options have failed or if the patient refuses to continue therapy.

The role of oral infections that may develop in isolation or concomitant with mIAS is not clear. Potentially, oral bacteria, viruses and fungi may contribute to the severity of oral ulceration [38,39]. Secondary candidiasis is a common side effect of topical steroid therapy. If this occurs, topical antifungal therapy should be initiated. However, it should be taken into consideration that systemically absorbed azole antifungal agents may increase the serum concentration of the mTOR inhibitor and may increase toxic effects through cytochrome P450-mediated interaction. In such cases a topical nonazole antifungal agent is preferred.

Table 2. Management options for mammalian target of rapamycin inhibitor-associated oral complications

Oral complications	**Management Options**
Prevention	Educate patients on mTOR-associated oral complications and the importance of maintaining good oral care; pay special attention to mouthwash with saline at least four times a day Advise regular dental check-ups and dental prophylaxis Eliminate sources of trauma (e.g., sharp edges and ill-fitting prostheses) Advise to avoid hard, hot, sharp or spicy food Assess the oral cavity regularly and advise to inform caregiver at first signs and symptoms of oral complications
Treatment of mild-to-moderate mIAS	Increase the frequency of the mouthwash with saline, for example, every 1–2 h; if mouthwash is painful, recommend to use pain medication beforehand Assess the oral cavity regularly Diagnose and treat oral mucosal infections when present Assess severity of oral sensitivity/pain Provide pain management (e.g., viscous lidocaine 2%, coating agents, calcium phosphate solution and, when needed, systemic approaches following the WHO pain management ladder) Consider a topical NSAID (e.g., amlexanox 5% oral paste) Consider high potency corticosteroids (dexamethasone [0.1% mg/ml]; clobetasol gel or ointment [0.05%])
Severe mIAS	Provide adequate pain management Consider intralesional triamcinolone (weekly; total dose 28 mg) and topical clobetasol gel or ointment (0.05%) In recurrent mIAS or esophageal lesions: consider systemic corticosteroids (high-dose pulse 30–60 mg oral prednisone or prednisolone [1 mg/kg for 1 week followed by dose tapering over the second week]) Consider dose reduction of mTOR inhibitor
Complaints of dry mouth	Advice adequate fluid intake Consider sugarless chewing gum or candy, salivary substitutes, or sialogogues in patients with oral dryness

This table is based, in part, on expert opinion-based recommendations provided by Pilotte et al. [10], de Oliveira et al. [11] and Scully [21].
mIAS: mTOR inhibitor-associated stomatitis; mTOR: Mammalian target of rapamycin.

Dry mouth can be managed with increased hydration and use of taste and mechanical stimulation of the salivary glands with sugar-free chewing gum or candies.

Palliation with mouth-wetting agents may provide temporary relief. In addition, the prescription of sialagogues can be considered in patients with hyposalivation [40]. In order to help patients coping with taste alterations, the addition of tastants to food, such as increased spices, sauces and umami flavoring, and elimination of tastes experienced as bitter or sour in the diet should be considered.

Conclusion & future perspective

mIAS and skin AEs are among the most frequent side effects of mTOR inhibitors used in anticancer treatment. However, oral complaints are probably under-reported in the literature since studies were not primarily directed to investigate oral complications and most available data originate from spontaneous patient reports in safety and efficacy studies of mTOR inhibitor agents. In addition, measurement scales and terminology differ among studies, which further complicates insight into the prevalence of these oral AEs.

Prospectively designed observational studies using well-defined terminology and appropriate assessment and grading tools are necessary to better characterize the prevalence and severity of mIAS and other associated oral complications. In addition, the prevalence of oral complications associated with mTOR inhibitors may differ between agents and different routes and schedules of administration.

An animal model of mIAS would allow better characterization of early events and mechanisms driving its pathology. Moreover, investigations into the relationship between oral and nonoral AEs, including those of the skin, may be helpful in obtaining a better understanding of potentially shared pathobiologic mechanisms and potentially lead to improved management strategies. In addition, new insights into mIAS pathogenesis and advances made in mIAS management may improve the management of aphthous stomatitis.

An exploratory study identified polymorphisms in genes encoding for metabolizing enzymes, efflux transporters and drug targets that are associated with sunitinib-related AEs [41]. Similarly a future study aimed at identifying genetic markers of the pharmacokinetic and pharmacodynamic pathways of mTOR inhibitors that may predispose for the development of AEs might predict the risk of developing mIAS. This in combination with a better understanding of nongenetic determinants of mTOR toxicity should help to optimize drug treatment in individual patients.

New mTOR inhibitor compounds are currently under development as anticancer agents. These agents have the ability to block both mTORC1 and mTORC2. These dual inhibitors are likely to be more efficacious than presently available mTOR inhibitors that only inhibit mTORC1, and induce the activation of other signaling pathways mediated by mTORC2, resulting in proliferative and survival signals that impede their anticancer efficacy. In addition, combinations of mTOR inhibitors, conventional cytostatic therapy and agents targeting growth factor receptors, such as EGFR, may result in enhanced anticancer efficacy [42]. However, these combined treatment approaches, particularly

those involving EGFR inhibitors, may increase the incidence and severity of mucosal and skin AEs [4].

A growing number of cancer patients will be treated with mTOR inhibitors, most frequently as outpatients and over a long time span. This indicates a need for awareness and early recognition of oral complications not only among oncologists and oncology nurses, but also among community healthcare specialists, such as primary care doctors and dental professionals. Healthcare professionals should educate patients on the importance of early reporting of oral complaints. A combination of basic oral care measures, pain management and topical corticosteroid therapy appears to be an effective approach to management, but well-designed prospective studies are required.

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Executive summary

Mammalian target of rapamycin inhibitors

- Three mammalian target of rapamycin (mTOR) inhibitors are currently used in oncology: temsirolimus, everolimus and ridaforolimus.

Terminology

- mTOR inhibitor-associated stomatitis (mIAS) is preferred to distinguish this entity from conventional chemotherapy-associated mucositis.

Clinical presentation & prevalence of mIAS & other oral complications

- Lesions are usually found on the nonkeratinized mucosa of the lips, floor of mouth, lateral tongue, buccal mucosa and soft palate. mIAS usually develops early after the administration of mTOR inhibitors and is self-limiting in most cases.

Pathobiology

- The pathobiology of mIAS is poorly understood, but may have similarities with mechanisms involved in aphthous stomatitis. These include immune mechanisms such as antibody-dependent, cell-mediated cytotoxicity and immune complex formation; this is different from what is considered to occur in conventional oral mucositis.

Other mTOR inhibitor-associated oral complaints

- These include oral pain and mucosal sensitivity, xerostomia, dysphagia, altered or loss of taste and decreased oral intake.

Assessment scales

- The development of separate assessment and grading tools for mIAS seems justified. Scales that are driven by ulceration size may under-report mIAS, since even small ulcers can be very painful. Modified versions of existing scales may be of value and should be validated for mTOR inhibitor-associated oral adverse events. An mIAS-specific assessment tool has been generated.

Prevention & treatment implications

- To date, evidence-based interventions for managing mIAS are not available. Principles of basic oral care including patient education on oral hygiene measures and avoiding hot, hard, spicy or acid foods are advised. In addition, other management strategies for aphthous stomatitis including pain management and the use of corticosteroids seem effective.

Conclusion & future perspective

- Prospective studies investigating the prevalence and clinical presentation of mIAS and other oral complications should be performed. In order to obtain meaningful outcomes, the use of well-defined terminology together with development of appropriate assessment and grading scales is mandatory. Experimental and clinical studies are required to characterize the pathogenesis of mIAS and clinical trials should be developed to evaluate interventions. Oncologists, oncology nurses, oral healthcare professionals, dermatologists, pharmacologists and basic scientists should be involved in these efforts.

Concluding remarks

- mIAS is a frequent but typically mild-to-moderate complication that is often self-limiting. When necessary, management is generally effective. The relationship with other oral adverse events is less clear but these can also typically be managed conservatively. In some cases, patients may require dose reduction.

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat. Rev. Drug. Discov. 5(8), 671–688 (2006).
2. Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors: how pathway complexity informs therapeutic strategy. J. Clin. Invest. 121(4), 1231–1241 (2011).
3. Bukowski RM. Systemic therapy for metastatic renal cell carcinoma in treatment naive patients: a risk-based approach. Expert Opin. Pharmacother. 11(14), 2351–2362 (2010).

4. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: a narrative literature review. Oral. Oncol. 47(6), 441–448 (2011).

***Summarizes oral complications of targeted cancer therapies including mammalian target of rapamycin (mTOR) inhibitors.**

5. Li E, Trovato JA. New developments in management of oral mucositis in patients with head and neck cancer or receiving targeted anticancer therapies. Am. J. Health Syst. Pharm. 69(12), 1031–1037 (2012).
6. Lee WJ, Lee JL, Chang SE et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br. J. Dermatol. 161(5),1045–1051 (2009).
7. Sonis S, Treister N, Chawla S et al. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 116(1), 210–215 (2010).

**** First paper describing mTOR inhibitor-associated stomatitis (mIAS).**

8. Bellmunt J, Szczylik C, Feingold J et al. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann. Oncol. 19(8), 1387–1392 (2008).
9. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. Dent. Clin. North Am. 52(1), 61–77 (2008).
10. Pilotte AP, Hohos MB, Polson KM et al. Managing stomatitis in patients treated with Mammalian target of rapamycin inhibitors. Clin. J. Oncol. Nurs. 15(5), E83–E89 (2011).

**** Informative paper with practical management recommendations for mIAS.**

11. de Oliveira MA, Martins F, Wang Q et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol. 47(10), 998–1003 (2011).

**** Describes the clinical presentation and management options for mIAS.**

12. Elad S, Zadik Y, Hewson I et al. A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridea. Support. Care Cancer 18(8), 993–1006 (2010).
13. Boers-Doets CB, Epstein JB, Raber-Durlacher JE et al. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist 17(1), 135–144 (2012).
14. Porta C, Osanto S, Ravaud A et al. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. Eur. J. Cancer 47(9), 1287–1298 (2011).
15. Kwitkowski VE, Prowell TM, Ibrahim A et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. Oncologist 15(4), 428–435 (2010).
16. Martins F, de Oliviera MA, Wang Q et al. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral. Oncol. 49(4), 293–298 (2013).
17. Chawla SP, Staddon AP, Baker LH et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. J. Clin. Oncol. 30(1), 78–84 (2012).

18. Dancey JE, Monzon J. Ridaforolimus: a promising drug in the treatment of soft-tissue sarcoma and other malignancies. Future Oncol. 7(7), 827–839 (2011).
19. Sessa C, Tosi D, Vigano L et al. Phase Ib study of weekly mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) with weekly paclitaxel. Ann. Oncol. 21(6), 1315–1322 (2010).
20. Messadi DV, Younai F. Aphthous ulcers. Dermatol. Ther. 23(3), 281–290 (2010).
21. Scully C. Aphthous ulceration. N. Engl. J. Med. 355(2), 165–172 (2006).

*** Landmark paper on aphthous stomatitis.**

22. Lewkowicz N, Lewkowicz P, Dzitko K et al. Dysfunction of CD4+CD25high T regulatory cells in patients with recurrent aphthous stomatitis. J. Oral Pathol. Med. 37(8), 454–461 (2008).

**** Presents provocative and new thoughts about the pathobiology of aphthous stomatitis.**

23. Weichhart T, Saemann MD. The multiple facets of mTOR in immunity. Trends Immunol. 30(5), 218–226 (2009).
24. Morelon E, Stern M, Israel-Biet D et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. Transplantation 72(5), 787–790 (2001).
25. Saemann MD, Haidinger M, Hecking M et al. The multifunctional role of mTOR in innate immunity: implications for transplant immunity. Am. J. Transplant. 9(12), 2655–2661 (2009).
26. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. Nat. Rev. Cancer 4(5), 335–348 (2004).
27. Sonis ST, Elting LS, Keefe D et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100(9 Suppl.), S1995–S2025 (2004).
28. Brennan MT, von Bültzingslöwen I, Schubert MM et al. Alimentary mucositis: putting the guidelines into practice. Support. Care Cancer 14(6), 573–579 (2006).
29. Sonis ST, Eilers JP, Epstein JB et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer 85(10), 2103–2113 (1999).
30. Boers-Doets CB, Lalla RV. The mIAS scale: a scale to measure mTOR inhibitor-associated stomatitis. Support. Care Cancer 21(S1),S140 (2013).
31. Cooperstein E, Gilbert J, Epstein JB et al. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck 34(6), 797–804 (2012).
32. Bhojani N, Jeldres C, Patard JJ et al. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. Eur. Urol. 53(5), 917–930 (2008).
33. Keefe DM, Schubert MM, Elting LS et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 109(5), 820–831 (2007).

34. Bensinger W, Schubert M, Ang KK et al. NCCN Task Force report. prevention and management of mucositis in cancer care. J. Natl Compr. Canc. Netw. 6(Suppl. 1), S1–S21 (2008).
35. Hudes GR, Carducci MA, Choueiri TK et al. NCCN Task Force report: optimizing treatment of advanced renal cell carcinoma with molecular targeted therapy. J. Natl Compr. Canc. Netw. 9(Suppl. 1), S1–S29 (2011).
36. Campistol JM, de Fijter JW, Flechner SM et al. mTOR inhibitor-associated dermatologic and mucosal problems. Clin. Transplant. 24(2), 149–156 (2010).
37. Hutson TE, Figlin RA, Kuhn JG et al. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. Oncologist 13(10), 1084–1096 (2008).
38. van der Beek MT, Laheij AM, Raber-Durlacher JE et al. Viral loads and antiviral resistance of herpesviruses and oral ulcerations in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 47(9), 1222–1228 (2012).
39. Laheij AM, de Soet JJ, von dem Borne PA et al. Oral bacteria and yeasts in relationship to oral ulcerations in hematopoietic stem cell transplant recipients. Support. Care Cancer 20(12), 3231–3240 (2012).
40. Jensen SB, Pedersen AM, Vissink A et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. Support. Care Cancer 18(8), 1061–1079 (2010).
41. van Erp NP, Eechoute K, van der Veldt AA et al. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J. Clin. Oncol. 27(26), 4406–4412 (2009).
42. Dufour M, Dormond-Meuwly A, Demartines N et al. Targeting the mammalian target of rapamycin (mTOR) in cancer therapy: lessons from past and future perspectives. Cancers 3(2), 2478–2500 (2011).

**** Provides an in-depth insight into the mechanisms of mTOR inhibitors used in cancer treatment.**

Websites

101. US FDA. (1-6-2007) FDA approval for temsirolimus. www.cancer.gov/cancertopics/druginfo/fdatemsirolimus (Accessed 20 October 2010)
102. US FDA. (11-1-2010) Everolimus. www.fda.gov/AboutFDA/CentersOffices/CDER/ucm127799.htm (Accessed 20 October 2010)
103. National Cancer Institute. (4-9-2012) FDA approval for everolimus. www.cancer.gov/cancertopics/druginfo/fdaeverolimus (Accessed 22 October 2012)
104. National Cancer Institute. www.cancer.gov/clinicaltrials (Accessed 12 September 2012)

105. Novartis Pharmaceuticals Corporation. (5-9-2011) Novartis drug Afinitor® gains EU approval to treat patients with advanced pancreatic neuroendocrine tumors. www.novartis.com/newsroom/media-releases/en/2011/1543887.shtml. (Accessed 1 June 2011)
106. Pfizer. (2010) Full prescribing information temsirolimus (TORISEL). www.pfizerpro.com/content/showlabeling.asp?id=490 (Accessed 12 November 2010)
107. Novartis Pharmaceuticals Corporation. (2010) Full prescribing information everolimus (AFINITOR®). www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf (Accessed 15 November 2010)
108. National Cancer Institute. (17-5-2012) Oral complications of chemotherapy and head/neck radiation (PDQ®) www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5 (Accessed 22 October 2012)
109. National Cancer Institute. (9-8-2006) Common terminology criteria for adverse events v3.0 (CTCAE) www.eortc.be/services/doc/ctc/ctcaev3.pdf (Accessed 11 September 2009)
110. National Cancer Institute Cancer Therapy Evaluation Program. (15-12-2010) Common terminology criteria for adverse events and common toxicity criteria [v4.0]. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40 (Accessed 1 June 2011)

04 | Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up.

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terminology

Oral and gastrointestinal mucositis caused by high-dose chemotherapy and/or radiation continues to be an important clinical problem. Fortunately, there have been strategic advances over the past decade relative to understanding the molecular basis of the injury, which in turn continues to provide opportunity for development of drugs and devices to manage the toxicity. The guidelines delineated below represent updates from the version published in the 2011 Annals of Oncology [1] which were primarily based on the previous version of the guidelines produced by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) [2].

Three key advances have occurred in the three years following publication of the most recent ESMO mucositis guidelines. Both of these advances, as listed below have been completed at the international, interprofessional level:

- A comprehensive update of oral and gastrointestinal tract mucositis guidelines previously produced by the Mucositis Study Group of MASCC in 2007 [2]. The most recent updated evidence-based guidelines, published in 2014 [3],represent the state-of-the-science for mucositis management in patients receiving conventional chemotherapy and/or head & neck radiation.
- Expert opinion on management of oral mucosal lesions caused by targeted cancer therapies such as mammalian target of rapamycin (mTOR) inhibitors and multi-targeted tyrosine kinase inhibitors (mTKI's) [4].
- Novel approaches to enteral nutrition in patients receiving head and neck radiation [5-9]. In France and French-speaking countries, the Société Francophone de Nutrition et Métabolisme (SFNEP) and the Association Francophone pour les Soins Oncologiques de Support (AFSOS) published comprehensive recommendations for cancer patients [10-12].

Mucositis is defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract. Infectious disease, immune deficiency and medications can be causative. High dose cancer chemotherapy and radiotherapy in head and neck cancer are two of the major causes of mucositis.

The terms oral mucositis and stomatitis are often used interchangeably, but they do not reflect identical processes [4, 13].

'Mucositis' is a Medical Subject Heading term that describes inflammation of mucosa resulting from chemotherapeutic agents or ionising radiation. It typically manifests as erythema or ulcerations and may be exacerbated by local factors, such as secondary infections and trauma. Examples of chemotherapeutic agents which may cause oral mucositis are cyclophosphamide, doxorubicin, vincristine, etoposide, ifosfamide, methotrexate, docetaxel, paclitaxel, cisplatin, carboplatin, oxaliplatin, irinotecan, 5-fluorouracil (5-FU), leucovorin, and vinorelbine.

'Stomatitis' refers more generally to any inflammatory condition of oral tissues [13]. This term should be used for oral complaints not related to chemotherapeutic agents or ionising radiation, such as targeted therapies. Clinically important adverse events (AEs) that disrupt the normal oral function have been described related to use of targeted therapies. These include altered taste and taste loss, oral sensitivity and pain without the presence of clinical oral lesions, and xerostomia [4]. Compared with mTOR inhibitor-associated stomatitis, less attention has been paid to these AEs and they have not been accurately described. Examples of targeted agents which may cause stomatitis are bevacizumab, erlotinib, sorafenib, sunitinib, gefitinib, and lapatinib.

Regarding stomatitis induced by mTOR inhibitors, Sonis et al. proposed the term 'mTOR inhibitor-associated stomatitis' (mIAS) in order to provide clarity and delineation from oral mucositis due to conventional cytotoxic chemotherapy and radiation [14]. There is consensus among oral medicine specialists managing patients with oral mucosal lesions associated with mTOR inhibitors that the term mIAS is preferable to the term oral mucositis [4, 15–18]. Examples of mTOR inhibitors are temsirolimus and everolimus.

'Alimentary tract mucositis' refers to the expression of mucosal injury across the continuum of oral and gastrointestinal mucosa, from the mouth to the anus.

oral mucositis in patients receiving head and neck radiation

Incidence of World Health Organization (WHO) grade 3 or 4 oral mucositis in patients receiving head and neck radiation (e.g., 60-70 Gy) to the oral cavity approaches 85%, but all treated patients have some degree of oral mucositis. Mucositis is one of the prime limiting factors of chemoradiation for advanced head and neck carcinoma. The oral pain associated with the lesions frequently leads to the need for enteral nutritional support with or without use of a feeding tube or gastrostomy, as well as use of opioids, with the objective of maintaining dose intensity throughout the entire radiation regimen.

oral and gastrointestinal mucositis in patients undergoing hematopoietic stem-cell transplantation

Incidence of WHO grade 3 or 4 oral mucositis can be as high as 75% in patients undergoing hematopoietic stem-cell transplantation (HSCT), depending on the intensity of the conditioning regimen used and the use of methotrexate prophylactically to prevent graft-versus-host disease. Management of oral and gastrointestinal

mucositis is one of the main challenges during the period of aplasia, with risk of sepsis related to degree of mucosal barrier breakdown and depth of marrow suppression.

alimentary tract mucositis associated with standard multi-cycle chemotherapy (with or without radiotherapy)

A wide range of standard or high-dose chemotherapeutic regimens continues to be causative of clinically significant oral and gastrointestinal mucositis [1].

Chemotherapy with 5-FU, capecitabine, irinotecan, or tegafur can lead to a clinically significant incidence of alimentary tract mucositis (e.g. ∼25% of advanced colorectal cancer patients experiencing grade 3–4 diarrhoea secondary to irinotecan and oxaliplatin [2]). Eighteen percent of patients receiving carboplatin and paclitaxel plus radiotherapy develop severe oesophagitis. Phase I modelling of drug dose and sequence may be of benefit to future patients relative to these treatment paradigms.

stomatitis in patients undergoing targeted therapy

In recent years, unique oral mucosal lesions have been reported in association with administration of targeted cancer therapeutics (e.g. TKIs and mTOR inhibitors).

Elting et al. determined via meta-analysis that mucosal toxicities associated with selected targeted agents were most frequent among patients treated with bevacizumab, erlotinib, sorafenib, or sunitinib, although this difference was confined to low-grade stomatitis [19]. The clinical significance of these findings is unclear given its low incidence and mild severity. This analysis by Elting et al. shows that stomatitis, gastritis, oesophagitis, and xerostomia are occasional complications of therapy with the targeted agents that they studied, but these problems are not significantly more common or more serious than those observed with standard of care regimens.

In a systematic review evaluating 44 studies of mTOR inhibitors, mIAS has been identified as the most frequent AE overall (73.4%) [20]. The lesion was the third most frequent severe AE (20.7%), accounting for 27.3% of dose reductions, and 13.1% of discontinuations, and was the most frequent dose-limiting toxicity (52.5%). The majority of mIAS occurs soon after initiation of the agent [21].

gastrointestinal mucositis in patients undergoing targeted therapy

The study by Elting et al. further showed most of the targeted agents studied were associated with significantly higher risks (2- to 8-fold) of developing either all-grade or high-grade diarrhea than the conventional regimens [19]. Their analysis showed that patients treated with erlotinib, gefitinib, lapatinib, sorafenib, and sunitinib have a significantly higher risk of having both allgrade and high-grade diarrhoea than those receiving conventional regimens. The risk can be as high as 8-fold for patients treated with lapatinib. These results are consistent with prior reviews and case series on this topic. Keefe et al. indicated that diarrhoea is a common side-effect of targeted therapy

and, when used in combination with chemotherapy, these targeted drugs can cause severe diarrhoea [22]. Harandi et al. also reported that diarrhoea is strongly associated with the use of anti-EGFR TKIs [23]. Other studies cited diarrhoea as a common side-effect as well [24, 25].

Mechanisms underlying diarrhoea caused by targeted therapies have been less extensively studied than diarrhoea occurring secondary to chemotherapy. Additional research is thus needed relative to pathobiology of targeted therapy-associated diarrhoea, as well as optimal strategies for its prevention and treatment.

diagnosis and pathology/molecular biology

Diagnosis of oral and gastrointestinal mucositis caused by high dose cancer therapy is typically based upon history and clinical examination. The temporal relationship between timing of administration of chemotherapy or radiation in relation to the symptoms and signs is often sufficient to clinically document the condition.

Diagnosis of oral mucosal lesions caused by targeted cancer therapies can typically be clinically confirmed by history and clinical examination. However, unlike oral mucositis caused by conventional cancer therapy, oral mucosal lesions may first occur several weeks or months after the initial dose exposure [14].

staging and risk assessment

staging

A variety of assessment scales exist for staging of oral and/or gastrointestinal injury. The WHO scale is frequently utilised in the context of grading mucosal injury as a primary outcome. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [26] instrument is also commonly utilised in oncological clinical trials. Scales developed for oral mucositis secondary to conventional chemotherapy and radiation therapy have several limitations when applied to targeted agents. Two assessment tools, the Vanderbilt Head and Neck Symptom Survey version 2.0 (VHNSS2.0) [27] and the mIAS scale [28] can be of use within this population. The VHNSS was designed to screen both for tumour and for treatment-specific symptoms in patients with head and neck cancer undergoing concurrent chemoradiation and following cancer therapy. The list of possible symptoms is quite detailed. Since the oral complaints associated with targeted therapies are not fully explored, the VHNSS2.0 can be used to assess signs and symptoms of oral complaints, also not developed for this population [27]. In addition, the Bristol stool chart is available for the assessment of the consistency of the stool [29].

oral mucositis grading

Two of the most commonly utilised scales for oral mucositis are the WHO and NCI-CTCAE scales [26]:

WHO scale for oral mucositis

Grade 0 = no oral mucositis
Grade 1 = erythema and soreness
Grade 2 = ulcers, able to eat solids
Grade 3 = ulcers, requires liquid diet (due to mucositis)
Grade 4 = ulcers, alimentation not possible (due to mucositis)

National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [26]

The definition used for this grading is “A disorder characterized by inflammation of the oral mucosal [sic: “mucosa”]”.

Grade 1 = asymptomatic or mild symptoms; intervention not indicated
Grade 2 = moderate pain; not interfering with oral intake; modified diet indicated
Grade 3 = severe pain; interfering with oral intake
Grade 4 = life-threatening consequences; urgent intervention indicated
Grade 5 = death

Most of the scales that are utilized for clinical care incorporate the collective measurement of oral symptoms, signs and functional disturbances. By comparison, some scales are primarily centered in clinician-based observation of mucosal tissue injury (e.g., erythema, ulceration). These latter scales have particular value in clinical trial-based assessment of oral mucositis.

gastrointestinal mucositis grading

In contrast, there is a limited number of instruments available for assessment of gastrointestinal mucositis. These scales typically measure indirect outcomes of mucosal injury, including diarrhoea. However, interpretation of such data can be confounded by other clinical conditions and interventions that also contribute to the event being measured. New technologies may lead to enhanced assessment strategies for gastrointestinal mucositis. Tracheal mucositis, pharyngeal mucositis, laryngeal mucositis, small intestinal mucositis, rectal mucositis, and anal mucositis are terms that can be scored separately in the CTCAEv4.03 within the system organ class ‘Gastrointestinal disorders–Other, specify’. Diarrhoea is a term that is scored frequently within gastrointestinal mucositis also, which should not be confused with loose stool. The Bristol stool chart [29] is a useful tool to help identify variation in consistency of stool. The stools are classified into seven types, with types 5 and 6 tending towards diarrhoea but still loose stool and type 7 actually as diarrhoea, since that is watery stool. Since according to the NCI-CTCAE definition only watery stool is diarrhoea, this delineation between the two types is important. Furthermore, it is important to delineate this range of stool consistency in order to optimise clinical decision making for these patients. For example, one can consider low-dose loperamide, with no chemotherapy dose modification, for the patient with a loose or mushy stool. Conversely, either high-dose loperamide with risk for resultant constipation, and/or chemotherapy dose

delay/dose interruption, may be warranted in the patient with systematically graded severe diarrhoea.

diarrhea

Definition: A disorder characterized by frequent and watery bowel movements
NCI-CTCAE version 4.03 [26].

Grade 1 = increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline

Grade 2 = increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline

Grade 3 = increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL

Grade 4 = life-threatening consequences; urgent intervention indicated

Grade 5 = death

targeted therapy-associated stomatitis grading. There is no separate definition for targeted therapy-associated stomatitis defined in the NCI-CTCAE version 4.03 [26].

Undefined AE's can be graded within the system organ class "Gastrointestinal disorders - Other, specify" with the addition of stomatitis.

Grade 1 = asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 = moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL

Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL

Grade 4 = life-threatening consequences; urgent intervention indicated

Grade 5 = death

Use of clinical assessment tools that are primarily driven by ulceration size may underestimate mIAS and that assessment should include patient-reported outcomes. Boers-Doets and Lalla have thus proposed a new scale with a subjective component measuring pain and an objective component measuring duration of lesions [28]. It is suggested that dose-modification be considered only when both subjective and objective grades are 3, representing persistent lesions with significant pain, despite the use of analgesics or other palliative care. Measurement of mIAS using this scale is designed to facilitate optimal management of the underlying malignancy, resulting in improved outcomes.

Subjective

Grade 0 = no oropharyngeal pain attributed to mIAS

Grade 1 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 hours) reported as 2 or less on a 0-10 scale

Grade 2 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 hours) reported as 5 or less on a 0-10 scale

Grade 3 = oropharyngeal pain attributed to mIAS, with average oropharyngeal pain score (over the last 24 hours) reported as 6 or more on a 0-10 scale

Objective

Grade 0 = no visible mIAS (i.e. no erythema and no ulceration, attributed to mIAS, in the oropharyngeal area)

Grade 1 = oral and/or pharyngeal erythema, attributed to mIAS, but no ulceration

Grade 2 = visible oral and/or pharyngeal ulceration(s), attributed to mIAS, of duration < 7 days

Grade 3 = visible oral and/or pharyngeal ulceration(s), attributed to mIAS, with at least one ulceration persisting for ≥ 7 days

risk assessment

Risk of developing mucositis has classically been directly associated with modality, intensity, and route of delivery of the cancer therapy. Combination therapy (e.g. head and neck radiation with concurrent chemotherapy) may increase the severity of oral mucositis. Unlike success in reducing long-term salivary hypofunction and xerostomia when parotid glands are spared [30], incidence and severity of acute mucosal toxicity have not generally been significantly reduced by utilisation of state-of-the- science radiation technologies (e.g. volumetric modulated arc therapy).

While this modelling continues to be valid, there appear to be additional risk factors (e.g. genetic polymorphisms) in some cohorts that account for a degree of clinical expression. Further study of these more recently defined factors will likely strategically advance the pathobiological model in relation to clinical expression of toxicity.

Among patient-related risk factors, comorbidities (e.g. malnutrition) can contribute important risk. All patients should be screened for nutritional risk and early enteral nutrition initiated in the event swallowing difficulties develop. In addition, patients who develop clinically significant salivary hypofunction/xerostomia due to anti-emetic or other anti-cholinergic drugs administered during acute cancer treatment may experience increased discomfort from oral mucositis.

preventive measures

Preventive measures are important in reducing the severity of stomatitis. Sources of trauma (e.g. sharp edges and ill-fitting prostheses) should be eliminated and painful stimuli such as hot foods and drinks and hard, sharp, or spicy foods should be avoided. Effective oral hygiene is crucial; it is important that patients be appropriately educated about oral complications before treatment. The patient should also be advised to have regular dental examinations in order to have the oral cavity assessed and that they should inform the health care professional at first signs and symptoms of oral complications [4].

basic oral care and good clinical practice

mucositis caused by chemotherapy and/or head & neck radiation. Basic oral care is key in preventing and reducing oral injury; educating the patient regarding oral hygiene is thus very important. A comprehensive Basic Oral Care protocol is outlined in Table 1. McGuire et al. concluded that, due to inadequate and/or conflicting evidence, no guidelines for the prevention or treatment of oral mucositis were possible for the interventions of dental care, normal saline, sodium bicarbonate, mixed medication mouthwash, chlorhexidine in patients receiving chemotherapy or haematopoietic stem cell transplant, or calcium phosphate [31]. Based on this conclusion, no recommendation in favour of normal saline mouthwashes is possible. Rather, plain water can be used; this approach is typically well tolerated by patients and may promote patient adherence to basic mouth care practices.

mIAS. Comparable measures can be followed for basic oral care in patients on targeted therapy, with one exception. With targeted agents, saline-containing mouthwashes should be used instead of plain water because of the microbial burden that is considered to intensify formation of oral injury in this population. There is currently no systemically derived evidence for this approach, but since targeted therapies are associated with inflammation and localised and systemic infections, this mucosal hygiene approach may be considered until a more comprehensive, evidence-based approach has been developed.

Evidence related to this modelling provides guidance as to types of microbial colonisation and clinical infection. For example, in a retrospective study of 221 patients treated with EGFR inhibitors, 38% demonstrated evidence of infection at sites of dermatological toxic effect [32]. Furthermore, 22.6% had cultures positive for Staphylococcus aureus (S. aureus), and 5.4% of the 221 patients cultured positive for methicillin-resistant S. aureus. Less frequent infections included herpes simplex (3.2%), herpes zoster (1.8%), and dermatophytes (10.4%), with *Candida onychomycosis* being the most common yeast infection (5.9%). The seborrhoeic region is the most frequently documented site of infection. In addition, patients with leucopenia have higher risk for infection than those patients who do not experience leucopenia (P = 0.005). Others have reported dermatological infection and inflammation associated with EGFR inhibitors [33, 34] as well as with VEGFR inhibitors [35, 36].

Table 1. Example of a Basic Oral Care Protocol (expert opinion)

Two key strategies for mitigation of oral mucosal injury before and during treatment are:

- Maintenance of optimal nutritional support throughout the entire period of cancer therapy.
- Developing a daily oral hygiene routine, including four times daily brushing teeth with a soft brush and using mouth rinses. This approach can contribute to reduction and ideally prevention of oral tissue injury and associated pain, nutritional compromise and related adverse outcomes.

The following information is presented as a portfolio of patient-based instructions:

General measures:	• Inspect daily your oral mucosa. • Have your dental team eliminate sources of trauma (e.g., ill-fitting prostheses; fractured teeth). • Lubricate lips with (sterile) Vaseline/white paraffin, lip balm or lip cream. • Drink ample amount of fluids to keep the mouth moist.
Brushing teeth:	• Use a soft toothbrush or swab (as tolerated) after meals and before sleep. Brushing with a soft toothbrush reduces risk of bleeding. Each month you should utilise a new soft toothbrush. • Clean the dentition and gingiva with a mild fluoride-containing, non-foaming toothpaste. • Brush teeth twice a day (after meals and at bedtime) according to the Bass or modified Bass method. If using an electric toothbrush, utilise the techniques cited in the product description instead. • Rinse the brush thoroughly after use with water and store the toothbrush in a cup with the brush head facing upward. • If you are used to do so, clean the area between the teeth once a day. Consult a dental hygienist/dentist about the most appropriate interdental cleaner (floss, toothpick, brushes). In case you are not used to use interdental cleaners on a regular base, do not start with it while on cancer therapy, since it can break the epithelial barrier, visible through gingival bleeding.
Rinse mouth:	• Rinse mouth with an alcohol-free, mouthwash upon awakening and at least four times a day after brushing, for approximately 1 minute with 15 ml mouthwash; gargle and then spit out. During the first half hour after rinsing avoid eating and drinking.
Denture care:	• Remove the dentures before performing oral care. Brush the dentures with toothpaste and rinse with water; clean the gums. • Defer wearing dental prostheses as much as possible until the lining tissues of your mouth are healed. If in the hospital soak the denture for 10 minutes in chlorhexidine 0.2% (e.g. Hibident®) before inserting in your mouth.
Avoid painful stimuli:	• Smoking • Alcohol • Certain foods such as tomatoes, citrus fruits, hot drinks and, spicy, hot, raw, or crusty foods.

mTOR inhibitors such as everolimus and temsirolimus have immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens. Localised and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections (such as aspergillosis or candidiasis), and viral infections (including reactivation of hepatitis B virus) have occurred in patients taking everolimus.

Some of these infections can be severe, leading to sepsis, respiratory and/or hepatic failure, and fatality [37, 38].

It thus seems clinically prudent to optimise oral mucosal hygiene by utilising saline-based oral rinses. As is the case with other types of oral mucosal injury caused by cancer therapy, patient education relative to types and management of oral mucosal injury caused by mTOR inhibitors is of prime importance to reducing severe oral ulcerations, maximising patient compliance, and clinical outcomes.

management

Several health professional organizations have reported strategies for management of oral and/or gastrointestinal mucositis caused by high-dose cancer therapies. These organizations include:

- Multinational Association of Supportive Care in Cancer/ International Society of Oral Oncology (MASCC/ISOO)
- Oncology Nursing Society (ONS)
- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Network (NCCN).

The strategy for development of this management information ranges from systematic reviews (e.g., MASCC/ISOO) to a combination of systematic reviews and expert opinion (e.g., NCCN).

The 2015 ESMO mucosal injury guidelines are comprised of three domains:

i. MASCC/ISOO guidelines for management of mucositis caused by chemotherapy and/or head and head radiation [3]
ii. Recently emergent data relative to systematic enteral nutrition [5–9]
iii. Expert opinion on management of mucosal injury caused by targeted cancer therapies [4, 17, 18, 39], in part based on previously reported management of recurrent aphthous ulceration [40].

a) MASCC/ISOO guidelines for management of mucositis caused by chemotherapy and/or head and head radiation.

These guidelines produced by MASCC/ISOO [3] represent the current state-of-the-science in this field at the systematic review level (Table 2).

Table 2. MASCC/ISOO Clinical Practice Guidelines for Oral and Gastrointestinal Mucositis [3] [(level of Evidence for each guideline is in brackets following the guideline statement)]

Oral mucositis

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)

1) The panel *recommends* that 30 minutes of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).
2) The panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II).
3) The panel *recommends* that low-level laser therapy (wavelength 630-680 nm, power of 40 to 150 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2), be used to *prevent* oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
4) The panel *recommends* that patient-controlled analgesia with morphine be used to *treat* pain due to oral mucositis in patients undergoing HSCT (II).
5) The panel *recommends* that benzydamine mouthwash be used to *prevent* oral mucositis in patients with H&N cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).

SUGGESTIONS **IN FAVOR** OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)

1) The panel *suggests* that oral care protocols be used to *prevent* oral mucositis in all age groups and across all cancer treatment modalities (III).
2) The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).
3) The panel *suggests* that low-level laser therapy (wavelength 630-680 nm, power of 40 to 150 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2) be used to *prevent* oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for H&N cancer (III).
4) The panel *suggests* that transdermal fentanyl may be effective to *treat* pain due to oral mucositis in patients receiving conventional and high-dose chemotherapy, with or without total body irradiation (III).
5) The panel *suggests* that 2% morphine mouthwash may be effective to *treat* pain due to oral mucositis in patients receiving radiation therapy for H&N cancer (III).
6) The panel *suggests* that 0.5% doxepin mouthwash may be effective to *treat* pain due to oral mucositis (IV).
7) The panel *suggests* that systemic zinc supplements administered orally may be of benefit to *prevent* oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (Level of Evidence III).

RECOMMENDATIONS **AGAINST** AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for head and cancer (II).
2) The panel *recommends* that iseganan antimicrobial mouthwash *not* be used to *prevent* oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for

HSCT (Level of Evidence II), or in patients receiving radiation therapy or concomitant chemoradiation for H&N cancer (II).

3) The panel *recommends* that sucralfate mouthwash *not* be used to *prevent* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for H&N cancer.
4) The panel *recommends* that sucralfate mouthwash *not* be used to *treat* oral mucositis in patients receiving chemotherapy for cancer (I), or in patients receiving radiation therapy (II) for H&N cancer.
5) The panel *recommends* that intravenous glutamine *not* be used to *prevent* oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for HSCT (II).

SUGGESTIONS **AGAINST** AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *suggests* that chlorhexidine mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III).
2) The panel *suggests* that granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).
3) The panel *suggests* that misoprostol mouthwash *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III).
4) The panel *suggests* that systemic pentoxifylline, administered orally, *not* be used to *prevent* oral mucositis in patients undergoing bone marrow transplantation (III).
5) The panel *suggests* that systemic pilocarpine, administered orally, *not* be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III), or in patients receiving high dose chemotherapy, with or without total body irradiation, for HSCT (II).

Gastrointestinal Mucositis (not including the oral cavity)

RECOMMENDATIONS **IN FAVOR** OF AN INTERVENTION (i.e. strong evidence supports effectiveness in the treatment setting listed)

1) The panel *recommends* that intravenous amifostine be used, at a dose of ≥340 mg/m^2, to *prevent* radiation proctitis in patients receiving radiation therapy (II).
2) The panel *recommends* that octreotide, at a dose of ≥100 µg subcutaneously twice daily, be used to *treat* diarrhea induced by standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective (II).

SUGGESTIONS **IN FAVOR** OF AN INTERVENTION (i.e. weaker evidence supports effectiveness in the treatment setting listed)

1) The panel *suggests* that intravenous amifostine be used to *prevent* esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (III).
2) The panel *suggests* that sucralfate enemas be used to *treat* chronic radiation-induced proctitis in patients with rectal bleeding (III).
3) The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to *prevent* radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).
4) The panel *suggests* that probiotics containing Lactobacillus species be used to *prevent* diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).
5) The panel *suggests* that hyperbaric oxygen be used to *treat* radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (IV).

RECOMMENDATIONS **AGAINST** AN INTERVENTION (i.e. strong evidence indicates lack of effectiveness in the treatment setting listed)

1) The panel *recommends* that systemic sucralfate, administered orally, *not* be used to *treat* gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (I).

2) The panel *recommends* that 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, *not* be used to *prevent* acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (I).
3) The panel *recommends* that misoprostol suppositories *not* be used to *prevent* acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).

SUGGESTIONS **AGAINST** AN INTERVENTION (i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed)

None.

Gy, grays; HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology.

Table 3: Oral Cavity Mucositis Guideline
Modified from: MASCC/ISOO Clinical Practice Guidelines for Oral Mucositis [3] (Level of Evidence for each guideline is in brackets following the guideline statement)

Diagnosis	Therapy	Prevention/ treatment	Intervention
Cancer of any kind	All cancer treatment modalities	Prevention	*Oral care protocols:* The panel *suggests* that oral care protocols be used to *prevent* oral mucositis in all age groups and across all cancer treatment modalities (III).
		Treatment	*Doxepin mouthwash:* The panel *suggests* that 0.5% doxepin mouthwash may be effective to *treat* pain due to oral mucositis (IV).
	Bolus 5-fluorouracil chemotherapy	Prevention	*Oral cryotherapy:* The panel *recommends* that 30 minutes of oral cryotherapy be used to *prevent* oral mucositis in patients receiving bolus 5-Fluorouracil chemotherapy (II).
	Bone marrow transplant	Prevention	*Pentoxifylline:* The panel *suggests against* that systemic pentoxifylline, administered orally, be used to *prevent* oral mucositis in patients undergoing bone marrow transplantation (III).
	Conventional and high-dose chemotherapy, with or without total body irradiation	Treatment	*Transdermal fentanyl:* The panel *suggests* that transdermal fentanyl may be effective to *treat* pain due to oral mucositis in patients receiving conventional and high-dose chemotherapy, with or without total body irradiation (III).
	Stem cell transplant	Prevention	*Low-level laser therapy:* The panel *recommends* that low-level laser therapy (wavelength 630-80 nm, power of 40 to 150 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2), be used to *prevent* oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
			GM-CSF: The panel *suggests against* that granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwash be used to *prevent* oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (II).
			Pilocarpine: The panel *suggests against* that systemic pilocarpine, administered orally, be used to *prevent* oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for HSCT (II).
			Glutamine: The panel *recommends against* that intravenous glutamine be used to *prevent* oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for HSCT (II).

			Iseganan antimicrobial mouthwash: The panel *recommends against* that iseganan antimicrobial mouthwash be used to *prevent* oral mucositis in patients receiving high dose chemotherapy, with or without total body irradiation, for HSCT (II).
		Treatment	*Morphine:* The panel *recommends* that patient-controlled analgesia with morphine be used to *treat* pain due to oral mucositis in patients undergoing HSCT (II).
	Chemotherapy	Prevention	*Sucralfate mouthwash:* The panel *recommends against* that sucralfate mouthwash be used to *prevent* oral mucositis in patients receiving chemotherapy for cancer (I)
	Radiation therapy	Treatment	*Sucralfate mouthwash:* The panel *recommends against* that sucralfate mouthwash be used to *treat* oral mucositis in patients receiving radiation therapy (II).
Head & neck cancer	Moderate dose radiation therapy without concomitant chemotherapy	Prevention	*Benzydamine mouthwash:* The panel *recommends* that benzydamine mouthwash be used to *prevent* oral mucositis in patients with H&N cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).
	Radiation therapy	Prevention	*Chlorhexidine mouthwash:* The panel *suggests against* that chlorhexidine mouthwash be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III). *Misoprostol mouthwash:* The panel *suggests against* that misoprostol mouthwash be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III). *Pilocarpine:* The panel *suggests against* that systemic pilocarpine, administered orally, be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer (III).
			PTA and BCoG: The panel *recommends against* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) antimicrobial lozenges and PTA paste be used to *prevent* oral mucositis in patients receiving radiation therapy for H&N cancer(II).
		Treatment	*Morphine mouthwash:* The panel *suggests* that 2% morphine mouthwash may be effective to *treat* pain due to oral mucositis in patients receiving radiation therapy for H&N cancer (III).
			Sucralfate mouthwash: The panel *recommends against* that sucralfate mouthwash be used to *treat* oral mucositis in patients receiving radiation therapy (II) for H&N cancer.

	Radiation therapy or concomitant chemoradiation — Prevention	*Iseganan antimicrobial mouthwash:* The panel *recommends against* that iseganan antimicrobial mouthwash be used to *prevent* oral mucositis in patients receiving radiation therapy or concomitant chemoradiation for H&N cancer (II). *Sucralfate mouthwash:* The panel *recommends against* that sucralfate mouthwash be used to *prevent* oral mucositis in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for H&N cancer.
	radiation therapy, without concomitant chemotherapy — Prevention	*Low-level laser therapy:* The panel *suggests* that low-level laser therapy (wavelength 630-80 nm, power of 40 to 150 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2) be used to *prevent* oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for H&N cancer (III).
Hematological malignancy	Stem cell transplant *revised from 2013 MASCC/ISOO Guidelines based on current labeling indication* — Prevention	*KGF-1/palifermin:* The panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post-transplant) in patients… • (Original MASCC/ISOO guideline): receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II). • (Updated ESMO guideline): …with hematologic malignancy treated with chemotherapy and/or targeted agents, and/or HSCT with or without TBI (local-regional radiotherapy alone not included), and who are anticipated to develop Grade 3 or Grade 4 oral mucositis.[41]
		Oral cryotherapy: The panel *suggests* that oral cryotherapy be used to *prevent* oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).
Oral cancer	Radiation therapy or chemoradiation — Prevention	*Zinc supplements:* The panel *suggests* that systemic zinc supplements administered orally may be of benefit to *prevent* oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION: i.e. strong evidence supports effectiveness in the treatment setting listed.

SUGGESTIONS IN FAVOR OF AN INTERVENTION: i.e. weaker evidence supports effectiveness in the treatment setting listed.

SUGGESTIONS AGAINST AN INTERVENTION: i.e. weaker evidence indicates lack of effectiveness in the treatment setting listed.
RECOMMENDATIONS AGAINST AN INTERVENTION: i.e. strong evidence indicates lack of effectiveness in the treatment setting listed.
MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; HSCT, hematopoietic stem cell transplantation; Gy, grays; BCoG, bacitracin, clotrimazole, gentamicin.

The authors of this version of ESMO guidelines have reformatted the content in the MASCC/ISOO guideline in order to further facilitate clinician use (Tables 3 and 4).

In addition to this reformatting the following revision has been included in Table 3, directed to the use of palifermin to prevent oral mucositis in patients undergoing haematopoietic cell transplantation:

> …with haematological malignancy treated with chemotherapy and/or targeted agents, and/or HSCT with or without total body irradiation (TBI) (local-regional radiotherapy alone not included), and who are anticipated to develop Grade 3 or Grade 4 oral mucositis.

This revision emerged as a result of changes in the labelling as approved by the United States Food and Drug Administration in recent years [41].

b) Recently emergent data relative to systematic enteral nutrition.

Recent data have emerged regarding the impact of systematic enteral nutrition as a prophylactic measure.

In this modelling, systemic enteral nutrition is administered before initiation of chemoradiation, to prevent oral mucositis-associated nutritional compromise and to optimise therapeutic dose intensity, during chemoradiation for head and neck and oesophageal carcinomas [5–9].

In French-speaking countries, SFNEP and AFSOS published comprehensive recommendations for cancer patients [10–12]. Due to mucositis incidence, and for the optimisation of cancer treatment of this type of patient, a prophylactic approach with systematic gastrostomy or feeding tube was explored in several trials in at-risk patients receiving chemoradiation for head and neck cancer. Unfortunately, only retrospective analyses or randomised trials with significant limitations are available [7–9]. No strong recommendation is possible in favour of this prophylactic approach.

Hence, identification of at-risk patients who would need systematic enteral nutrition before chemoradiation remains unclear and is at the discretion of the clinicians in charge of the patient's oncological treatment.

c) Expert opinion on management of mucosal injury caused by targeted cancer therapies

In the absence of confirmatory data from clinical trials, expert opinion-based recommendations in the review by Boers-Doets et al. [4] and others [17, 18] can be considered as delineated in Table 5. These statements reflect the state-of-the-science as it presently exists.

personalised medicine

In recent years, research has increasingly demonstrated that patient-specific genetic characteristics are an important variable in determining risk and incidence of cancer therapy-related toxicity, including, but not limited to, oral mucosal injury [42–44]. It is now clear that genetic variation across individuals, including single nucleotide polymorphisms, is a key contributor to the toxicity trajectory for mucosal injury as well as for other toxicities caused by cancer therapies. Additional research in this domain will likely allow the clinician to individualise the therapeutic approach for each patient before initiation of cancer treatment, to maximise tumour response while minimising toxicity.

Table 4. Gastrointestinal Mucositis Guideline
Modified from: MASCC/ISOO Clinical Practice Guidelines for Gastrointestinal Mucositis [3] (Level of Evidence for each guideline is in brackets following the guideline statement)

Diagnosis	Therapy	Prevention/ treatment	Intervention
Cancer of any kind	Radiation therapy	Prevention	*Amifostine:* The panel *recommends* that intravenous amifostine be used, at a dose of ≥340 mg/m^2, to *prevent* radiation proctitis in patients receiving radiation therapy (II).
		Treatment	*Sucralfate enemas:* The panel *suggests* that sucralfate enemas be used to *treat* chronic radiation-induced proctitis in patients with rectal bleeding (III).
	Radiation therapy to the pelvis	Prevention	*Sulfasalazine:* The panel *suggests* that systemic sulfasalazine, at a dose of 500 mg administered orally twice a day, be used to *prevent* radiation-induced enteropathy in patients receiving radiation therapy to the pelvis (II).
	Stem cell transplant	Treatment	*Octreotide:* The panel *recommends* that octreotide, at a dose of ≥100 µg subcutaneously twice daily, be used to *treat* diarrhea induced by standard- or high-dose chemotherapy associated with HSCT, if loperamide is ineffective (II).
Non-small cell lung carcinoma	Concomitant chemotherapy and radiation therapy	Prevention	*Amifostine:* The panel *suggests* that intravenous amifostine be used to *prevent* esophagitis induced by concomitant chemotherapy and radiation therapy in patients with non-small cell lung carcinoma (III).
Pelvic malignancy	Chemotherapy and/or radiation therapy	Prevention	*Probiotics:* The panel *suggests* that probiotics containing Lactobacillus species be used to *prevent* diarrhea in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (III).
	Radiation therapy		*ASA:* The panel *recommends against* that 5-acetyl salicylic acid (ASA), and the related compounds mesalazine and olsalazine, administered orally, be used to *prevent* acute radiation-induced diarrhea in patients receiving radiation therapy for a pelvic malignancy (I).

Prostate cancer	Radiation therapy	Prevention	*Misoprostol suppositories:* The panel *recommends against* that misoprostol suppositories be used to *prevent* acute radiation-induced proctitis in patients receiving radiation therapy for prostate cancer (I).
Solid tumors	Radiation therapy	Treatment	*Hyperbaric oxygen:* The panel *suggests* that hyperbaric oxygen be used to *treat* radiation-induced proctitis in patients receiving radiation therapy for a solid tumor (IV).
			Sucralfate: The panel *recommends against* that systemic sucralfate, administered orally, be used to *treat* gastrointestinal mucositis in patients receiving radiation therapy for a solid tumor (I).

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION: i.e. strong evidence supports effectiveness in the treatment setting listed.
SUGGESTIONS IN FAVOR OF AN INTERVENTION: i.e. weaker evidence supports effectiveness in the treatment setting listed.
RECOMMENDATIONS AGAINST AN INTERVENTION: i.e. strong evidence indicates lack of effectiveness in the treatment setting listed.
MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; HSCT, hematopoietic stem cell transplantation; ASA, acetyl-salicylic acid.

Table 5. Expert opinion recommendations for targeted therapy associated stomatitis (level of evidence is not applicable for these recommendations from the experts)

Diagnosis	Therapy	prevention/ treatment	Intervention
Cancer of any kind	All targeted therapy modalities	Prevention	*Oral care protocols:* Expert opinion *suggests* that oral care protocols be used to *prevent* stomatitis in all cancer groups and across all targeted therapy modalities
			Sodium bicarbonate containing mouthwash: Expert opinion *suggests* that patients should rinse their mouth with a bland non-alcoholic, sodium bicarbonate containing mouthwash 4-6 times a day to *prevent* stomatitis
		Treatment	*Sodium bicarbonate containing mouthwash:* Expert opinion *suggests* that the frequency of the bland non-alcoholic, sodium bicarbonate containing mouthwash be increased, if necessary up to each hour to *treat* stomatitis
			Analgesics: Expert opinion *suggests* that If patients find the mouthwash painful, they should be advised to use pain medication beforehand (e.g., viscous lidocaine 2%, coating agents, and, when needed, systemic approaches following the World Health Organization pain management ladder) to *treat* pain from stomatitis
			Chewing gum, candy, salivary substitutes or sialogogues: Expert opinion *suggests* that sugarless chewing gum or candy, salivary substitutes or sialogogues in patients with oral dryness should be considered to *treat* oral dryness
			Analgesics: Expert opinion *suggests* that adequate pain management e.g., anesthetic mouthwashes (viscous lidocaine 2%), coating agents, or systemic analgesics following the WHO pain management ladder may be provided to *treat* pain from stomatitis
			Analgesics: Expert opinion *suggests* that with moderate pain a topical NSAID (e.g., amlexanox 5% oral paste) may be considered

		to *treat moderate* pain from stomatitis. When NSAIDs are not tolerated, consider acetaminophen (paracetamol) as maintenance therapy in combination with an immediate release oral opioid or fast acting fentanyl preparation (e.g. 50 microgram fentanyl nasal spray) to relief pain short-term, for instance before dinner. Fast acting fentanyl preparations are registered for patients who are already treated with opioids, they may also be considered in this population because of their short term pain relief. *Analgesics:* Expert opinion *suggests* that with persistent severe pain more aggressive pain management may be considered to *treat severe pain from* stomatitis. Since oral complaints can complicate administration of drugs by mouth, one should consider other kinds of administration routes, such as transdermal or intranasal routes. *Other treatments:* Expert opinion *suggests* that other treatments, such as coating agents, topical analgesic or anti-inflammatory agents, topical anesthetics, and alternative mouthwashes may be considered to *treat* stomatitis
mTOR inhibitors	Treatment	*Steroids; topical:* Expert opinion *suggests* that with ulcers topical high potency corticosteroids should be considered first: dexamethasone mouth rinse (0.1 mg/ml); clobetasol gel or ointment (0.05%) to *treat* mIAS *Steroid; intralesional injection:* Expert opinion *suggests* that with no ulcer resolution, intralesional steroid injection (triamcinolone weekly; total dose 28 mg) in conjunction with oral expert AND topical clobetasol gel or ointment (0.05%) should be considered to *treat* mIAS *Steroids; systemic:* Expert opinion *suggests* that for highly symptomatic ulcers and for recurrent ulcers or esophageal lesions, *systemic corticosteroids* as initial therapy to bring symptom under control quickly (high-dose pulse 30–60 mg or 1 mg/kg) oral prednisone/prednisolone for 1 week followed by dose tapering over the second week should be considered to *treat* mIAS
SUGGESTIONS IN FAVOR OF AN INTERVENTION: based on expert opinion [17, 18]. WHO, World Health Organization; NSAID, nonsteroidal anti-inflammatory drug; mIAS, mTOR inhibitor-associated stomatitis.		

follow-up and long-term implications

Guidelines for prevention and treatment of mucositis caused by conventional cancer therapies as reported in this version of the ESMO Clinical Practice Guidelines are based on the recommendations of the recently updated guidelines from MASCC/ISOO. Those guidelines included a new recommendation directed to level II evidence regarding the use of low-level laser therapy to prevent oral mucositis caused by high-dose chemotherapy conditioning regimens in the haematopoietic cell transplant setting (Table 2).

In addition, new recommendations based on expert consensus opinion have been included, to address the state-of-the-science relative to oral mucosal lesions caused by targeted cancer therapies.

There continues to be key progress relative to the molecular pathobiology, computational biology, and clinical impact of mucosal injury in cancer patients that may generate strategic research and clinical advances in the future. These advances will likely result in revisions of mucositis guidelines in the next 2–5 years. Examples of novel, important future opportunities based on the recent advances include [45]:

Molecular modelling

- mucosal homeostasis
- naturally occurring mucosal disease
- oral pain
- oral mucosa and the oral microbiome
- molecular basis for cancer patient-based variation in incidence and severity of oral mucosal injury
- molecular imaging

Development of molecularly targeted drugs, biologics, and devices

- systems biological technologies to define key pathobiological pathways for targeting
- incorporation of patient-based risk profiling into clinical trial designs

Clinical practice - utilisation of state-of-the-science technologies for:

- dissemination
- measurement of clinical and health resource cost outcomes.

There is also need and opportunity to conduct clinical trials with devices that have been initially reported as effective and safe in reducing the incidence and severity of oral mucositis in cancer patients. Such studies are essential to (i) validate current commercial claims, (ii) identify which patients may experience highest benefit, and (iii) assess the feasibility for use by these patients.

It is important that basic, translational, and clinical research continue to investigate preventive and treatment modalities for oral mucositis, gastrointestinal mucositis, and stomatitis. This collective research could lead to the approval of new drugs and devices for which evidence-based, cancer patient-specific identification of risk and associated management of mucositis and stomatitis could become possible.

Table 6. Level of evidence used in the MASCC/ISOO guidelines and reported in Tables 2–5 [3]

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomised trials with low false-positive and false-negative errors (high power).
II	Evidence obtained from at least one well-designed experimental study; randomised trials with high false-positive and/or false-negative errors (low power).
III	Evidence obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pretest–posttest comparison, cohort, time, or matched case–control series.
IV	Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence obtained from case reports and clinical examples.

Adapted from [46].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system described in the MASCC/ISOO guidelines (Table 2) and Tables 3 and 4 and are published in the MASCC/ISOO Clinical Practice Guidelines for Oral and Gastrointestinal Mucositis [3] and shown in Table 6. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

The authors have declared no potential conflicts of interest.

references

1. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2011; 22(Suppl 6):vi78–vi84.
2. Keefe DM, Schubert MM, Elting LS et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007; 109: 820–831.
3. Lalla RV, Bowen J, Barasch A et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014; 120:1453–1461.
4. Boers-Doets CB, Raber-Durlacher JE, Treister NS et al. Mammalian target of rapamycin inhibitor-associated stomatitis. Future Oncol 2013; 9: 1883–1892.
5. Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. Cochrane Database Syst Rev 2013; 1: CD007904.
6. Koyfman SA, Adelstein DJ. Enteral feeding tubes in patients undergoing definitive chemoradiation therapy for head-and-neck cancer: a critical review. Intl J Radiat Oncol Biol Phys 2012; 84: 581–589.
7. Williams GF, Teo MT, Sen M et al. Enteral feeding outcomes after chemoradiotherapy for oropharynx cancer: a role for a prophylactic gastrostomy? Oral Oncol 2012; 48: 434–440.
8. Rutter CE, Yovino S, Taylor R et al. Impact of early percutaneous endoscopic gastrostomy tube placement on nutritional status and hospitalization in patients with head and neck cancer receiving definitive chemoradiation therapy. Head Neck 2011; 33: 1441–1447.
9. Silander E, Nyman J, Bove M et al. Impact of prophylactic percutaneous endoscopic gastrostomy on malnutrition and quality of life in patients with head and neck cancer: a randomized study. Head Neck 2012; 34: 1–9.

10. SFNEP (Societe Francophone de Nutrition Enterale et Parenterale) SFNEP Oncology Nutrition Guidelines. In: Nutrition Clinique et Métabolisme, Vol. 26 (4), 2012; http://www.em-consulte.com/revue/NUTCLI/26/4/table-des-matieres/: (20 April 2015, date last accessed).
11. Bachmann P, Romero G, Deneuve S et al. Référentiel de pratiques professionnelles: prise en charge nutritionnelle des cancers des voies aérodigestives supérieures. Nutr Clin Métab 2014; 28: 207–215.
12. French Speaking Society of Clinical Nutrition and Metabolism. Clinical nutrition guidelines of the French Speaking Society of Clinical Nutrition and Metabolism (SFNEP): summary of recommendations for adults undergoing non-surgical anticancer treatment. Dig Liver Dis 2014; 46: 667–674.
13. National Cancer Institute PDQ®. Oral mucositis. In Oral Complications of Chemotherapy/Head & Neck Radiation; http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5 (9 April 2015, date last accessed).
14. Sonis S, Treister N, Chawla S et al. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer 2010; 116: 210–215.
15. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: a narrative literature review. Oral Oncol 2011; 47: 441–448.
16. Li E, Trovato JA. New developments in management of oral mucositis in patients with head and neck cancer or receiving targeted anticancer therapies. Am J Health Syst Pharm 2012; 69: 1031–1037.
17. Pilotte AP, Hohos MB, Polson KM et al. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. Clin J Oncol Nurs 2011; 15: E83–E89.
18. de Oliveira MA, Martins E Martins F, Wang Q et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol 2011; 47:998–1003.
19. Elting LS, Chang YC, Parelkar P et al. Risk of oral and gastrointestinal mucosal injury among patients receiving selected targeted agents: a meta-analysis. Support Care Cancer 2013; 21: 3243–3254.
20. Kwitkowski VE, Prowell TM, Ibrahim A et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. Oncologist 2010; 15: 428–435.
21. Rugo HS, Pritchard KI, Gnant M et al. Incidence and time course of everolimus related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol 2014; 25: 808–815.
22. Keefe D, Stringer A. The potential successes and challenges of targeted anticancer therapies. Curr Opin Support Palliat Care 2010; 4: 16–18.
23. Harandi A, Zaidi AS, Stocker AM, Laber DA. Clinical efficacy and toxicity of anti-EGFR therapy in common cancers. J Oncol 2009; 2009: 567486 (9 April 2015, date last accessed).

24. Elez E, Macarulla T, Tabernero J. Handling side-effects of targeted therapies: safety of targeted therapies in solid tumours. Ann Oncol 2008; 19(Suppl 7): vii146–vii152.
25. Pessi MA, Zilembo N, Haspinger ER et al. Targeted therapy-induced diarrhea: a review of the literature. Crit Rev Oncol Hematol 2014; 90: 165–179.
26. National Cancer Institute CTCAE; http://evs.nci.nih.gov/ftp1/CTCAE/About.html (9 April 2015, date last accessed).
27. Cooperstein E, Gilbert J, Epstein JB et al. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck 2012; 34: 797–804.
28. Boers-Doets CB, Lalla RV. The mIAS scale: a scale to measure mTOR inhibitor-associated stomatitis. Support Care Cancer 2013; 21: S140.
29. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32: 920–924.
30. Nutting CM, Morden JP, Harrington KJ et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011; 12: 127–136.
31. McGuire DB, Fulton JS, Park J et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013; 21: 3165–3177.
32. Eilers RE, Jr, Gandhi M, Patel JD et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. J Natl Cancer Inst 2010; 102: 47–53.
33. Duvic M. EGFR inhibitor-associated acneiform folliculitis: assessment and management. Am J Clin Dermatol 2008; 9: 285–294.
34. Amitay-Laish I, David M, Stemmer SM. Staphylococcus coagulase-positive skin inflammation associated with epidermal growth factor receptor-targeted therapy: an early and a late phase of papulopustular eruptions. Oncologist 2010; 15: 1002–1008.
35. Kajiya K, Sawane M, Huggenberger R, Detmar M. Activation of the VEGFR-3 pathway by VEGF-C attenuates UVB-induced edema formation and skin inflammation by promoting lymphangiogenesis. J Invest Dermatol 2009; 129: 1292–1298.
36. Roigas J. Clinical management of patients receiving tyrosine kinase inhibitors for advanced renal cell carcinoma. Europ Urol Suppl 2008; 7: 593–600.
37. Novartis Pharmaceutical Corp. Highlights of prescribing information; http://www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf (9 April 2015, date last accessed).
38. Malizzia LJ, Hsu A. Temsirolimus, an mTOR inhibitor for treatment of patients with advanced renal cell carcinoma. Clin J Oncol Nurs 2008; 12: 639–646.
39. Boers-Doets CB, Epstein JB, Raber-Durlacher JE et al. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist 2012; 17:135–144.

40. Scully C. Clinical practice. Aphthous ulceration. N Engl J Med 2006; 355:165–172.
41. National Cancer Institute. FDA approval for palifermin; http://www.cancer.gov/cancertopics/druginfo/fda-palifermin (9 April 2015, date last accessed).
42. Venkatesh GH, Manjunath VB, Mumbrekar KD et al. Polymorphisms in radioresponsive genes and its association with acute toxicity among head and neck cancer patients. PLoS One 2014; 9: e89079.
43. Sonis S, Antin J, Tedaldi M, Alterovitz G. SNP-based Bayesian networks can predict oral mucositis risk in autologous stem cell transplant recipients. Oral Dis 2013; 19: 721–727.
44. Peterson DE, Keefe DM, Sonis ST. New frontiers in mucositis. In Govindan R (ed.) Am Soc Clin Oncol Educ Book 2012; 545–551.
45. Jensen SB, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. J Oral Pathol Med 2014; 43: 81–90.
46. Somerfield MR, Padberg JR, Pfister DG, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Class Pap Curr Comments 2000; 4:881–886.

05 | Xerosis and pruritus as major EGFRI-associated adverse events.

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ABSTRACT

Purpose The objective of this sub-analysis of the BeCet study (NCT01136005) was to examine health-related quality of life (HRQoL) of patients experiencing dermatological adverse events (AEs) during the first 6 weeks of epidermal growth factor receptor inhibitor (EGFRI) treatment.

Methods Patients (n=85) treated with EGFRI completed five questionnaires during the first 6 weeks of treatment. 77 patients provided enough data for the sub-analysis. Experienced AEs were reported in the Dermatological Reactions Targeted Therapy–Patients (DERETT-P), a symptom experience diary for patients treated with targeted therapy. The impact of EGFRI-associated dermatological adverse events on HRQoL was examined using four HRQoL questionnaires; the Functional Assessment of Cancer Therapy–EGFRI (FACTEGFRI-18), the Functional Assessment of Cancer Therapy–General (FACT-G), the 36-Item Short Form Health Survey (SF-36), and the Skindex-16.

Results During the first 6 weeks of EGFRI treatment, physical discomfort was the most significantly affected domain. In the entire study population, xerosis (dry skin) (22.3 %) and pruritus (itchy skin) (16.9 %) were reported as the most impactful AEs. For patients experiencing a papulopustular eruption (acneiform rash) pruritus (24.2 %), xerosis (18.9 %), and papulopustular eruption (6.3 %) were reported as the most impactful AEs. Papulopustular eruption, xerosis, and pruritus all showed a significant negative effect on HRQoL, displayed in FACT-EGFRI-18 scores.

Conclusions In addition to papulopustular eruption, xerosis and pruritus are major EGFRI-associated dermatological AEs with an impact on HRQoL, which warrant more attention in clinical practice and research.

Background

Epidermal growth factor receptor inhibitors (EGFRIs) are frequently used in treatment regimens of patients with solid tumors. Compared with cytotoxic chemotherapeutic agents, which may cause myelosuppression, nausea, vomiting, neuropathy, and alopecia, EGFRIs are associated with a lower incidence of systemic adverse events (AEs). However, patients treated with EGFRIs experience dermatological AEs (dAEs), such as papulopustular eruption (acneiform rash), xerosis (dry skin), pruritus (itchy skin), and paronychia (periungual inflammation), as well as mucosal and hair abnormalities [1, 2].

The most common AE of EGFRI treatment is a papulopustular eruption, occurring in 75 to 95 % of patients [1, 2]. The papulopustular eruption consists of acneiform follicular and perifollicular papules and sterile pustules, most pronounced on the face, scalp, upper back, and chest and is often accompanied by xerosis and pruritus. The papulopustular eruption is a relatively early-onset AE, usually occurring between 1 to 3 weeks after initiation of treatment. The incidence is higher with monoclonal antibodies like cetuximab and panitumumab (more than 88 %) than with tyrosine kinase inhibitors like gefitinib, erlotinib, lapatinib, and afatinib (43–75 %). In about 80 to 90 % of the skin reactions, the worst recorded severity is mild (grade 1) to moderate (grade 2), but in 10 % a more severe skin reaction (grade 3) is seen [1, 2]. In several studies, the presence and severity of the eruption has shown a correlation with a positive response to cancer treatment, as expressed in higher median survival rates [1–3]. However, patients reported that the papulopustular eruption interferes in their daily activities and in the appearance of their skin, because the EGFRI-associated dAEs, often in visible areas, make them worried, frustrated, and depressed and cause withdrawal from social activities [3, 4].

The physical discomfort caused by EGFRI treatment has been identified as having the most impact on health-related quality of life (HRQoL), especially the sensations of pain, burning, and skin sensitivity. The dAEs may lead to a decreased HRQoL and to dose reduction or discontinuation of anticancer treatment, even though the treatment might be effective in treating the cancer and reducing the dose may negatively affect cancer outcome [4]. At present, the consequence of the dAEs on HRQoL in patients with cancer receiving EGFRI treatment remains poorly understood.

This sub-analysis of the ongoing BeCet study (NCT01136005) is aimed to provide a better understanding of HRQoL in patients with cancer receiving EGFRI treatment, using five different questionnaires.

Patients and materials

Patients

The study population was derived from the ongoing BeCet study. This phase III randomized double-blinded trial compares Bepanthen against cetomacrogol cream on their preventive effect in decreasing the incidence of grade ≥2 EGFRI associated papulopustular eruption and assesses the Dutch version of Functional Assessment of Cancer Therapy- EGFRI (FACT-EGFRI-18) for reliability and validity [5, 6].
The study has been approved by the Medical Ethics Review Committees of each participating hospital. Twelve Dutch centers are currently recruiting patients starting with an EGFRI treatment for any type of cancer (i.e., panitumumab, cetuximab, lapatinib, gefitinib, erlotinib, or afatinib). Patients need to have an Eastern Co-operative Oncology Group performance status ≤2 and need to be able to complete questionnaires.

The first 85 consecutive patients were included for this sub analysis between July 2010 and May 2014. This analysis studies the impact of the dAEs on the HRQoL, while the main study analyses the appearance and severity of dAEs. There are no strict criteria for the sample size in HRQoL studies. Within a homogenous population there is lower variability in answers on HRQoL items, making a smaller sample size acceptable.

Materials

During the 6-week study period, patients completed five different questionnaires. They completed the symptom experience diary Dermatological Reactions Targeted Therapy–Patients (DERETT-P) and the FACT-EGFRI-18 weekly. Within the BeCet trial, these two questionnaires are measured weekly to provide detailed information about the incidence and severity curve of dAEs. For this sub-analysis, fewer data than in the main study collected are of relevance. These are the data of weeks 0, 2, and 4.

In week 4, the Functional Assessment of Cancer Therapy–General (FACT-G), the 36-Item Short Form Health Survey (SF-36), and the Skindex-16 questionnaires were completed for validation purposes of the FACT-EGFRI-18. Week 4 of treatment was chosen, because then most patients will have experienced a papulopustular eruption [7]. In this analysis, scores of these generic questionnaires were compared with previously published articles, to put the HRQoL of cancer patients treated with EGFRIs in perspective to similar samples.

DERETT

The Dermatological Reactions Targeted Therapy (DERETT) is available in two versions, for patients (DERETT-P) and HCP (DERETT-H), consisting of 61 and 50 items, respectively. These tools gather information such as area involved, severity and duration of the symptoms, products used to treat symptoms, effectiveness of the supportive care interventions, treatment adherence, and symptom-related distress [8]. DERETT provides a more precise and clinically relevant information on the patient's

condition than Common Terminology Criteria for Adverse Events (CTCAE) grading alone.

FACT-EGFRI-18

The Functional Assessment of Cancer Therapy Questionnaire–EGFRI has been developed to assess HRQoL related to EGFRI-associated dAEs. The translation, linguistic validation, and qualitative assessment of the FACT-EGFRI-18 have been described [5, 6, 9]. The validations of the English and Support Care Cancer Dutch versions are ongoing. The FACT-EGFRI-18 consists of 18 items in three HRQoL domains: physical (7 items), social/ emotional (6 items), and functional (5 items). Scores are rated on a numerical analogue scale (0=not at all, 4=very much). A high domain score reflects a low HRQoL. On the other hand, a high total score indicates a high HRQoL [10].

FACT-G

The FACT-G version 4 is a patient reposted outcome (PRO) measure with numerical analogue scales (0=not at all, 4=very much). The FACT-G version 4 consists of 27 items in four HRQoL domains: physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items). High total scores indicate a high HRQoL. The FACT-G has been validated for patients with cancer in general [11].

SF-36

The 36-Item Short Form Health Survey (SF-36) is a generic HRQoL survey. The questionnaire consists of 36 items, covering eight scales: physical functioning, role limitations due to physical health and due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. A high total scale score represents a high HRQoL. The SF-36 can be used to measure HRQoL in general and specific populations, and has been validated for Dutch citizens, and patients with cancer [12].

Skindex-16

The Skindex-16 is a 16-item PRO assessing dermatological symptoms on a numerical analogue scale (0=never bothered, 6=always bothered), where high scores represent a low HRQoL. It contains three domains: symptoms (4 items), emotions (7 items), and functioning (5 items). The Skindex-16 is reliable and valid for general skin diseases. It has been used more often to assess HRQoL in patients receiving EGFRI treatment, but does not address symptoms related to hair, nails, or mucous membranes, that are specific targets for EGFRIs [13].

Statistical analysis

Descriptive statistics were used to describe the study population. In DERETT-P, the incidences of the AEs with the highest impact on HRQoL (Fig. 1) were determined per week and in total. The domain and total scores of FACT-EGFRI-18 during the first 6 weeks of EGFRI treatment are displayed in a time plot (Fig. 2). With a one-way ANOVA, item and domain scores during treatment were compared to baseline,

followed by a Bonferroni procedure to correct for multiple testing. Using the Mann–Whitney test, FACT-EGFRI-18 scores during week 2 to 4 and Skindex-16 scores of week 4 were compared between different subgroups, i.e., gender, type of cancer,

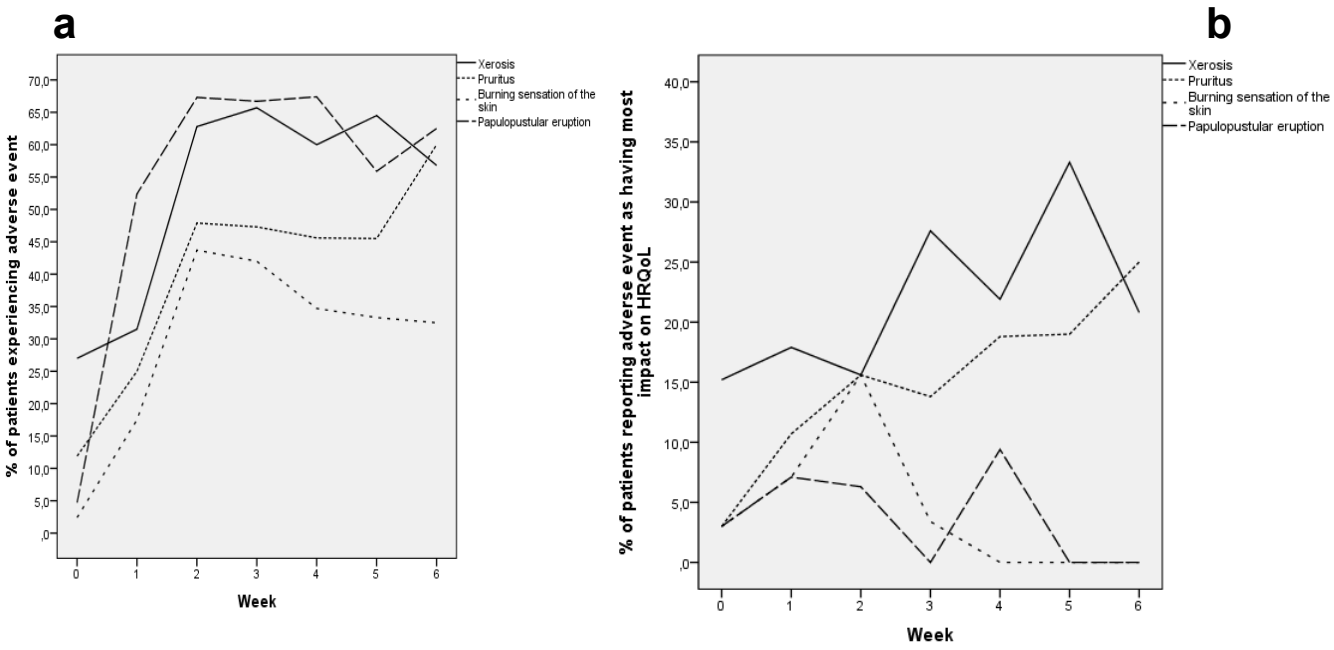

Fig 1a Adverse events that patients reported as present in DERETT-P compared to **b** adverse events as having most impact on HRQoL as measured by DERETT-P. In (**a**), papulopustular eruption is reported as the most common adverse event, while (**b**) displays that xerosis and pruritus have a more profound impact on HRQoL. *HRQoL* health related quality of life.

EGFRI agent, and age, as mainly in those weeks papulopustular eruption manifests [1]. To analyze HRQoL for patients experiencing a papulopustular eruption, their FACT-EGFRI-18 scores were compared with pre-treatment scores, also using the Mann–Whitney test. With manual two-sample t tests and one-sample Wilcoxon signed-rank tests, mean and median scores of FACT-G, SF-36, and Skindex-16 were both compared to scores in previously published articles, in order to determine how HRQoL relates to these populations. DERETT-P and FACT-EGFRI-18 scores have not been described before and could, therefore, not be compared. All data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 20. Overall, $p<0.05$ was accepted as a statistically significant result.

Results

Demographics

Between July 2010 and May 2014, a total of 85 patients were included. Eight patients (9.4 %) with disease progression were excluded as they stopped EGFRI treatment before week 4 and, consequently, did not complete FACT-G, SF-36, and Skindex-16. In total, 77 patients were evaluable. Six (7.79 %) of them stopped EGFRI treatment after week 4 because of disease progression and/or death, but produced enough

Table 1 Patient demographics (*n* = 77)

Characteristic	Number of patients (%)
Gender	
Male	46 (59.7)
Female	31 (40.3)
Age in years	65.0 (9.91) [41 - 87]*
Race	
Caucasian	74 (96.1)
Other	3 (3.9)
Type of cancer	
NSCLC	32 (41.6)
Colorectal	30 (39.0)
HNC	8 (10.4)
Mamma	3 (3.9)
Pancreas	3 (3.9)
Osteosarcoma	1 (1.3)
EGFRI type	
panitumumab	29 (37.7)
erlotinib	25 (32.5)
cetuximab	10 (13.0)
gefitinib	10 (13.0)
lapatinib	3 (3.9)

SD standard deviation, *NSCLC* non-small cell lung cancer, *HNC* head and neck cancer
*Expressed in mean (SD) [range]

data to be considered evaluable for this study. The mean age of the included study population (n=77) was 65.0 years (SD 9.91). Forty-six patients (59.7 %) were male. The majority of the patients were of Caucasian origin (96.1 %) and three patients of other origin (Asian and Hindu) (Table 1). Patients were mainly diagnosed with non-small cell lung cancer (NSCLC) and colorectal cancer, 41.6 and 39.0 %, respectively. Panitumumab (37.7 %) and erlotinib (32.5 %) were the most prescribed EGFRI drugs. Of the DERETT-P, FACT-EGFRI-18, FACT-G, SF-36, and Skindex-16 questionnaires, 50, 47.4, 25.9, 25.9, and 23.5 %, respectively, were not completed. The main reasons for the uncompleted questionnaires were that the healthcare provider did not hand out the questionnaire in the uneven weeks (weeks 1, 3, and 5) and early discontinuation due to disease progression. Some patients did not complete the questionnaires because they did not feel the need to do so since their AEs stayed almost the same as during the previous measures, most prominent in patients with many or nearly none experienced AEs. Patient burden and burn out may also play a role.

Impact of various adverse events

The DERETT-P questionnaire asks patients to report if they experienced certain AEs and in which severity. Secondly, the questionnaire asks from which AE they experienced the most hinder. Xerosis and pruritus were reported most often: mean 22.3 and 16.9 %, respectively. The remaining dAEs were reported by means less than 4.8 %. Fig. 1a displays the incidence of the four AEs which have the highest impact on HRQoL during the 6-week study period, while Fig. 1b displays the AEs with the highest impact on HRQoL over time. The peak of impact of xerosis on HRQoL was in week 5 (33.3 %), and at week 6 for pruritus (25.0 %). Papulopustular

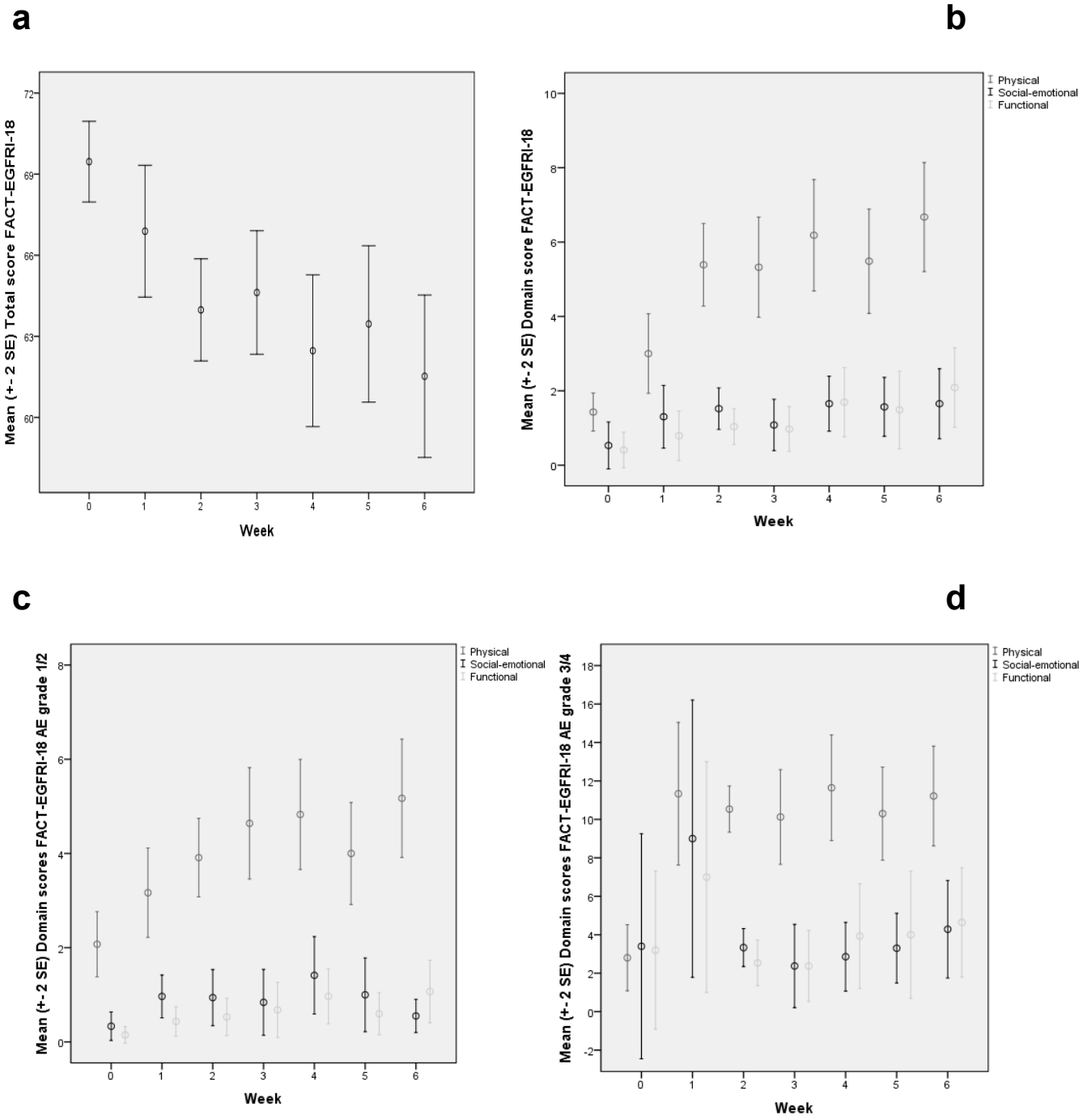

Fig. 2a Mean (standard error of the mean) FACT-EGFRI-18 total scores per week. **b** Mean (standard error of the mean) of all grade FACT-EGFRI-18 domain scores per week. **c** Mean (standard error of the mean) of grade 1/2 FACT-EGFRI-18 domain scores per week. **d** Mean (standard error of the mean) of grade 3/4 FACT-EGFRI-18 domain scores per week. *FACTEGFRI-18* Functional Assessment of Cancer Therapy–EGFRI, *EGFR*I epidermal growth factor receptor inhibitor

eruption was reported as having the most impact on HRQoL by 4.2 % of all patients, with a peak in week 4 (9.4 %).

Since a papulopustular eruption may overlap xerosis and pruritus and, therefore, the outcome may be different in patients who did develop a papulopustular eruption

compared to those who did not, we explored the patients that experienced a papulopustular eruption separately. Even in this subgroup, AEs having most impact on HRQoL remained pruritus (24.2 %), xerosis (18.9 %), a burning sensation of the skin (8.4 %), and lastly a papulopustular eruption (6.3 %).

Table 2 Domain and total scores FACT-EGFRI-18 per week

Week	Domain scores			Total score
	Physical 7 items	**Social-emotional** 6 items	**Functional** 5 items	
0	1.41 (1.80)	0.490 (2.20)	0.470 (1.69)	69.5 (5.23)
1	2.90 (3.49)	1.29 (2.80)	0.760 (2.21)	67.0 (8.03)
2	5.42 (4.13)	1.45 (2.01)	1.200 (1.86)	63.8 (7.00)
3	5.32 (4.10)	1.08 (2.10)	0.970 (1.83)	64.6 (6.95)
4	6.00 (5.14)	1.57 (2.60)	1.780 (3.27)	62.6 (9.75)
5	5.41 (4.24)	1.86 (3.02)	1.410 (2.69)	63.2 (8.97)
6	6.65 (5.01)	1.70 (3.28)	1.870 (3.13)	61.6 (10.1)

Scores are presented in mean (standard deviation). Domain scores are calculated as the sum of all corresponding items, with taking into account that at least 50% of the items need to be answered for a reliable calculation. The total score is calculated by subtracting the domain scores from 72 (the maximum possible total score), and correct for the number of answered items. Resulting, a low HRQoL is reflected by a high domain score and a low total score.
FACT-EGFRI-18 Functional Assessment of Cancer Therapy–EGFRI

Quality of life during EGFRI treatment

Table 2 and Fig. 2 show the development of total and domain scores of FACT-EGFRI-18 over time. Scores on the physical domain were significantly higher during all 6 weeks compared to baseline ($p<0.001$). The functional domain for all grades showed a significantly higher score in the sixth week compared to baseline ($p=0.039$). In patients with grade 1/2, the dispersion in these domains is relatively low (Fig. 2c). However, the social-emotional domain did show significant changes within the grade 3/4 sample (Fig. 2d).What stands out is the large spread on the domains of “social-emotional” and “functional” in patients with grade 3/4 at weeks 0 and 1. This was also the case prior to the start of the EGFRI treatment; in week 0, the standard error is negative and as the weeks pass this spread decreases. For all domains and items, a higher score represents lower HRQoL. The total FACT-EGFRI-18 score decreased during treatment, reflecting decrease in HRQoL.

There were no significant differences between FACTEGFRI-18 scores for gender (total score men 63.40, women 63.92) or cancer type (total scores ranging from 63.7 to 68.00). Patients younger than 50 years scored significantly ($p=0.015$) lower on the functional domain (score 0.91 <50 years versus 1.61 61–70 years (mean age)). Patients above 81 years experienced more impact on the physical domain ($p=0.028$) (2.94 versus 5.06 in the mean age group of 61–70) and total score ($p=0.020$) (68.56

by >81; 63.84 by 61–70), compared to patients in the mean age range between 61 and 70 years.

The presence of papulopustular eruption during the study period significantly decreased HRQoL as measured by FACTEGFRI-18 (p<0.001). This was most prominent for the physical domain (Table 3). FACT-EGFRI-18 scores were also analyzed separately for xerosis and pruritus, showing a significant reduced HRQoL (p<0.014).

Table 3 HRQoL with papulopustular eruption displayed in FACT-EGFRI-18 scores

Week	Papulopustular eruption	Domain scores FACT-EGFRI-18		
		Physical	Social-emotional	Functional
0	n = 0	1.41 (1.80)	0.490 (2.20)	0.470 (1.69)
1	n = 19	4.58 (4.03)*	2.21 (3.65)*	1.42 (3.06)*
2	n = 31	6.97 (3.70)*	2.00 (2.21)*	1.61 (1.94)*
3	n = 24	6.54 (3.98)*	1.50 (2.45)*	1.42 (2.15)*
4	n= 30	7.27 (5.75)*	1.77 (2.85)*	2.43 (3.95)*
5	n = 19	6.79 (4.13)*	2.37 (3.29)*	1.84 (3.08)*
6	n = 24	7.13 (4.16)*	1.92 (2.80)*	1.92 (2.21)*

Scores presented in mean (SD)

FACT-EGFRI-18 Functional Assessment of Cancer Therapy–EGFRI, *HRQoL* Health-related quality of life

*p < 0.05, a significantly lower HRQoL compared with week 0 (baseline)

FACT-G scores were compared with the scores of Cella et al. [11], which included other types of cancer, i.e., leukemia, lymphoma, prostate cancer, and ovarian cancer without EGFRI treatment. Our study population scored significantly higher on the physical (p=0.014) and emotional domains (p=0.013),with higher scores indicating a higher HRQoL. Scores on the social family and functional domains did not differ significantly.

Scores on SF-36 were first compared to scores of a sample of a Dutch healthy control population in order to examine the difference in HRQoL of EGFRI treated cancer patients with healthy individuals [14]. The current study population had a higher mean age and scored significantly lower on all domains (p<0.028), meaning lower HRQoL. Secondly, SF-36 scores were compared with a group of cancer patients about to start chemotherapy or radiotherapy. The current study population was older, consisted of fewer females, had more patients with NSCLC and colorectal cancer, and fewer with breast cancer. Scores were similar for most SF-36 domains. Only for physical functioning (p=0.042) and general health (p<0.001), the current study population scored significantly lower, meaning a lower HRQoL [14].

Skindex-16 separately identified a significant lower total score when papulopustular eruption was present (p<0.002), but not for the presence of xerosis or pruritus. The Skindex-16 scores did not differ significantly between patients experiencing papulopustular eruption, xerosis, or pruritus (Table 4).

Table 4 Comparison of mean and median Skindex-16 scores for patients experiencing dermatological adverse events

Skindex-16 domains	Current study Papulopustular eruption	Current study Xerosis	Current study Pruritus	Joshi et al.[4] EGFRI AEs	Rosen et al.[14] Targeted therapy AEs	Rosen et al.[14] Non-targeted therapy AEs
	n = 30	*n* = 24	*n* = 21	*n* = 67	*n* = 163	*n* = 120
Symptoms						
Mean (SD)	27.2 (26.4)	22.9 (26.5)	35.6 (28.9)	45.3[a,b,c]		
Median (95% CI)	20.8 (12.5-33.3)	16.7 (0.00-29.2)	29.2 (20.8-37.5)		37.5 (29.2-54.2)[b,c]	39.6 (25.0-45.8)[b,c]
Emotions						
Mean (SD)	17.2 (21.9)	14.7 (19.3)	21.4 (24.2)	50.0[a,b,c,d]		
Median (95% CI)	9.53 (4.77-21.4)	9.53 (0.00-21.4)	14.3 (4.77-26.2)		50.0 (40.5-57.1)[b,c,d]	38.1 (30.4-47.6)[b,c,d]
Functioning						
Mean (SD)	10.0 (17.1)	7.23 (14.3)	10.5 (15.7)	31.3[a,b,c,d]		
Median (95% CI)	0.00 (0.00-10.2)	0.00 (0.00-3.34)	3.34 (0.00-16.7)		16.7 (8.2-26.7)[b,c,d]	13.3 (3.3-20.0)[b,c]

Joshi et al. [4] displayed mean scores while Rosen et al. [14] displayed median scores. Therefore in the current study both are displayed to make comparison possible

AE adverse event

[a]No standard deviations were given in Joshi et al. [4]

[b]A statistically significant result compared with patients from the current study experiencing (papulopustular) eruption

[c]A statistically significant result compared with patients from the current study experiencing xerosis

[d]A statistically significant result compared with patients from the current study experiencing pruritus

The current Skindex-16 scores were compared with the data of Joshi et al. [4] and Rosen et al. [15], both a retrospective investigation of Skindex-16 scores of patients with dAEs due to cancer treatment in a specialty referral clinic. The study of Joshi et al. is the most comparable to the current study as they focused on patients treated with EGFRIs. Joshi et al. [4] analyzed more women, more patients younger than 50 years, and more patients treated with cetuximab and erlotinib. Rosen et al. [15] included patients with targeted as well as non-targeted therapy, who were generally younger, more often female, and less often of Caucasian ethnicity. Our study patients with papulopustular eruption and xerosis scored higher HRQoL on all Skindex-16 domains as patients in Joshi et al. [4] ($p<0.001$) and in Rosen et al. [15] ($p<0.032$). This was most marked on the emotional level. Our patients with pruritus had equal scores on the physical domain compared to both studies, and a comparable score on the functional domain with patients in Rosen et al. [15] receiving non-targeted therapy (Table 4). Even though not significant in the relatively small sample size, patients with pruritus showed a trend of higher scores on Skindex-16 and FACT-EGFRI-18 (indicating a lower HRQoL) than patients with papulopustular eruption or xerosis.

Discussion

The current results show that xerosis and pruritus have a major negative impact on HRQoL during the first 6 weeks of EGFRI treatment. This also applies for the patients affected by papulopustular eruption, from which only 6.3 % report the presence of papulopustular eruption as having the highest impact on HRQoL. These findings were confirmed also in the STEPP trial [16, 17].

In Gandhi et al. [18], patients reported xerosis as having the most negative impact on HRQoL and pruritus as the third most impactful of all dAEs. In addition, xerosis was reported as having the second most negative impact on HRQoL of all unexpected AEs due to cancer treatment. Since xerosis and pruritus are less frequent reported EGFRI-associated dAEs, not all patients are counseled about these possible dAEs before initiating treatment. Therefore, they cannot engage in anticipatory coping; a method to deal with anticipated AEs. In an interview study of Frith et al. [19], strategies were identified for patients to cope with anticipated cancer treatment AEs. First, patients try to foresee the amount of distress and accompanying emotions through “affective rehearsal,” followed by acceptance of possible AEs and gathering resources to manage them through “behavioral rehearsal,” a method to modify interpersonal skills and social interactions. The final strategy is finding ways to control the development of the AEs and the personal emotional reactions on them [19].

Since this is the first report of FACT-EGFRI-18 scores, we are not able to compare our data to data from other trials. Our analysis showed that during the first 6 weeks of EGFRI treatment, patients experience influence on their HRQoL primarily due to physical symptoms, especially irritation, xerosis, pruritus, and nail sensitivity. The reversed FACT-EGFRI-18 scores of papulopustular eruption, xerosis and pruritus decreased significantly on the total scores ($p<0.014$) indicating a high HRQoL. The non-reversed FACT-EGFRI-18 scores increased significantly on the domain scores ($p<0.012$) reflecting a low HRQoL. Only patients experiencing xerosis in week 1 and patients experiencing pruritus in week 5 did not have a significant higher score on the functional domain, meaning a non-significant different score compared to before treatment.

Cella et al. [11] used the FACT-G questionnaire in a population with different cancer types and treatments, and EGFRI-treated patients were not included. EGFRI treatment is considered more tolerable compared to conventional cytotoxic treatments, because systemic AEs are less frequent [20]. This could explain the higher score on the physical and emotional domains in the current study population. Aaronson et al. [14] measured pre-treatment SF-36 scores, resulting in fewer AEs, which explain a higher physical functioning and general health.

The study of Joshi et al. [4] analyzed Skindex-16 scores at any time of AE development instead of the current fixed measurement at week 4 of treatment. In addition, the referral to a specialty clinic might have increased patients’ worry about the severity of the AEs. Rosen et al. [15] measured patients at any moment during all types of cancer treatment, causing a broader range of dAEs, which influences Skindex-

16 scores. This could also explain a better HRQoL for patients with papulopustular eruption or xerosis. In addition, patients with pruritus had similar Skindex-16 scores on the physical domain as the patients in the specialty referral clinic in Joshi et al. [4] and Rosen et al. [15]. These findings suggest that the impact of pruritus on HRQoL might be larger than papulopustular eruption and xerosis. The similar score on the physical domain of Skindex-16 of patients with acne vulgaris suggests clinical similarities with EGFRI papulopustular eruptions. Patients with EGFRI-associated papulopustular eruption are generally more likely to accept the temporary eruption as part of their treatment for cancer, especially since they are usually informed about its association with effectiveness of treatment, which can clarify the different impact on emotions and functioning [17, 20, 21].

This study required a substantial effort for patients to complete consecutive questionnaires at the intended assessments. There might be a selection bias as missing data were from relatively sicker patients, which could result in overestimating the overall HRQoL and underestimating the impact of dAEs on HRQoL. Another cause may be the missing data from patients who did not experience noticeable AE changes and, therefore, did not complete the questionnaires in the weeks without AE changes. The incidence of dAEs might be reduced as all patients received close monitoring and preventive and reactive treatment. As all factors mentioned above are more likely to have improved HRQoL of patients, the expectation is that the current results are indeed realistic and may be even more profound when less confounding factors would be present. Because the study population consisted mainly of patients from Caucasian origin, with NSCLC or colorectal cancer, current results may not apply to all EGFRI-treated cancer patients.

Conclusion

Clinical and research endeavors in patients with various cancers who receive medical management consisting of EGFRIs have focused mainly on papulopustular eruption as an EGFRI-associated AE, which resulted in an important decrease in HRQoL. However, the current study shows that xerosis and pruritus are also important AEs with a major impact on HRQoL. This justifies more focus on HRQoL related to these symptoms and on their prevention and treatment in future research.

In clinical practice, xerosis and pruritus are infrequently discussed during patient counseling prior to treatment, as they are less visible than the more common papulopustular eruption. Providing patients adequate information about treatment and possible AEs has shown a positive result on patients' emotional and physical well-being. Counseling patients prior to EGFRI treatment about potential xerosis and pruritus is therefore important, as well as taking preventive measures against these AEs [18, 19, 22, 23].

Conflict of interest MEL has consulted for Roche, BMS, BI, Genentech, AZ, and Merck. The other authors have no conflict of interest to declare in relation to this work.

References

1. Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, Epstein JB, Eaby-Sandy B, Murphy BA (2011) Clinical practice guidelines for the prevention and treatment of EGFR inhibitor associated dermatologic toxicities. Support Care Cancer 19(8): 1079–1095. doi:10.1007/s00520-011-1197-6
2. Abdullah SE, Haigentz M, Jr., Piperdi B (2012) Dermatologic toxicities from monoclonal antibodies and tyrosine kinase inhibitors against EGFR: pathophysiology and management. Chemother Res Pract 2012:351210.doi: 10.1155/2012/351210
3. Wagner LI, Lacouture ME (2007) Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective. Impact on health-related quality of life and implications for clinical management of psychological sequelae. Oncology (Williston Park) 21(11 Suppl 5):34–36
4. Joshi SS, Ortiz S, Witherspoon JN, Rademaker A, West DP, Anderson R, Rosenbaum SE, Lacouture ME (2010) Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 116(16):3916–3923. doi:10.1002/ cncr.25090
5. Boers-Doets CB, Gelderblom H, Lacouture ME, Bredle JM, Epstein JB, Schrama NA, Gall H, Ouwerkerk J, Brakenhoff JA, Nortier JW, Kaptein AA (2013) Translation and linguistic validation of the FACT-EGFRI-18 quality of life instrument from English into Dutch. Eur J Oncol Nurs 17(6):802–807. doi:10.1016/j.ejon. 2013.03.004
6. Boers-Doets CB, Gelderblom H, Lacouture ME, Epstein JB, Nortier JW, Kaptein AA (2013) Experiences with the FACTEGFRI-18 instrument in EGFRI-associated mucocutaneous adverse events. Support Care Cancer 21(7):1919–1926 Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L,
7. Kemeny NE, Halpern AC (2007) Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab associated acne-like eruption. J Clin Oncol 25(34):5390–5396
8. Boers-Doets CB (2014) The Target System - approach to assessment, grading, and management of dermatological & mucosal side effects of targeted anticancer therapies. 1 ed. Wormer: IMPAQTT

9. Wagner LI, Lai SE, AnejaM, LoRusso P, Perez-Soler R, O'Brien B et al. (2007) Development of a functional assessment of side-effects to therapy (FAST) questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors (EGFRI): the FAST-EGFRI. ASCO, Meeting Abstracts 25[18 Suppl], 19532.
10. Wagner LI, Berg SR, Gandhi M, Hlubocky FJ, Webster K, Aneja M, Cella D, Lacouture ME(2013) The development of a Functional Assessment of Cancer Therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors (FACT-EGFRI-18). Support Care Cancer 21(4): 1033–1041. doi:10.1007/s00520-012-1623-4
11. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11(3):570–579
12. Newnham EA, Harwood KE, Page AC (2007) Evaluating the clinical significance of responses by psychiatric inpatients to the mental health subscales of the SF-36. J Affect Disord 98(1-2):91–97. doi: 10.1016/j.jad.2006.07.001
13. Chren MM, Lasek RJ, Sahay AP, Sands LP (2001) Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Cutan Med Surg 5(2):105–110. doi:10.1007/s102270000010
14. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, Velde AtT, Verrips E (1998) Translation, validation, and norming of the Dutch language version Support Care Cancer of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 51(11):1055–1068
15. Rosen AC, Case EC, Dusza SW, Balagula Y, Gordon J, West DP, Lacouture ME (2013) Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. Am J Clin Dermatol 14(4):327–333. doi:10.1007/s40257-013-0021-0
16. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, Xu F, Yassine M (2010) Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 28(8):1351–1357. doi:10.1200/JCO.2008.21.7828
17. Coleman S, Jatoi A (2010) STEPP for the EGFR inhibitor-induced rash—definitely a step in the right direction. Curr Oncol Rep 12(4): 223–225. doi:10.1007/s11912-010-0102-7
18. Gandhi M, Oishi K, Zubal B, Lacouture ME (2010) Unanticipated toxicities from anticancer therapies: survivors' perspectives. Support Care Cancer 18(11):1461–1468. doi:10.1007/s00520-009-0769-1
19. Frith H, Harcourt D, Fussell A (2007) Anticipating an altered appearance: women undergoing chemotherapy treatment for breast cancer. Eur J Oncol Nurs 11(5):385–391. doi:10.1016/j.ejon.2007. 03.002

20. White KJ, Roydhouse JK, Scott K (2011) Psychosocial impact of cutaneous toxicities associated with epidermal growth factor receptor-inhibitor treatment. Clin J Oncol Nurs 15(1):88–96. doi: 10.1188/11.CJON.88-96
21. Balagula Y, Garbe C, Myskowski PL, Hauschild A, Rapoport BL, Boers-Doets CB, Lacouture ME (2011) Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. Int J Dermatol 50(2):129–146. doi:10.1111/j. 1365-4632.2010.04791.x
22. Haley AC, Calahan C, Gandhi M, West DP, Rademaker A, Lacouture ME (2011) Skin care management in cancer patients: an evaluation of quality of life and tolerability. Support Care Cancer 19(4):545–554. doi:10.1007/s00520-010-0851-8
23. Siminoff LA (1992) Improving communication with cancer patients. Oncology (Williston Park) 6(10):83–87 Support Care Cancer

06 | Translation and linguistic validation of the FACT-EGFRI-18 quality of life instrument from English into Dutch.

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ABSTRACT

Purpose: The Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) is a patient-reported outcomes questionnaire developed to assess the effect of EGFRI on patients. The FACT-EGFR-18 was translated into Dutch and evaluated in order to document that the translation adequately captures the concepts of the original English-language version of the questionnaire and is readily understood by subjects in the target population.

Method: Translation of the FACT-EGFRI-18 from English to Dutch was accomplished by employing the Functional Assessment of Chronic Illness Therapy (FACIT) multilingual translation methodology. Ten native-speaking residents of the target country who reported EGFRI associated dermatological adverse events (dAEs) were asked to review the translation of the harmonized FACT-EGFRI-18.

Results*:* Participants generally found the Dutch FACT-EGFRI-18 easy to understand and complete. In addition, the translation retained the original meaning of the FACT-EGFRI-18 items and instructions. Based on the results of the cognitive debriefing interviews, no changes to improve clarity and comprehension of translations were identified.

Conclusions: The Dutch FACT-EGFRI-18 demonstrates content validity and linguistic validity, and was found conceptually equivalent to its English source, thus confirming linguistic validation. The results suggest that the Dutch FACT-EGFRI-18 can be applied to measure dAE related health related quality of life in Dutch-speaking patients undergoing EGFRI therapy. Formal validation of the Dutch FACT-EGFRI-18 is ongoing.

Introduction

EGFRI

Several types of anticancer agents lead to dermatological adverse events (dAEs); dAEs are the primary side effects associated with targeted anticancer agents, especially those targeting the epidermal growth factor receptor (EGFR) signal transduction pathway (Balagula et al., 2011). The most common dAEs are defined as those affecting the skin, hair, nail bed, mucosa or eyelids. DAEs can result in skin rash (papulopustular eruption), itching (pruritus), abnormally dry skin (xerosis cutis), painful mucosal surfaces, dry conjunctivae of the eye, periungual inflammation, and oedema in up to 90% of patients during treatment with EGFR Inhibitors (EGFRI) (Iacovelli, 2007; Lacouture and Melosky, 2007; Perez-Soler and van Cutsem, 2007). They can have significant impact on quality of life because they can hinder daily activities and make it difficult to maintain patients' privacy about their illness, even when the treatment is effective in combating the cancer. The aesthetic discomfort, which is frequently associated with a burning sensation, itching or painful skin or nails, can lead to a decreased health related quality of life (HRQoL), dose reduction and even to a refusal to continue with further treatment (Hu et al., 2007). Oral complications can cause pain and affect oral function such as oral intake of food and medications, may impact nutrition, affect speech, ability to maintain oral hygiene and patients may be forced to remove their oral prostheses.

HRQoL

The concept of HRQoL can be defined as the extent to which one's usual or expected physical, emotional, and social well-being is affected by a medical condition or its treatment (Cella, 1994). One difficulty for clinicians trying to conceptualize a patient's HRQoL is due to its multidimensional nature that encompasses multiple aspects of a person's well-being (Ratanatharathorn et al., 2001). Empirical investigation of the aspects of dAEs that have the most detrimental impact on patients' HRQoL can help guide interventions to manage these toxicities and maximize patients' HRQoL (Wagner et al., 2007). Joshi et al. measured the effect of EGFRI-induced dAEs on HRQoL. They concluded that toxicities including rash, xerosis, paronychia, and pruritus adversely affect HRQoL, with rash associated with a greater decrease. Younger patients reported a lower overall HRQoL than older patients undergoing the same toxicities (Joshi et al., 2010).

dAE related HRQoL assessment

Having accurate baseline and post treatment data is essential to evaluating the HRQoL of patients and subsequently determining the effectiveness of management (Ikeda et al., 2003), which can range from counselling to pharmacologically based therapies. Prior to this study, Dutch patients with dAEs due to EGFRI treatment were not likely to have a formal assessment or reassessment of their dAEs related HRQoL because there was no Dutch EGFRI associated dAE specific HRQoL measurement

tool available. If EGFRI treatment-related HRQoL is to be improved, data on the prevalence, severity, and impact of dAE on HRQoL must be obtained and the effectiveness of various interventions on the HRQoL documented.

FACT-EGFRI-18

To date there have been two HRQoL questionnaires developed for EGFRI treated patients: the Functional Assessment of Side- Effects to Therapy-EGFRI (FAST-EGFRI) (Wagner et al., 2007) and the Functional Assessment of Cancer Therapy-EGFRI-18 (FACTEGFRI- 18) (Wagner et al., 2010). The 38-item FAST-EGFRI was the first EGFRI specific HRQoL questionnaire. The FACT-EGFRI-18 is based on the FAST-EGFRI and is a symptom specific subscale of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system used for assessing dAEs (FACIT.org, 2010). The FACT-EGFRI-18 is an 18-item Likert-scaled questionnaire, arranged in three HRQoL dimensions: physical (7 items), social/emotional (6 items), and functional well-being (5 items) (Wagner et al., 2007). To provide a better fit for scale items, the item groups are reorganized in skin, nail and hair side effect domains. The response scores ranged from 0 to 4 and the response categories include ‘Not at all’, ‘A little bit’, ‘Somewhat’, ‘Quite a bit’, and ‘Very much’. Negatively worded items (e.g. “My skin bleeds easily” or “My skin condition affects my mood”) are reverse-scored so that all participants who experience a higher severity of symptoms receive a lower score. The FACT-EGFRI-18 was developed according to the FACIT measurement system (FACIT.org, 2010; Webster et al., 2003). Table 1 shows the 18 items by subscale.

Instrument equivalence

Dutch is the native language spoken in The Netherlands and in about sixty percent of the populations of Belgium and Suriname, the three member states of the Dutch Language Union. Most speakers live in the European Union, where it is a first language for about 23 million and a second language for another 5 million people (not including speakers of closely related Afrikaans) (Ardizzoni et al., 2002; European Commission, 2006; Nederlandse Taalunie, 2012). It also holds official status in the Caribbean island nations of Aruba, Curacao, and Saint Maarten, as well as Australia, Canada, France (French Flanders), Germany, Indonesia, South Africa, and the United States.

When adapting measures for use in non-English-speaking populations, the translation process is a key factor in ensuring the appropriateness of the instrument in the target language. Qualitatively translation issues inevitably arise, such as issues related to semantic nuance, differences in dialect, or use of colloquial or idiomatic expressions. Employing a comprehensive translation methodology seeks to resolve all conceptual or linguistic concerns.

Ensuring conceptual equivalence among the adapted versions is critical, as translations that deviate from the intended meaning could affect how individuals perceive the connotation associated with specific test items: Patients may seem to understand the intent, but their perception and understanding of the intent may differ

from that of the English source. In this manner, linguistic nuances can create conceptual inequalities that can go undetected. This happens when there are significant differences in cultural values between the source and target cultures or when there are differences in how individuals of different groups qualify their symptoms (Guyatt, 1993; Kleinman, 1987; Marquis et al., 2005). This limits comparison of results from different studies, and also negates the possibility of pooling data for larger studies (Chang et al., 1999; Sireci, 1997; Yu et al., 2004) and ultimately inhibits a clinician's ability to interpret and apply assessment results because he or she may inadvertently over- or under-represent the severity of their patient's health status.

Table 1

FACT-EGFRI-18 items by subscale.

Physical well-being
1. I am bothered by a change in my skin's sensitivity to the sun
2. My skin or scalp itches
3. My skin bleeds easily
4. My skin or scalp is dry or "flaky"
5. My skin or scalp feels irritated
6. My eyes are dry
7. I am bothered by sensitivity around my fingernails or toenails
Social/emotional well-being
1. My skin condition affects my mood
2. I feel unattractive because of how my skin looks
3. I am embarrassed by my skin condition
4. I avoid going out in public because of how my skin looks
5. I am bothered by increased facial hair
6. I am bothered by hair loss
Functional well-being
1. My skin condition interferes with my social life
2. Sensitivity around my fingernails makes it difficult to perform household tasks
3. My skin condition interferes with my ability to sleep
4. Changes in my skin condition make daily life difficult
5. The skin side effects from treatment have interfered with household tasks

FACT-EGFRI-18 = Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor.

Translation & cultural adaptation of patient reported outcome measures

European regulatory bodies have raised concerns over the validity of measures developed in one language and then used in other languages (Chassany et al., 2002). The European Regulatory Issues and Quality of Life Assessment (ERIQA) group recommends that a rigorous approach is taken in the translation of patient-reported

outcome (PRO) measures for use in international settings to achieve conceptual and semantic equivalence across languages (Acquadro et al., 2008). Because of the increased need to translate and culturally adapt PRO measures, content integrity during translation has to be maintained (Wild et al., 2009; Wild et al., 2005; Wyrwich et al., 2013). In response to a growing demand for more global and universally applicable clinical assessment instruments, a number of outcome based assessment tools have been developed from a cross-culturally sensitive perspective. This is in an effort to aid clinicians and researchers to more accurately understand the multifaceted attributes of what constitutes HRQoL and associated well-being. The literature shows a myriad of HRQoL assessment measures being adapted and validated for use with non-English-speaking populations (Butt et al., 2005; Eremenco et al., 2005a; Eremenco et al., 2004; Peterman et al., 1997).

FACIT translation system

The Functional Assessment of Chronic Illness Therapy (FACIT) translation measurement system (Bonomi et al., 1996; Eremenco et al., 2005b) utilizes health-care and translation experts from culturally appropriate geographic regions in order to develop linguistic and culturally equivalent translations that are appropriate for individuals with an average education level for the target culture. The methodology also calls for pilot testing of the translations to ascertain if patients from different backgrounds and with similar health symptoms understand the terminology in a consistent manner. Even with these safeguards, there is the possibility of psychometric inequivalence, which may be due to small sample size used in pilot studies or the sociodemographic profile of a particular sample (Arnold et al., 2009a,b).

The present study sought to conduct a linguistic validation of the FACT-EGFRI-18 questionnaire for the Dutch speaking population in The Netherlands. The purpose is to examine whether the Dutch translation adequately captures the concepts of the original English-language version of the questionnaire and is readily understood by participants in The Netherlands.

Methods

The FACT-EGFRI-18 was originally developed and validated in English (Wagner et al., 2010 2359/id). To create a Dutch version, we followed the standard multilingual translation and validation methodology developed by Bonomi et al. (1996) and adopted by the FACIT organization (FACIT.org, 2010). Due to the non-interventional design of this study, it was exempt from review by an ethics committee, per national and institutional standards and policies.

Participants

Following the FACIT validation methodology (FACIT.org, 2010), the required ten participants were recruited by clinical investigators from three hospitals in The Netherlands. The hospitals were selected from the participating hospitals for the BeCet trial (NCT01136005), where the formal validation of the Dutch FACT-EGFRI-18 is ongoing. Participants were eligible if they spoke Dutch as their native and primary language and had the ability to read standard Dutch; had been diagnosed with cancer; treated with an EGFRI; experiencing dAEs; if they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2; were at least 18 years of age and provided verbal informed consent to participate in the study. Demographic data collected included age, sex, diagnosis, date of diagnosis, primary language spoken, country of origin, current place of residence, and functional performance status. Table 2 summarizes the major demographic variables that were collected.

Table 2

Demographic and clinical characteristics of the validation sample (N = 10).

Characteristics	Mean (range)	N
Age	70 (63-81)	
Gender		
Male		6
Female		4
Diagnosis of cancer		
Colon cancer		6
Lung cancer		3
Breast cancer		1
EGFRI treatment		
Panitumumab		6
Erlotinib		2
Gefitinib		1
Lapatinib		1
ECOG PS; rating (0-4)		
0		3
1		4
2		3

ECOG PS = Eastern Cooperative Oncology Group Performance Status.

Procedure

Translation of the English FACT-EGFRI-18 into Dutch was conducted according to the FACIT translation methodology (Cella and Webster, 1997; Eremenco et al., 2005a; FACIT.org, 2010; Webster et al., 2003). Two forward translations, one reconciliation of the two forward translations, a back translation into English, and a review by Dutch-speaking health-care experts were required, along with field testing on a small patient population. A schematic overview of a typical linguistic validation process is illustrated in Table 3.

During the translation from English to Dutch, priority was given to achieving appropriate translation of the meaning/intent of each question in a grammatically correct manner, as opposed to simple translation of every individual word. Additional reviews by the FACIT organization and a committee of bilingual Dutch EGFRI therapy experts confirmed that the Dutch version was a harmonized translation of the English questionnaire. The translations were then tested via cognitive debriefing interviews in participants with EGFRI associated dAEs residing in The Netherlands. Cognitive

debriefing is a standardized interview conducted by a trained interviewer following a subject's review and completion of a PRO instrument.

Participants were interviewed in their homes as it was assumed they would feel more comfortable and talk more candidly there. A field tester monitored the administrations and then participants were asked to complete the FACT-EGFRI-18. Afterwards the field tester conducted a cognitive debriefing interview with each participant to assess if they experienced any difficulty understanding items, to see if items were irrelevant or offensive to them, to assess the items' personal and cultural relevance as well as the patients' overall comprehension of them, and to determine if any translations were poorly phrased or overly colloquial. Interviewing was conducted using a script that was read to the participants: "As you know, we are testing a questionnaire for use in clinical trials and want to know if it can be easily understood. Would you please tell me which items were difficult to understand and why they were difficult? Also, could you suggest a better way to phrase these items?" The interviewer judged whether items were correctly paraphrased and recorded any comprehension problems or proposed changes to the wording. In keeping with regulatory guidelines and good clinical practice, cognitive debriefing information was captured on a data collection form.

In the subsequent qualitative analysis, linguistic validation teams, consisting of the original translators, back translator, project manager, interviewer, and survey research expert, evaluated the debriefing results. The teams categorized problems that emerged during the debriefing as: conceptual e a function of the original English; linguistic e a function of the words used to translate the English concept; or stylistic e a function of the subject's preference for a different wording. When warranted, the original translators of the questionnaire created a new harmonized translation of problem words or sentences and the back translator created a new back translation for review by a survey research expert. Once all issues were resolved, final forward and back translations were created.

Results

Participants

After creating comprehensive translations which were approved by the translators, project manager, and survey research expert involved in its production, debriefing interviews were conducted with 10 participants with EGFRI associated dAEs from the Netherlands. Participants were a-select recruited. The study coordinator contacted the hospitals to find out if they had patients who met the inclusion criteria. All patients who were approached were included. No one refused. The participants ranged in age from 63 to 81 years, mean age was 70 years. Among the 10 participants, 6 patients were male and colon cancer was the most common cancer diagnosis (Table 2).

Translation

The translation process went smoothly except one phrase. In the item 'I am bothered by a change in my skin's sensitivity to the sun', 'I am bothered by' was first back translated into 'annoying' ('dat ik last heb'), which was not acceptable to the FACIT organization based on Dutch translations of the item in other linguistically validated FACIT questionnaires. The FACIT organization provided the phrase 'Ik vind het vervelend'. However, that phrase was too long and vague in this context; participants would not understand what this item was about. Because it was strongly recommended that we used this phrase, we were limited in providing a fluent sentence. We agreed to be consistent with this item but be inconsistent with the word 'sensitivity' in order to be able to create a fluent Dutch sentence.

The word 'sensitivity' was first back translated into 'has become more sensitive', which was not acceptable to the FACIT organization. The forward translation from

Table 3
FACIT translation methodology (FACIT.org, 2010).

Step	Process	Personnel	Requirements/ Purposes
1	Using the English source, produce two forward translations of each item	2 native speakers of target language (1 in the US and 1 in native country)	Use simple language and capture meaning
2	Reconcile the initial translation of the items based on the two forward translations	1 native speaker, familiar with multiple dialects	Resolve discrepancies
3	The reconciled translation is back-translated by a native English speaker fluent in the target language	1 native English speaker	Use simple language
4	Three independent professional bilingual translation experts review the reconciled translation	3–4 bilingual experts and coordinating team	Review steps 1–3 and finalize translations
5	The translation team finalizes and subsequently harmonizes the translations across all countries and/or languages within the scope of the project	Language coordinator and bilingual expert	Proof-read
6	Final translations are proofread	2 bilingual experts from the translation team	Proof-read
7	The translated questionnaire is field tested with cancer patients from the target population to determine if further revisions are necessary	Native speaking patients (10) with relevant diagnosis	Assess comprehension and acceptability
8	The final instrument is considered conceptually equivalent to its English source and is ready to be used in clinical or research settings	-	-

'sensitivity' was 'gevoeliger is geworden'. The FACIT organization provided the word 'gevoeligheid' because this was the word used in other Dutch FACIT questionnaires. I

few would have used this word, the literal back translation then would be: 'I am bothered that the sensitivity of my skin for the sun is changed' which was not acceptable for the translators. So we agreed to be inconsistent with the translation of this word compared to previous translations of other FACIT questionnaires and use the Dutch word 'gevoeliger' ('more sensitive') instead of 'gevoeligheid' ('sensitivity').

Cognitive debriefing

During the linguistic validation process, special attention was paid to ensure that the translated items communicated the desired intent. Since the forward translators had some discussions during the translation process about the phrase 'I am bothered by a change in my skin's sensitivity to the sun', additional questions about this item were added by the FACIT Translation Services to the 'Patient Interview Form'. Questions were: "What does the phrase 'I am bothered' mean in this item?", "What are some examples of 'change in your skin's sensitivity to the sun'?" and "The idea of this item is to ask if you are distressed, both physically and emotionally. Is there a better way to express this idea? If so, please provide your suggestion." The term 'bothered' was described by our participants as 'not being allowed to do what you want to'; 'limited in opportunities', 'troublesome because others have to take you into account', 'you have to adapt', and 'you must remember to take a cap and sunscreen with you'. Participants' responses confirmed that the meaning of this item is correctly understood and the item 'Ik vind het vervelend' captured the original concept. Further, to confirm that participants were appropriately interpreting items, they were asked to give examples of undesirable events. For example, for the phrase 'change in your skin's sensitivity to the sun', participants reported that they have to sit in the shade, others needed to be more considerate with the patients, and they needed to wear a hat, even in the car. Qualitative analysis of all translations derived from employing the FACIT translation methodology revealed no important issues to change.

Overall, patients commented that the Dutch FACT-EFRI-18 was easy to complete and the items were relevant. Results from the post-questionnaire debriefing interviews suggested that the translations were accurately understood by the participants in a manner that was conceptually equivalent to the English source.

Discussion

As more and more patients will be treated with targeted therapies including EGFRI, it becomes increasingly important to understand the multidimensional experiences of these agents associated dAE related HRQoL. The FACT-EGFRI-18 is the first instrument measuring dAE related HRQoL in Dutch cancer patients undergoing EGFRI therapy. Further, use of validated and standardized tools will allow comparison of outcomes in different studies and in meta-analyses, to advance patient care and improve outcomes.

In our study, use of the established FACIT translation methodology in conjunction with the qualitatively based debriefing interview indicated that the constructs being

measured in the Dutch version of the FACT-EGFRI-18 were conceptually equivalent with the original English version prior to field testing with patients. All patients responded that the FACT-EGFRI-18 was easy to understand and items were relevant to measuring HRQoL. This methodology facilitated the translation of the instrument, and use in further translations of this and other survey tools is therefore recommended.

Study limitations

Study limitations included participants with different kinds of cancer, EGFRI treatment, and dAEs. At the same time, different cancers and treatment allows testing of the questionnaire across a range of patients. Another limitation was the relatively small participant sample, however, the number of 10 participants was prescribed by the FACIT organization. All participants were residents from the Netherlands as spoken Dutch tends to vary based on geography and differences in dialect could be present in different regions. Since demographic, economic, geographic, political, and sociological differences make each culture unique, linguistic and conceptual equivalence may not necessarily assume generalizability of results across cultures (Anderson and Gerbing, 1988). The Dutch questionnaire is only linguistically validated for the population from The Netherlands. To cover a Dutch version for all the native Dutch speakers around the world, validation should be done in those countries and in other languages.

Clinical and research implications

The results of the linguistic validation suggest that the Dutch version of the FACT-EGFRI-18 can be applied to measure EGFRI associated dAE related HRQoL in Dutch speaking cancer patients in The Netherlands. Before the Dutch version can be used in other Dutch speaking countries like Belgium, the Caribbean island nations of Aruba, Curacao, and Saint Maarten, as well as Australia, Canada, France (French Flanders), Germany, Indonesia, South Africa, and United States the linguistic validation should be performed in at least in Belgium and Surinam before we called it a universal version. A single (universal) Dutch version of the questionnaire is warranted.

This scale development will help clinicians in the Netherlands to collect more information about the impact of dAEs on the HRQoL due to EGFRI. The result of this scale development process can be applied to all patients treated with EGFRI. The instrument can help researchers and clinicians to assess mcAE related HRQoL, to be able to select interventions, and evaluate their effectiveness. Thus, the use of this tool will be able to improve patients' dAEs treatment and HRQoL.

Formal validation and reliability testing of the Dutch FACTEGFRI-18 is being conducted in the BeCet multicenter trial (NCT01136005) of 160 patients with all dAEs severity grades (National Cancer Institute Cancer Therapy Evaluation Program, 2010). In addition, the translation and linguistic validation of the FACT-EGFRI-18 into German is ongoing. The FACT-EGFRI-18 is available at www.facit.org.

Conclusions

Translations of the FACT-EGFRI-18 questionnaire from English into Dutch adequately captured the concepts in the original English version of the questionnaire, thereby demonstrating the conceptual, semantic, and cultural equivalence of the translation. Participants experiencing EGFRI associated dAEs demonstrated an ability to understand the concepts in the questionnaire. Based on the results of the cognitive debriefing interviews, no changes to improve clarity and comprehension of translations were needed. Additionally, by utilizing the FACIT translation methodology and incorporating translation experts, the translation of the Dutch FACT-EGFRI-18 is considered a promising clinical tool for evaluating the HRQoL of Dutch speaking patients with EGFRI associated dAEs from The Netherlands. These methods and this current study have implications for HRQoL questionnaire development using different questionnaires and in different languages.

Conflict of interest

The authors declare no conflicts of interest. All authors had full control of all primary data and agree to allow the journal to review the data, if requested.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ejon.2013.03.004.

References

Acquadro, C., Conway, K., Hareendran, A., Aaronson, N., 2008. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value in Health 11 (3), 509e521.

Anderson, J., Gerbing, D.W., 1988. Structural equation modeling in practice: a review and recommended two-step approach. Psychological Bulletin 103 (3), 411e423.

Ardizzoni, A., Tjan-Heijnen, V.C., Postmus, P.E., Buchholz, E., Biesma, B., Karnicka-Mlodkowska, H., et al., 2002. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: a prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. Journal of Clinical Oncology 20 (19), 3947e 3955.

Arnold, B.J., Debb, S.M., Bruce, J., Bredle, J., 2009a. Using the FACT-leukemia Subscale to Evaluate Quality of Life in Leukemia Patients Worldwide. In: Poster Presented at the 12th Annual Conference of the International Society for

Pharmacoeconomics and Outcomes Research October 24e27, 2009, Paris, France.

Arnold, B.J., Debb, S.M., Hiramatsu, T., Bruce, J., Cella, D., 2009b. Using the FACTlymphoma Subscale to Evaluate Quality of Life in Non-Hodgkin's Lymphoma Patients from across the Globe. In: Poster Presented at the 16th Annual Conference of the International Society for Quality of Life Research, October 28e31, New Orleans, USA.

Balagula, Y., Garbe, C., Myskowski, P.L., Hauschild, A., Rapoport, B.L., Boers-Doets, C.B., et al., 2011. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. International Journal of Dermatology 50 (2), 129e146.

Bonomi, A.E., Cella, D.F., Hahn, E.A., Bjordal, K., Sperner-Unterweger, B., Gangeri, L., et al., 1996. Multilingual translation of the Functional Assessment of Cancer Therapy (FACT) quality of life measurement system. Quality of Life Research 5 (3), 309e320.

Butt, Z., Webster, K., Eisenstein, A.R., Beaumont, J., Eton, D., Masters, G.A., et al., 2005. Quality of life in lung cancer: the validity and cross-cultural applicability of the Functional Assessment of Cancer Therapy-Lung scale. Hematology/ Oncology Clinics of North America 19 (2), 389e420. viii.

Cella, D.F., 1994. Quality of life: concepts and definition. Journal of Pain and Symptom Management 9 (3), 186e192.

Cella, D., Webster, K., 1997. Linking outcomes management to quality-of-life measurement. Oncology 11 (11A), 232e235.

Chang, A.M., Chau, J.P., Holroyd, E., 1999. Translation of questionnaires and issues of equivalence. Journal of Advanced Nursing 29 (2), 316e322.

Chassany, O., Sagnier, P., Marquis, P., Fulleton, S., Aaronson, N., 2002. Patient reported outcomes and regulatory issues: the example of health-related quality of life - a European guidance document for the improved integration of HRQL assessment in the drug regulatory process. Drug Information Journal 36 (1), 209e238.

Eremenco, S., Webster, K., Kutikova, L., Bowman, L., Cella, D., 2004. Development and multilingual validation of the fact-lymphoma instrument. Quality of Life Research 13 (9), 1501.

Eremenco, S., Webster, K., Arnold, B., Cella, D., 2005a. Multilingual validation of the Fact-Leukemia in 5 languages. Quality of Life Research 14 (9), 1991.

Eremenco, S.L., Cella, D., Arnold, B.J., 2005b. A comprehensive method for the translation and cross-cultural validation of health status questionnaires. Evaluation & the Health Professions 28 (2), 212e232.

European Commission, 2006. Special Eurobarometer 243: Europeans and Their Languages (Survey). Available at: http://ec.europa.eu/public_opinion/archives/ebs/ebs_243_en.pdf (accessed 02.10.12.).

FACIT.org., 2010. Functional Assessment of Chronic Illness Therapy (FACIT). Available at: http://www.facit.org/FACITOrg/Questionnaires (accessed 31.05.11.).

Guyatt, G.H., 1993. The philosophy of health-related quality of life translation. Quality of Life Research 2 (6), 461e465.

Hu, J.C., Sadeghi, P., Pinter-Brown, L.C., Yashar, S., Chiu, M.W., 2007. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. Journal of the American Academy of Dermatology 56 (2), 317e326.

Iacovelli, L., 2007. Clinical management of EGFRI-associated dermatologic toxicities: pharmacy perspective. Oncology 21 (11 Suppl. 5), 31e33.

Ikeda, Y., Saku, M., Kawanaka, H., Nonaka, M., Yoshida, K., 2003. Features of second primary cancer in patients with gastric cancer. Oncology 65 (2), 113e117.

Joshi, S.S., Ortiz, S., Witherspoon, J.N., Rademaker, A., West, D.P., Anderson, R., et al., 2010. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 116 (16), 3916e3923.

Kleinman, A., 1987. Anthropology and psychiatry. The role of culture in crosscultural research on illness. The British Journal of Psychiatry 151, 447e454.

Lacouture, M.E., Melosky, B.L., 2007. Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: a dermatology-oncology perspective. Skin Therapy Letter 12 (6), 1e5.

Marquis, P., Keininger, D., Acquadro, C., de la Loge, C., 2005. Translating and evaluating questionnaires: cultural issues for international research. In: Fayers, P.M., Hays, R.D. (Eds.), Assessing Quality of Life in Clinical Trials. Oxford University Press, New York, pp. 77e94.

National Cancer Institute Cancer Therapy Evaluation Program, 2010. Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [v4.0]. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40 (accessed 01.06.11.).

Nederlandse Taalunie, 2012. Nederlands, Wereldtaal (Dutch). Available at: http://taalunieversum.org/taal/feiten_en_weetjes/#feitencijfers (accessed 02.10.12.).

Perez-Soler, R., van Cutsem, E., 2007. Clinical research of EGFR inhibitors and related dermatologic toxicities. Oncology 21 (11 Suppl. 5), 10e16.

Peterman, A.H., Cella, D., Mo, F., McCain, N., 1997. Psychometric validation of the revised Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) quality of life instrument. Quality of Life Research 6 (6), 572e584.

Ratanatharathorn, V., Sirilerttrakul, S., Jirajarus, m., Silpakit, C., Maneechavakajorn, J., Sailamai, P., et al., 2001. Quality of life, functional assessment of cancer therapygeneral. Journal of The Medical Association of Thailand 84 (10), 1430e1442.

Sireci, S.G., 1997. Problems and issues linking assessments across languages. Educational Measurement: Issues and Practice 16 (29), 12e19.

Wagner, L.I., Lai, S.E., Aneja, M., LoRusso, P., Perez-Soler, R., O'Brien, B., et al., 2007. Development of a functional assessment of side-effects to therapy (FAST) questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors (EGFRI): the FAST-EGFRI. Journal of Clinical Oncology (Meeting Abstracts) 25 (18 Suppl.), 19532.

Wagner, L.I., Rosenbaum, S.E., Gandhi, M., Webster, K., Aneja, M.S., Cella, D., et al., 2010. Development of a functional assessment of chronic illness therapy questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors: FACT-EGFRI. Journal of Clinical Oncology 28 (15S Suppl.). Abstr 9046.

Webster, K., Cella, D., Yost, K., 2003. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health and Quality of Life Outcomes 1, 79e84.

Wild, D., Grove, A., Martin, M., Eremenco, S., McElroy, S., Verjee-Lorenz, A., et al., 2005. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value in Health 8 (2), 94e104.

Wild, D., Eremenco, S., Mear, I., Martin, M., Houchin, C., Gawlicki, M., et al., 2009. Multinational trials-recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data: the ISPOR Patient-reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force report. Value in Health 12 (4), 430e440.

Wyrwich, K.W., Norquist, J.M., Lenderking, W.R., Acaster, S., 2013. Methods for interpreting change over time in patient-reported outcome measures. Quality of Life Research 22 (3), 475e483.

Yu, D.S., Lee, D.T., Woo, J., 2004. Issues and challenges of instrument translation. Western Journal of Nursing Research 26 (3), 307e320

07 | Experiences with the FACT-EGFRI-18 instrument in EGFRI-associated mucocutaneous adverse events.

Support Care Cancer, 2013. 21(7): p. 1919-26.

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ABSTRACT

Purpose The functional assessment of cancer therapy epidermal growth factor receptor inhibitor 18 (FACT-EGFRI- 18) is a patient-reported outcomes questionnaire developed to assess the effect of EGFRI on health-related quality of life (HRQoL).

Methods Ten native-speaking residents of The Netherlands who reported EGFRI-associated mucocutaneous adverse events (mcAEs) were administered the questionnaire. Patients were subsequently asked a standardized series of questions about the items' personal relevance.

Results Responses reflected a major negative impact of mcAEs due to EGFRI on physical, social/emotional, and functional domains. In some cases, especially in the social/-emotional domain, the responses to the qualitative interview indicated a greater impact on HRQoL than the numerical ratings previously selected for the Dutch FACT-EGFRI-18 questions.

Conclusions Based on these interviews, we identified that the physical items associated with mcAEs interfere most with HRQoL. The results suggest that the FACT-EGFRI-18 can be applied to measure mcAE-related HRQoL in cancer patients undergoing EGFRI therapy. In addition, patients feel the need to rate their symptom burden, too, and we recommend additional adverse event items to be incorporated into the questionnaire.

Background

Epidermal growth factor receptor inhibitors

The use of targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors is increasing. It is well know that mucocutaneous adverse events (mcAEs) are the primary side effects associated with agents targeting the EGFR signal transduction pathway [1]. The most common mcAEs are defined as those affecting the skin, hair, nail bed, mucosa, or eyelids. mcAEs can result in skin rash (papulopustular eruption), itching (pruritus), abnormally dry skin (xerosis cutis), painful mucosal surfaces, dry conjunctivae of the eye, periungual inflammation, and edema in up to 90 % of patients during treatment with EGFR inhibitors (EGFRI) [2–4]. They can have significant impact on health-related quality of life (HRQoL) because they can hinder daily activities and make it difficult to maintain the patients' privacy about their illness, even when the treatment is effective in combating the cancer. The mcAEs result in discomfort, which is frequently associated with a burning sensation, itching, or painful skin or nails and can lead to a decreased HRQoL, that may lead to dose reduction and even to a refusal to continue with further treatment [5]. Oral complications can cause pain and affect oral function such as oral intake of food and medications; they may impact nutrition, affect speech, the ability to maintain oral hygiene, and patients may be forced to remove their oral prostheses. Other oral symptoms can include taste change or taste reduction and dry mouth.

Many practitioners assume the cosmetic appearance of the rash to be the most bothersome for patients, but they may have a tainted perspective on patient's mcAEs influence on HRQoL. However, patients' concerns and emotions were most adversely impacted by associated symptoms of irritation, pain, stinging, and itching [6]. This discrepancy may exist because the mcAE grade seems inversely correlated with the impact on the HRQoL. This discrepancy between assessment of mcAEs and the effect on HRQoL may lead to inadequate management.

Symptom burden and HRQoL

Symptoms are subjectively experienced responses of a patient to a disease, injury, a physical disturbance, or produced by treatment side effects and can cause changes in HRQoL. Conversely from signs that can be observed by others, symptoms can only be known from reports provided by the patient [7–9]. The concept of symptom burden can be described as a summary of the severity and impact of symptoms, reported by patients with a specific disease, or due to a certain treatment. It is not only measurements of HRQoL that can be divided in physical and mental domains; symptoms also can be described to be either physical, psychological (more associated with well-being and mental health), or emotional (frustration, worry), where the classification relates to the origin of the symptoms [7, 9, 10]. Symptom burden can be pronounced and can thereby negatively influence different domains in life, leading to an impaired HRQoL [11].

The concept of HRQoL can be defined as the extent to which one's usual or expected physical, emotional, and social well-being is affected by a medical condition or its treatment [12]. One difficulty for clinicians trying to conceptualize a patient's HRQoL is due to its multidimensional nature that encompasses multiple aspects of a person's wellbeing [13]. Empirical investigation of the aspects of mcAEs that have the most detrimental impact on patients' HRQoL can help guide interventions to manage these toxicities and maximize patients' HRQoL [14]. Joshi et al. measured the effect of EGFRI-induced mcAEs on HRQoL. They concluded that toxicities including rash, xerosis, paronychia, and pruritus adversely affect HRQoL, with rash associated with a greater decrease. Younger patients reported a lower overall HRQoL than older patients with the same toxicities [11].

Assessment of symptom burden and HRQoL in EGFRI patients with patient reported outcomes

In the care of EGFRI-treated patients, it is essential to explore the patient's experiences and effects of living with mcAEs. A patient-reported outcomes (PROs) instrument is defined as any measure of a patient's health status that is elicited directly from the patient and assesses how the patient "feels or functions with respect to his or her health condition" [15], giving valuable information and cannot be replaced by health-care provider assessments. PROs can be achieved by interview, diaries, or questionnaires [7, 16]. Assessment of symptom burden and HRQoL can be the primary outcome during a treatment or after an intervention [17, 18].

If EGFRI treatment-related HRQoL is to be improved, data on the prevalence, severity, and impact of mcAE on HRQoL must be obtained, and the effectiveness of various (medical) interventions on the HRQoL, documented. Efforts have been made to develop objective documentation of the effects of mcAEs on HRQoL due to these agents. Documentation by the health-care provider can be achieved by using the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) scoring [19], and the Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18 (FACT-EGFRI-18) can be used by patients to assess HRQoL associated with dermatological side effects.

FACT-EGFRI-18 questionnaire

The FACT-EGFRI-18 [20] is a symptom-specific subscale of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system used for assessing dermatological adverse events [21]. The FACT-EGFRI-18 is an 18-item Likert-scaled questionnaire, arranged in three HRQoL dimensions: physical (seven items), social/emotional (six items), and functional well-being (five items) [14]. To provide a better fit for scale items, the item groups are reorganized in skin, nail and hair side effect domains. The response scores ranged from 0 to 4, and the response categories include "not at all," "a little bit," "somewhat," "quite a bit," and "very much." Negatively worded items (e.g. "My skin bleeds easily" or "My skin condition affects my mood") are reverse-scored, so that participants who experience a higher impact of

symptom burden on HRQoL receive a lower score. The FACT-EGFRI-18 was developed according to the FACIT measurement system [21, 22].

The FACT-EGFRI-18 was originally developed and validated in English [20] and was recently translated and linguistic-validated into Dutch. To create a Dutch version, the standard multilingual translation and validation methodology developed by Bonomi et al. [23] and adopted by the FACIT organization [21, 22, 24, 25] was followed.

As part of the linguistic validation, a part of a translation process, participants with EGFRI-associated mcAEs residing in The Netherlands were invited to review the recently translated FACT-EGFRI-18 questionnaire. While for the linguistic validation itself, it is relevant whether the translation is culturally correct, linguistically correct, clear about the information the instrument is trying to elicit from the patient, and if the questions are understood; the actual answers given are not part of the linguistic validation. Here, we report these data.

The aim of this study was to identify how the18-item symptom specific, patient-reported outcome (PRO) measurement (FACT-EGFRI-18) reveals the impact of the mcAEs on HRQoL.

Patients and methods

Participants

Following the FACIT validation methodology [21], the required ten participants needed for the linguistic validation were recruited by clinical investigators from three hospitals in The Netherlands. The hospitals were selected from the participating hospitals for the BeCet trial (NCT01136005), where the formal validation of the Dutch FACT-EGFRI-18 is ongoing. Participants were eligible if they spoke Dutch as their native and primary language and had the ability to read standard Dutch; had been diagnosed with cancer; treated with an EGFRI; experiencing mcAEs; if they had an Eastern Cooperative Oncology Group Performance Status ≤2; and were at least 18 years of age and provided verbal informed consent to participate in the study. Demographic data collected included age, sex, diagnosis, EGFRI agent, primary language spoken, country of origin, current place of residence, and functional performance status.

Procedures

The newly developed Dutch FACT-EGFRI-18 was used in ten patients undergoing EGFRI treatment and experiencing mcAEs. Participants were interviewed in their homes as it was assumed that they would feel more comfortable and talk more candidly there. A field tester proctored the administrations, and then participants were asked to complete the FACT-EGFRI-18. Afterwards, the field tester conducted an interview with each participant in a structured interview fashion to assess the items' personal relevance as well as the patients' overall comprehension of them.

In keeping with regulatory guidelines and good clinical practice, interview information was captured on a data collection form. Any difficulties that the patients experienced with the questionnaire were recorded during the time they completed the

questionnaire. The patients' problems in completing the questionnaire were reviewed. Patients could rate the items of the three domains between 0 (not at all) and 4 (very much). In scoring the FACT-EGFRI-18, the possible range of scores is from 0 to 72. To obtain the 0–72 score, each item response was subtracted from 4 so that 0 indicates low HRQoL and 4 indicates high HRQoL [21].

Due to the noninterventional design of this study, it was exempt from review by the local ethics committee, per national and institutional standards and policies.

Results

All questionnaires were thoroughly checked when handed in, and if there were answers missing, the patients were approached and given the chance to complete.

Participants

Interviews were conducted with ten participants with EGFRI-associated mcAEs from The Netherlands. Participants were a select recruited. The study coordinator contacted the hospitals if they treated at that moment patients who met the inclusion criteria. All patients who were approached were included. No one refused. The participants ranged in age from 63 to 81 years; mean age was 70 years. Among the ten participants, six patients were male, and colon cancer was the most common cancer diagnosis. Three patients rated their Eastern Cooperative Oncology Group Performance Status a 0, four a 1, and two a 3. Table 1 summarizes the major demographic variables that were collected.

Response to the Dutch FACT-EGFRI-18 questionnaire

Most patients were able to complete the questionnaire by themselves, with little assistance from their partners/family. Based purely on the way the questions were worded, patients initially tended to rate the severity of the mcAEs without incorporating the impact of mcAEs on their HRQoL. Patients were instructed to circle or mark one number per line to indicate their response as it applied to the past 7 days. Table 2 shows the 18 items by subscale. Several subjects asked the researcher about the general aim of the questions, whether we were interested in the experienced intensity of the mcAEs or whether we wanted to know if they were emotionally or functionally distressed by it. After an explanation that their responses should incorporate the impact of the mcAEs on their HRQoL, patients often chose another response level than they had originally planned.

During the interviews, patients gave a wide range of information about their dermatological experiences with EGFRI therapy. Overall, patients commented that the FACT-EGFRI-18 items were relevant. They reported difficulties in questions 1, 2, 6, 16, and 17 pertaining to the exact location and the relationship of the experienced

Table 1 Demographic and clinical characteristics of the participants (N = 10)

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Gender	Female	Female	Male	Male	Male	Male	Male	Female	Male	Female
Year of Birth	1947	1946	1929	1937	1947	1943	1946	1933	1936	1936
Cancer Diagnosis	Colon	Colon	Lung	Lung	Colon	Colon	Lung	Colon	Colon	Breast
EGFRI therapy	Panitumumab	Panitumumab	Gefitinib	Erlotinib 4th package	Panitumumab (12x)	Panitumumab (4x)	Erlotinib	Panitumumab	Panitumumab	Lapatinib
Concurrent cytotoxics	No	No	No	No	No	No	No	No	No	Capecitabine
Patient Rated PS	2	0	2	1	1	1	0	1	0	2

EGFRI epidermal growth factor receptor inhibitor, *PS* performance status rating (0–4) (0 = fully active, able to carry on all pre-disease performance without restriction; 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair)

mcAEs with EGFRI treatment; e.g. how a flaky scalp should be scored if a patient already experienced dandruff, and how to respond on the question about the interference with household tasks when the patient does not have to do any, but is bothered by sensitivity around the fingernails (Table 3).

It was remarkable that with all the eight patients where a partner/child was present during the pilot testing, the partner/ child helped remind the patient that there was a greater impact of the symptom burden on the HRQoL than the patient wanted to rate in the first place. While patients stressed being grateful for receiving anticancer treatment, because of their strong will to live, their families were more focused on the HRQoL including the mcAEs. Patients did express an appreciation for the opportunity to discuss their difficulties coping with their mcAEs.

As outlined in Table 2, responses reflected a major impact of mcAEs on physical, social/emotional, and functional domains. The physical domain items received the highest ratings (indicating a more negative impact), followed by the functional domain and the social/emotional domain. The mcAEs “change in the skin’s sensitivity to the sun,” “itching of skin or scalp,” and “easy skin bleeding” had the greatest impact on patients’ HRQoL.

As per the FACIT.org protocol, patients rated first the influence of the mcAEs on their HRQoL and then provided comments about their ratings (why they gave that rating). We found that some comments matched the rating and some were discordant.

Table 2 FACT-EGFRI 18 questionnaire, arranged by the original sub scores and by highest numerical ratings

Instructions to the Patients: Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

			Patient no.										
			1	2	3	4	5	6	7	8	9	10	SUM
PHYSICAL	Q5	I am bothered by a change in my skin's sensitivity to the sun	4	2	2	1	4	1	4	2	2	0	22
	Q3	My skin or scalp itches	3	2	3	3	2	1	0	3	1	3	21
	Q4	My skin bleeds easily	3	0	2	3	2	4	1	4	2	0	21
	Q2	My skin or scalp is dry or "flaky"	2	3	3	2	1	0	0	3	3	2	19
	Q1	My skin or scalp feels irritated	2	2	2	1	1	1	0	3	2	3	17
	Q14	My eyes are dry	1	3	3	1	3	1	0	3	0	2	17
	Q15	I am bothered by sensitivity around my fingernails or toenails	1	0	1	2	2	2	0	4	0	1	13
SOCIAL/EMOTIONAL	Q7	My skin condition affects my mood	2	1	0	0	2	1	0	3	0	1	10
	Q11	I feel unattractive because of how my skin looks	4	0	0	0	0	1	0	2	2	0	9
	Q9	I am embarrassed by my skin condition	0	0	0	0	3	1	0	1	0	0	5
	Q10	I avoid going out in public because of how my skin looks	3	0	0	0	1	1	0	0	0	0	5
	Q18	I am bothered by increased facial hair	3	0	0	0	0	0	1	0	0	0	4
	Q17	I am bothered by hair loss	0	0	0	1	1	0	0	0	0	0	2
FUNCTIONAL	Q8	My skin condition interferes with my social life	3	0	0	0	4	1	0	2	1	0	11
	Q16	Sensitivity around my fingernails makes it difficult to perform household tasks	2	0	0	1	1	2	0	4	0	0	10
	Q6	My skin condition interferes with my ability to sleep	0	0	2	0	2	1	0	3	0	0	8
	Q12	Changes in my skin condition make daily life difficult	2	0	0	0	3	1	0	0	1	1	8
	Q13	The skin side effects from treatment have interfered with household tasks	3	0	0	0	2	1	0	1	0	0	7
		Sum individual item score	38	13	18	15	34	20	6	38	14	13	
		FACT-EGFRI symptom index score	34	59	54	57	38	52	66	34	58	59	

FACT-EGFRI symptom index score, the possible range of scores is from 0 to 72. To obtain the 0–72 score, each item response was subtracted from 4 so that 0 indicates low QoL and 4 indicates high QoL. Numerical ratings: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much

FACT-EGFRI-18 Functional Assessment of Cancer Therapy Epidermal Growth Factor Receptor Inhibitor 18; *Q* question number of FACT-EGFRI-18; *SUM* item subscore: responses of all ten patients per item together

Table 3 Site of Adverse event and symptom burden

Patient no.	Question by the interviewer: Would you please tell me which items were difficult to understand and why they were difficult?	Answers given
4	Q16: Sensitivity around my fingernails makes it difficult to perform household tasks.	Q16: I do not have household tasks, but I experience hinder from the sensitivity around my fingernails.
	Q17: I am bothered by hair loss.	Q17: I have hair loss, but I'm not bothered by it
5	Q1: My skin or scalp feels irritated.	Q1: Depending on where it is. On the scalp since a little while (appeared first in the face, body). Now also on the head, neck & sideburns.
	Q6: My skin condition interferes with my ability to sleep.	
	Q17: I am bothered by hair loss.	Q6 & Q17: do you want to know if it developed or if I suffer from it?
7	Q2: My skin or scalp is dry or "flaky".	Q2: I had already dandruff, that's why difficulty to tell.
	Q17: I am bothered by hair loss.	Q17: hair is flatter and curlier, so different.

Patient no 1, 2, 3, 6, 8, 9, and 10 reported no difficulties

Patient no. 5 experienced the highest impact of symptom burden on his HRQoL. He rated question no. 5, physical domain about skin's sensitivity to the sun, with a 4 (very much), while his comment was as follows:

> I wear shirts with long sleeves and long trousers; I wear a cap, even when swimming. It has been a torture. If I do not do this, I get second degree burns (I had these on hands). It hinders in the freedom and interaction with others. The situation is just worthless, restricting movement, 'bothered' is too mild; I have had a lot of trouble. It is now limited, because I always sit under the umbrella out of the sun now.

Patient no. 8 rated with a 3 (quite a bit) on question no. 7, social/emotional domain: "My skin condition affects my mood," while her comment was the following:

> Do you see how I look? I even no longer have a face; I look stupid; that makes me sad.

Patient no. 5 rated with a 3 (quite a bit), on question no. 12, functional domain: "Changes in my skin condition make daily life difficult," while his comment was as follows:

> I have very much difficulty with sitting and lay down because of my pimples between my buttocks, and all day care; I rub twice a day with various ointments.

On the other hand, there were comments from the patient which did not match the previously given numerical ratings of the same question. For example, patient no. 6 rated a 1 (a little bit) on question no. 5, physical domain: "I am bothered by a change in my skin's sensitivity to the sun," while his comment was the following:

It burns while sitting in the car and the sun burns on the window; then I have to change my seat to the opposite side in the car.

The greatest inconsistency between the numerical rating and the given comments was in the social/emotional domain. Patient no. 9 rated a 0 (not at all) on question no. 7, social/emotional domain: “My skin condition affects my mood,” while his comment was as follows:

I get grumpy, easily irritated; I don’t allow the grandchildren to kiss me, I find it unpalatable.

Also, patient no. 9 rated a 1 (a little bit) on question no. 8, functional domain: “My skin condition interferes with my social life,” while his comment was the following:

Greetings are cooler and I avoid touching others.

Six patients gave feedback that not all the mcAEs they wanted to report were included in the questionnaire. For example, questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and tingling sensations, and pain touching the hair were symptoms patients mentioned that, in their view, should be added to the questionnaire.

Discussion

Major findings

In our study, a number of major findings are noted. Items that assess physical symptoms cause the highest HRQoL impact; an inverse correlation between the intensity of mcAEs and HRQoL is found. Patients wanted additional items added to the FACT-EGFRI-18 questionnaire. Overall, patients found it useful to discuss their experienced mcAE burden.

Many health-care practitioners assume the cosmetic appearance of rash to be most troublesome to the patients; however, this was not supported by patient data. Based on the interview results, we identified that symptom burden associated with mcAEs are interfering most with HRQoL. The physical discomfort, “Increased sensitivity to sunlight (burning sensation),” “itching of the skin or scalp,” and “bleeding of the skin” were symptoms patients identified as having the most impact on their HRQoL. Results of our study were consistent with the results in the study of Wagner and Lacouture [6], who also identified physical discomfort as the most troublesome with sensations of pain, burning, and skin sensitivity having the most HRQoL impact.

The patients’ natural inclination was to rate their symptom severity rather than the extent to which it interfered with HRQoL. Based on some inconsistencies between numerical rating and the associated comments, there is a possibility that our instructions were not clear enough. Our participants felt the need to rate the experienced mcAEs instead of the experienced influence of the mcAEs on their HRQoL. When patients can separately rate the mcAEs and the influence of the mcAEs on their HRQoL, they may be able to better capture the effects on HRQoL. Combining

the mcAE-related HRQoL with the experienced mcAEs in a two-part scale could be interesting for future research. As more and more patients will be treated with EGFRI, it will become increasingly important to understand the multidimensional experiences of mcAE-associated HRQoL. This is an important challenge for health-care providers in their effort to assess PROs.

During the qualitative interviews, patients gave a wide range of information about their experiences regarding the FACT-EGFRI-18. They gave additional information regarding the mcAEs they experienced and their struggle to cope with them. It was interesting that patients emphasized being grateful for receiving anticancer treatment, while their family was focused on the HRQoL including the experienced mcAEs.

Six patients responded that they miss the possibility to rate some mcAEs in the FACT-EGFRI-18 (Table 4). This suggests that not all the mcAEs can be reported while patients feel the need to do so. Questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and tingling sensations, and pain touching the hair and some space for additional comment were mentioned by the participants as items that should be added. Other oral issues like sensitive teeth, taste changes, oral sensitivity/pain at rest, eating, and oral burning sensation are additional mcAEs to consider for assessment. As it is important to cover relevant symptoms and domains to find valuable information without making a questionnaire too lengthy, we recommend adding these mcAEs in a next version, since not all mcAEs are assessed now.

Table 4 Participant recommendations for additional mcAE items

Patient no.	Question by the interviewer: Is there anything else that should have been included related to your skin condition? Would you please tell me what should be added?
1	Dry mouth, little saliva, also in the nose
2	Nothing to add
3	Nothing to add
4	Dry mouth
	Nasal crusts
	I often have to blow my nose (runny nose), at night it is the opposite: very dry
5	Nosebleed because of the pimples in the nose and thin skin on the whole body
6	Hands and feet; cracks, very hard cuticles
	Pain occurs in the skin, not beneath the skin
	Sensitive eyes
	Seeing double
	Rub the eyes
7	Nothing to add
8	Space for notes on the answers chosen
9	Nothing to add
10	Tickling sensation on the skin like an insect walking
	Tore scalp, painful/ stinging, (as though you throat is being cut)
	Tingling on hair border, touching the hair hurts

Study limitations

One of the study limitations was the relatively small patient sample; however, the data collected were qualitative, and no statistical analyses were completed. It has to be mentioned that the ten patients are required by the FACIT organization as mentioned in the “Background” section. Patients had different kinds of cancer, EGFRI treatment, and mcAEs, which may have caused unbalanced data. At the same time, different cancers and treatment allow testing of the questionnaire across a range of patients. To develop a questionnaire suitable for all mcAEs can be challenging. Different mcAEs can be present with a more or less pronounced symptom burden and the interference with the patients’ life situation depending of the experienced mcAEs. The questionnaire addresses mainly the cutaneous AEs (17 questions) and only one question addresses mucosal AEs (dry eyes).

Clinical and research implications

As more and more patients will be treated with targeted therapies including EGFRI, it becomes increasingly important to understand the multidimensional experiences of these agents associated mcAE-related HRQoL. Use of validated and standardized tools will allow comparison of outcomes in different studies and in meta-analyses, to advance patient care and improve outcomes.

A mcAE PRO should consist of three separate parts where part I describes demographic data, part II, the mucocutaneous-specific symptom burden, and part III, the impact of the mucocutaneous-specific symptom burden on HRQoL. Further development with more mcAE items incorporated and combined with symptom assessment will provide more complete information. Since mcAEs are also elicited by other targeted anticancer therapies such as non-EGFRI tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and BRAF inhibitors, it would be worthwhile to develop one questionnaire suitable for all these targeted agents instead of only for EGFRIs.

Conclusion

Results from the first experiences with the FACT-EGFRI-18 described how negatively affected patients who receive EGFRI can be with a pronounced symptom burden and impaired HRQoL. Based on the interview data, we identified that the physical items associated with mcAEs are interfering most with HRQoL. These results are consistent with the results in the study of Wagner and Lacouture, who also identified physical discomfort as the most troublesome and having the most HRQoL impact.

Since participants wanted to rate the prevalence, intensity, and also the duration of the symptoms, while we were interested in the distress from the symptoms, a two-step measurement tool assessing both symptom burden and HRQoL would be more appropriate in this population. The fact that the FACT-EGFRI-18 only evaluates HRQoL, not symptoms, that not all the experienced mcAEs can be assessed, and that is developed for one kind of targeted therapy, implicates further research needs.

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Conflict of interest The authors declare no conflicts of interest. All authors had full control of all primary data and agree to allow the journal to review the data, if requested.

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References

1. Balagula Y, Garbe C, Myskowski PL, Hauschild A, Rapoport BL, Boers-Doets CB, Lacouture ME (2011) Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. Int J Dermatol 50(2):129–146
2. Iacovelli L (2007) Clinical management of EGFRI-associated dermatologic toxicities: pharmacy perspective. Oncology (Williston Park) 21(11 Suppl 5):31–33
3. Lacouture ME, Melosky BL (2007) Cutaneous reactions to anticancer agents targeting the epidermal growth factor receptor: a dermatology-oncology perspective. Skin Therapy Lett 12(6):1–5
4. Perez-Soler R, van Cutsem E (2007) Clinical research of EGFR inhibitors and related dermatologic toxicities. Oncology (Williston Park) 21(11 Suppl 5):10–16
5. Hu JC, Sadeghi P, Pinter-Brown LC, Yashar S, Chiu MW (2007) Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. J Am Acad Dermatol 56(2):317–326
6. Wagner LI, Lacouture ME (2007) Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective. Impact on health-related quality of life and implications for clinical management of psychological sequelae. Oncology (Williston Park) 21(11 Suppl 5):34–36
7. Cleeland CS (2007) Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr 37:16–21
8. Fayers PM, Hand DJ, Bjordal K, Groenvold M (1997) Causal indicators in quality of life research. Qual Life Res 6(5):393–406
9. Wilson IB, Cleary PD (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 273(1):59–65
10. Ferrans CE, Zerwic JJ,Wilbur JE, Larson JL (2005) Conceptual model of health-related quality of life. J Nurs Scholarsh 37(4):336–342
11. Joshi SS, Ortiz S, Witherspoon JN, Rademaker A, West DP, Anderson R, Rosenbaum SE, Lacouture ME (2010) Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 116(16):3916–3923

12. Cella DF (1994) Quality of life: concepts and definition. J Pain Symptom Manag 9(3):186–192
13. Ratanatharathorn V, Sirilerttrakul S, Jirajarus M, Silpakit C, Maneechavakajorn J, Sailamai P, Sirisinha T (2001) Quality of life, functional assessment of cancer therapy-general. J Med Assoc Thail 84(10):1430–1442
14. Wagner LI, Lai SE, Aneja M, LoRusso P, Perez-Soler R, O'Brien B et al (2007) Development of a functional assessment of side-effects to therapy (FAST) questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors (EGFRI): the FAST-EGFRI. J Clin Oncol ASCO Meet Abstr 25(18Suppl):19532
15. U.S. Food and Drug Administration (2009) Guidance for industry: patient-reported outcomes measure: use in medical product development to support labeling claims. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
16. Willke RJ, Burke LB, Erickson P (2004) Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin Trials 25(6):535–552
17. Calvert MJ, Freemantle N (2003) Use of health-related quality of life in prescribing research. Part 1: why evaluate health-related quality of life? J Clin Pharm Ther 28(6):513–521
18. Calvert MJ, Freemantle N (2004) Use of health-related quality of life in prescribing research. Part 2: methodological considerations for the assessment of health-related quality of life in clinical trials. J Clin Pharm Ther 29(1):85–94
19. National Cancer Institute Cancer Therapy Evaluation Program (2010) Common terminology criteria for adverse events and common toxicity criteria [v4.0]. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40
20. Wagner LI, Rosenbaum SE, Gandhi M, Webster K, Aneja MS, Cella D et al (2010) Development of a functional assessment of chronic illness therapy questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors: FACTEGFRI. J Clin Oncol 28 [15s], (suppl; abstr 9046)
21. FACIT.org (2010) Functional Assessment of Chronic Illness Therapy (FACIT). http://www.facit.org/FACITOrg/Questionnaires
22. Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 1:79–84
23. Bonomi AE, Cella DF, Hahn EA, Bjordal K, Sperner-Unterweger B, Gangeri L, Bergman B, Willems-Groot J, Hanquet P, Zittoun R (1996) Multilingual translation of the Functional Assessment of Cancer Therapy (FACT) quality of life measurement system. Qual Life Res 5(3):309–320

24. Eremenco SL, Cella D, Arnold BJ (2005) A comprehensive method for the translation and cross-cultural validation of health status questionnaires. Eval Health Prof 28(2):212–232
25. Cella D,Webster K (1997) Linking outcomes management to quality of-life measurement. Oncology (Williston Park) 11(11A):232–235

08 | General discussion, summary & future perspectives

General discussion and summary

This thesis presents three notable findings: the voice of the patient is inconsequently incorporated in scientific research regarding AEs; available instruments may be of limited value for approaching targeted therapy-associated mucocutaneous AEs; and available knowledge about a patient-driven approach to AEs is not broadly incorporated in research and clinical care.

The voice of the patient is inconsequently incorporated in scientific research and the HCP plays the central role in AE diagnosis and management. The incidence of the AEs is mainly measured by HCP's with suboptimal scales. As a result there may be underreporting of AEs. In addition, the non-validated CTCAE scoring system for the grading of the AEs is most commonly used while more precise grading instruments are available. Currently, most AE grading is performed by HCP's rather than by patients.

The instruments evaluated in this thesis may be of limited value for the education, assessment, reporting, grading, and evaluation of targeted therapy-associated mucocutaneous AEs since:

- there is no consensus on AE terminology, and therefore the same AEs may be diagnosed and named differently
- the majority of the instruments currently used were not developed for the AEs associated with targeted therapies
- some instruments were developed specifically for subgroups of the targeted agents; EGFRI, mTORI, and TKI
- not all the known symptoms and signs of AEs are incorporated in current instruments
- the majority of the instruments are not validated, and
- the majority of the instruments are not available in multiple languages.

In addition, the number proven approaches for the treatment of skin and mucosal AEs is limited. Studies to date mainly report secondary outcomes of larger studies with other primary outcomes. Furthermore, the AE studies are based on inconsistent terminology and the AEs are assessed and graded with suboptimal scales. There is a lack of prospective studies investigating the terminology, symptoms and signs of AEs, their impact on health related HRQoL, the reporting of AE characteristics, grading the AEs, and management of AEs with scales specifically developed for targeted agents. Instruments for PRO and CRO are available, but they are not used consequently.

Current knowledge about a patient-driven approach including education, terming, assessing, reporting, grading, evaluating, and treating targeted therapy specific AEs is not imbedded broadly in research.(1) In the several manuscripts of this dissertation

one or more of these crucial steps is addressed. The instruments evaluated in this dissertation are listed in **box 1**.

Box 1. Evaluated instruments listed in alphabetical order

- **Bristol Stool Chart:** The Bristol Stool Chart focuses on variation in consistency of stool.(2) The stools are classified into seven types, with types 5 and 6 tending towards diarrhea but still loose or mushy stool and type 7 actually diarrhea, watery stool. Since according to the NCI-CTCAE definition only type 7, the watery stool, is diarrhea, the differences between the two types is important.
- **DERETT:** The Dermatological Reactions Targeted Therapy (DERETT) is a targeted therapy specific instrument with focus on the assessment of the mucocutaneous AEs and the influence of these AEs on HRQoL. DERETT is available in two versions, a symptom experience diary for patients (DERETT-P) and a symptoms & signs assessment instrument (DERETT-H) for HCPs. These instruments gather information such as area involved, severity and duration of the symptoms, products used to treat symptoms, effectiveness of the supportive care interventions, treatment adherence, and symptom-related distress.(3)
- **EA:** The Experimental Assessment (EA) is an oral assessment instrument that assesses a number of symptoms using Visual Analogue Scale (VAS) (0–10) including dysgeusia, dysphagia, odynophagia, and oral mucosal pain which are subjective parameters. The scale adds an objective measure of mucosal erythema and ulceration.(4) The EA may have utility in assessing TKI- and mTORI-induced oral AEs.
- **FACT-EGFRI-18:** The Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18 (FACT-EGFRI-18) is an 18-item Likert-scaled PRO questionnaire. It is arranged in three HRQoL domains: physical (7 items), social/emotional (6 items), and functional well-being (5 items).(5-7) The validation of the Dutch Version of the FACT-EGFRI-18 is part of the BeCet trial.
- **FACT-G:** The Functional Assessment of Cancer Therapy-General (FACT-G) is a cancer specific instrument with focus on PRO measures using numerical analogue scales (0=not at all, 4=very much). The FACT-G version 4 consists of 27 items in four HRQoL domains: physical (7 items), social/family (7 items), emotional (6 items), and functional well-being (7 items).(8)
- **FAST-EGFRI:** The Functional Assessment of Side-Effects to Therapy-EGFRI (FAST-EGFRI) is an EGFRI specific instrument with focus upon the assessment of HRQoL.(7) The 38-item FAST-EGFRI was the first EGFRI specific HRQoL questionnaire.
- **MESTT**: The MASCC EGFR Inhibitor Skin Toxicity Tool© (MESTT) is a grading system for the most common EGFRI-associated mucocutaneous AEs.(9) The MESTT is an event-specific grading system that can be used to standardize assessment, optimize the use of EGFRIs, and enable researchers to conduct more

informative, controlled studies in this patient population. The scale is consistent with grading principles and language of the CTCAEv4.0.

- **mIAS scale:** The mammalian target of rapamycin inhibitor (mTORI)-associated stomatitis (mIAS) scale is a mTORI specific instrument with focus on mIAS.(10) This scale has a subjective component measuring pain and an objective component measuring duration of lesions.
- **MOATT**: The MASCC Oral Agent Teaching Tool© (MOATT) was developed to meet an identified need for HCPs involved in the education of patients receiving oral anticancer agents. The MOATT provides a structured format to ensure that all key areas of patient assessment and teaching are addressed. It allows for individualized teaching and uses evidence-based tenets in patient education. The MOATT is well researched and easy to use.(11)
- **NCI-CTCAE:** The National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE) is a general instrument used by clinicians to report toxic effects of cancer treatment. Currently, decisions about dose modifications due to AEs are based on clinician assessment utilizing the CTCAE grading system. Despite its widespread use and its utility, the CTCAE has not been validated.(12)
- **NCI-PRO-CTCAE**: The National Cancer Institute's Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE) system provides a web-based platform to collect patient reports of symptoms for the purpose of enhancing AE reporting and grading.(12, 13)
- **OMAS:** the Oral Mucositis Assessment Scale (OMAS) focuses on objective measure of mucosal ulceration and erythema.(14)
- **Oral Care Protocol** is a generic education instrument with focus on oral hygiene.(15)
- **SF-36:** The 36-Item Short Form Health Survey (SF-36) focuses upon the measurement of functional status in general and specific populations, including oncology.(16) The questionnaire covers eight scales: physical functioning, role limitations due to physical health and due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.
- **SKINDEX-16:** The Skindex-16 is a PRO assessing dermatological symptoms for general skin diseases using a numerical analogue scale. It contains three domains: symptoms (4 items), emotions (7 items), and functioning (5 items). It has been used to assess HRQoL in patients receiving EGFRI, but does not address symptoms related to hair, nails, or mucous membranes, that are specific targets for EGFRIs.(17)
- **VHNSS2.0:** The Vanderbilt Head and Neck Symptom Survey (VHNSS) version 2.0 was designed to screen both for tumor and treatment-related symptoms in patients with head and neck cancer undergoing concurrent chemoradiation. It assesses patient-reported symptom burden in the head and neck area and function loss within symptom subscales, including nutrition, taste, pain, voice, swallow, and mucous/dry mouth.(18, 19) The **modified VHNSS2.0** is adapted from the original

VHNSS2.0 to make it suitable for the targeted therapy population and is being tested in the COMTT trial.(3)

- **WHO OTS:** The World Health Organization (WHO) Oral Toxicity Scale (OTS) classification of oral toxicity that combines descriptions of mucosal changes, pain, and functionality into a single composite score(20, 21) that is mainly driven by the patient's ability to eat and drink.

In **chapter 2** the terminology of TKI and mTORI-associated oral AEs, assessment of symptoms and signs, grading and treatment of the AEs as one entity were addressed. The objective of this study was to provide an overview of the prevalence and characteristics of oral AEs with TKI and mTORI treatment and the current oral assessment instruments commonly used in clinical trials. It was discussed how these novel AEs can be assessed because current mucositis instruments have limitations for this patient population. Also explored were the correlations between oral AEs and HFSR and rash.

No consensus on AE terminology was found. This finding is consistent with the findings in the literature. The terminology and classification of oral AEs associated with targeted therapies has been inconsistent throughout different clinical trials. This makes comparison of AE data difficult. In the literature, the terms mucositis and stomatitis are used interchangeably, however, they do not reflect the same clinical condition.(12, 22) 'Stomatitis' refers more generally to any inflammatory condition of oral tissues,(12) but has been recommended for use in oncology in lesions with aphthous-like appearance such as oral lesions associated with targeted therapies. In a review article on the AEs of temsirolimus for the treatment of renal cell carcinoma, the frequencies of mucositis, stomatitis, aphthous stomatitis and mouth ulceration were reported as distinct categories, while the differences between these descriptors were not defined.(23) Moreover, mucosal inflammation and tongue ulceration were reported as distinct oral AEs.(24) There is consensus among oral medicine specialists managing patients with oral mucosal lesions associated with mTORIs that the specific term of mTOR inhibitor-associated stomatitis (mIAS) is preferable to the general term oral mucositis which is associated with cytotoxic chemo- and radiotherapy.(22, 25-28)

The newly developed PRO DERETT-P and CRO DERETT-H,(3) wherein common mucocutaneous AEs are listed by subtype, and the modified VHNSS2.0 may be of help in assessing the signs and symptoms of the related AEs in detail.

Generic oral AE scales OMAS and WHO OTS are available, however these are not specific for targeted therapies. No controlled trials have assessed the management of TKI- and mTORI-induced oral AEs as the primary outcome measure. Interventions for persistent TKI- or mTORI-related oral AEs, currently may include corticosteroids and other anti-inflammatory agents as well as supportive treatments such as local anesthetics and antimicrobials.(29)

Chapter 3 addressed the prevention, terming, assessment of AE symptoms and signs, reporting, grading, and treatment of the AE as one entity and by subtype of mTORI-associated mucosal AEs. The objective of this chapter was to provide an up-to-date review of the clinical presentation, terminology, pathogenesis, assessment and management of mIAS and other mTORI-associated oral AEs.

For the prevention of conventional oral mucositis and targeted therapy-associated stomatitis, most recommendations begin with oral care plans coupled with patient education.(15, 30) A range of products are currently in development for the prevention and management of oral AEs that fall into four main categories: cell resistance modifiers, mechanism specific inhibitors, damage control agents, and healing accelerators. However, to date, proven approaches for the prevention and treatment of oral AEs are limited.(30, 31)

Generic and specific CRO instruments are available to assess the incidence of targeted therapy-associated oral AEs. In the majority of the papers the CTCAE grading instrument(12) is used to assess the incidence of AEs, while this instrument is not developed for this purpose. The CTCAE is a blunt instrument, developed to grade the severity of AEs. For assessing the incidence of targeted therapy-associated oral AEs the oral assessment instruments OMAS(14) and WHO OTS(20, 21) are available. Because of the symptoms of targeted agents-associated stomatitis, the modified version of the VHNSS, version 2.0,(3) the mIAS scale(10) and the EA(4) are potentially useful to assess oral AEs. The Bristol Stool Chart can be used to measure the gastrointestinal mucosal injury, namely the consistency of stool to be able to make a distinction between e.g. diarrhea and loose or mushy stool.(2)

We found that a variety of grading scales for staging the severity of targeted therapy-associated mucocutaneous AEs are available, while these scales are rarely used in research and daily practice. There is a gap between the availability and the use of these scales as seen in the literature. Currently, the CTCAE is commonly utilized in oncology clinical trials by clinicians to report overall toxic effects of cancer treatment.(12) Consequently, decisions about dose modifications due to AEs are based on clinician assessment utilizing the CTCAE grading system. It is noted that, despite its widespread use and utility, drawing conclusions out of the CTCAE for the treatment of the AE is sub-optimal, since the CTCAE is not a validated instrument, and has weaknesses in differentiation levels of severity of AE and does not specifically assess the impact on HRQoL.

In **chapter 4** the prevention, terming, assessment of AE symptoms and signs, grading, and treatment of the AEs of chemotherapy, radiation therapy and targeted therapy-associated mucosal injury in the ESMO guidelines was discussed. Accurate assessment of the morbidity of the mucosal AEs will allow for informed decisions on dose modification and interruption, which may have far reaching consequences. The development of specific instruments for targeted therapy-associated mucosal AEs seems justified.

It was found that no controlled trials have assessed the management of targeted therapy-associated mucosal AEs as a primary outcome measure. While there is currently no systemically derived evidence for an approach to management, since targeted therapies are associated with inflammation and localized and systemic infection, mucosal hygiene, anti-inflammatories, and pain management may be considered until a more comprehensive, evidence-based approach has been defined. In the absence of confirmatory data from clinical trials, expert opinion-based recommendations can be considered. These statements reflect the state-of-the-science as it presently exists.(22, 27, 28)

In **chapter 5** we report that xerosis and pruritus have a major negative impact on HRQoL during the first 6 weeks of EGFRI treatment. The objective of this sub-analysis of the BeCet study was to examine HRQoL of patients experiencing skin AEs during the first 6 weeks of EGFRI treatment, using five different questionnaires. AEs were reported in DERETT-P. The impact of EGFRI-associated dermatological AEs on HRQoL was examined using four HRQoL questionnaires; FACT EGFRI-18, FACT-G, SF-36, and the Skindex-16. The findings are congruent with the findings in the STEPP trial.(32, 33) In literature, xerosis and pruritus are less frequently addressed EGFRI-associated skin AEs. As a result, not all patients are counseled about these possible skin AEs before initiating treatment. However, providing patients adequate information about possible AEs and their treatment has shown a positive result on patients' emotional and physical well-being.(34-36) Counseling patients prior to EGFRI treatment about potential xerosis and pruritus is therefore important, as well as taking preventive measures against these AEs.(37-40)

The targeted therapy specific instruments that have been evaluated in these studies, are the DERETT-P,(41, 42) FAST-EGFRI,(7) and FACT-EGFRI-18.(6) The DERETT-P is mainly a symptom and signs scale but includes questions like "which symptoms bothered you most?", "why?", and "How much did the symptoms influence your HRQoL?" The FAST-EGFRI is the preliminary version of the FACT-EGFRI-18 and in this thesis we report the use of an English and Dutch version of the FACT-EGFRI-18. Because measures of HRQL describe the patient's experience as the result of therapeutic care, they are valuable and vital additions to physiological or biological measures of health status.(43) The HRQoL assessment instruments we have used are the SF-36,(36) the FACT-G,(8, 35) and Skindex-16.(17)

There is a discongruity in functional domains in the different scales that were evaluated throughout this thesis. The SF-36 covers eight scales: physical functioning, role limitations due to physical health and due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.(16) Within the FACT-G the following three HRQoL domains are addressed: physical, emotional, and social well-being /family.(44) Skindex-16 addresses symptoms, emotions, and function,(45) while the FAST-EGFRI and the FACT-EGFRI-18 are constituted by physical, social/emotional, and functional well-being domains.(6, 7) These different

formats complicate the comparison of the outcomes of the different scales and differences between studies.

It was found that there are no reporting instruments available which address solely the AE characteristics. The targeted therapy specific instruments DERETT-P and DERETT-H have items regarding reporting AE characteristics incorporated. The DERETT-P questionnaire also allows report of the severity of the AEs and which AE was most impactful. In the open fields in the diary, patients can elucidate their AEs. In a drawing they can record the site of the AEs; questions about the appearance of the symptoms and signs and the duration of the AEs are incorporated.(3, 41) In addition, the 'objective' reporting of AE characteristics may be supported by photographs, biopsies and swabs.

Evaluation of the outcome of an intervention and education is critical in ongoing care. It was found that no evaluation instruments in the literature exist that specifically address the outcome of the applied measures for targeted therapy-associated AEs. The targeted therapy specific instruments DERETT-P and DERETT-H have evaluation items incorporated, however. Questions about the taken measures and the effect of the taken measures are incorporated in both versions of DERETT.(3, 41)

Chapter 6 addressed the translation and linguistic validation of the FACT-EGFRI-18 instrument from English into Dutch. The translation was accomplished by employing the Functional Assessment of Chronic Illness Therapy (FACIT) multilingual translation methodology. The FACT-EGFRI-18 only evaluates HRQoL and not symptoms, not all skin and mucosal AEs can be assessed, and it is only available for one type of targeted therapy. The above points justify further development of this questionnaire for use in targeted therapy.

Despite the fact that the Dutch version of the FACT-EGFRI-18 seems to be content-wise and linguistically valid (chapter 6), we found in **chapter 7** that from the patients' point of view, the questionnaire can be improved on several points. FACT-EGFRI-18 evaluations show:

1. The FACT-EGFRI-18 provides 17 items addressing the skin and only one item addressing the mucosa.
2. In addition to assessing the impact of the AEs on a patients' HRQoL, patients also felt the need to rate their symptom burden. The patients' natural inclination was to rate the prevalence, intensity, and duration of the symptoms rather than the extent to which it interfered with HRQoL, based on the interpretation of the questions.
3. Some inconsistencies between numerical rating and the associated comments suggest that clear instructions regarding completion of the instrument needs to be provided.
4. Six out of the ten patients gave feedback that not all the skin and mucosal AEs were included in the questionnaire. Questions regarding sensitive eyes, a runny nose, bloody or crusty nasal cavity due to pimples, dry mouth, tickling and

tingling sensations, pain touching the hair, and some space for additional comment were mentioned by the participants as items that should be incorporated into the questionnaire.

5. Patients reported difficulties in 5 of the 18 items pertaining to the location and the relationship of the skin and mucosal AEs with EGFRI treatment; e.g. how a flaky scalp should be scored if a patient already experienced dandruff, and how to respond on the question about the interference with household tasks when the patient does not do any, but is bothered by sensitivity around the fingernails.
6. The partner/child of a patient noticed that there was a greater impact of the symptom burden on the HRQoL than the patient rated. While patients stressed being grateful for receiving anticancer treatment, their families appeared to be more focused on the HRQoL of the patient including skin and mucosal AEs.
7. Patients expressed an appreciation for the opportunity to discuss their difficulties coping with their skin and mucosal AEs.

The above points justify further development of this questionnaire for use in targeted therapy. Additional mucocutaneous AE items in combination with symptom assessment will provide more complete information. Since skin and mucosal AEs are also elicited by other targeted anticancer therapies such as non-EGFRI tyrosine kinase inhibitors, mTORI, immuno-oncology and BRAF inhibitors, it would be worthwhile to develop a questionnaire suitable for all these targeted agents instead of only for EGFRIs.

In the various articles for this thesis, one or more of the six components of a systematic AE approach are addressed. In addition, the preventive measures including education, AE terminology, assessment of the AE symptoms and signs, reporting the AE characteristics, grading the severity of the AEs, evaluating and (re-) education about the taken AE measures, and AE treatment are discussed. **Table 1** provides an overview of AE steps referred and studied in each manuscript. As outlined in **Table 2**, there are instruments developed to assess targeted therapy-associated AEs by PRO and CRO. In addition, instruments not specific developed for these agents can be considered for use as well.

Future perspectives

The approach to AEs and effective prevention and treatment of AEs are an important part of the optimal treatment for patients receiving targeted therapies. Figure 1 uses this base and illustrates a new model of a patient-driven AE co-care approach.

Patients and HCPs start and end the AE approach together, while the assessments before and during therapy can be performed separately but in close collaboration with each other, yielding more comprehensive evaluation and leading to improved

TABLE 1. Overview of the adverse event steps referred and studied in each manuscript

Chapter	**Adverse Events**		**Education**	**Terming**	**Assessment** Symptoms & Signs of AEs			**Reporting**	**Grading** AE Severity		**Evaluation**	**Treatment**
	skin	mucosal	preventive measures	AEs	by CRO	by PRO	impact on HRQoL	AE characteristics	by CRO	by PRO	taken measures	AEs
2. Oral AE's associated with TKI & mTORI in RCC	referred (2)*	studied (11)*	no	studied	studied	studied	no	no	studied	referred	no	referred
3. mTORI-associated stomatitis	no	studied (7)*	studied	studied	studied	studied	no	referred	referred	referred	no	referred
4. Management of oral & gastrointestinal mucosal injury: ESMO Guideline	referred (1)*	studied (3)*	studied	studied	studied	studied	no	no	studied	studied	no	studied
5. Xerosis & pruritus as major EGFRI-associated AE's	studied (29)*	studied (10)*	referred	studied	referred	studied	studied	studied	referred	studied	referred	referred
6. Translation & linguistic validation FACT-EGFRI-18	studied (17)*	referred (1)*	no	studied	no	studied	studied	no	no	no	no	no
7. Experiences with the FACT-EGFRI-18	studied (17)*	referred (1)*	no	studied	no	studied	studied	no	no	studied	no	no

AE = adverse event, HRQoL = Health Related Quality of Life, CTCAE = Common Terminology Criteria for Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; TKI = tyrosine kinase inhibitor; RCC = renal cell carcinoma; mTORI = Mammalian Target of Rapamycin Inhibitor; EGFRI = Epidermal Growth Factor Receptor Inhibitor; *= number of AEs addressed; AEs = adverse events; CRO = clinician rated outcome; PRO = patient reported outcome; HRQoL = Health Related Quality of Life; light grey = referred; dark grey = studied

TABLE 2. Instruments that may be used to chart targeted therapy-associated adverse events

Instruments	**Adverse Events**	**Education**	**Terming**	**Assessment AE Symptoms & Signs**			**Reporting**	**Grading AEs**		**Evaluation**	**Treatment**
	addressed	preventive measures	AEs	by CRO	by PRO	impact on HRQoL	AE characteristics	severity by CRO	severity by PRO	taken measures	AEs
Specific developed for targeted therapies	Generic										
	Skin										
	Mucosa			mIAS scale	modified VHNSS2.0 mIAS scale EA			mIAS scale	modified VHNSS2.0 mIAS scale		
	Muco-cutaneous			Derett-H	Derett-P FACT-Egfri18 FAST-Egfri	Derett-P FACT-Egfri18 FAST-Egfri	Derett-P Derett-H	Derett-H MESTT	Derett-P	Derett-P Derett-H	
General or developed for other treatments	Generic	MOATT				SF-36 FACT-G		CTCAE	PRO-CTCAE		
	Skin					Skindex-16					
	Mucosa	Oral Care protocol		OMAS WHO OTS	VHNSS2.0 Bristol Stool chart			OMAS WHO OTS			
	Muco-cutaneous										

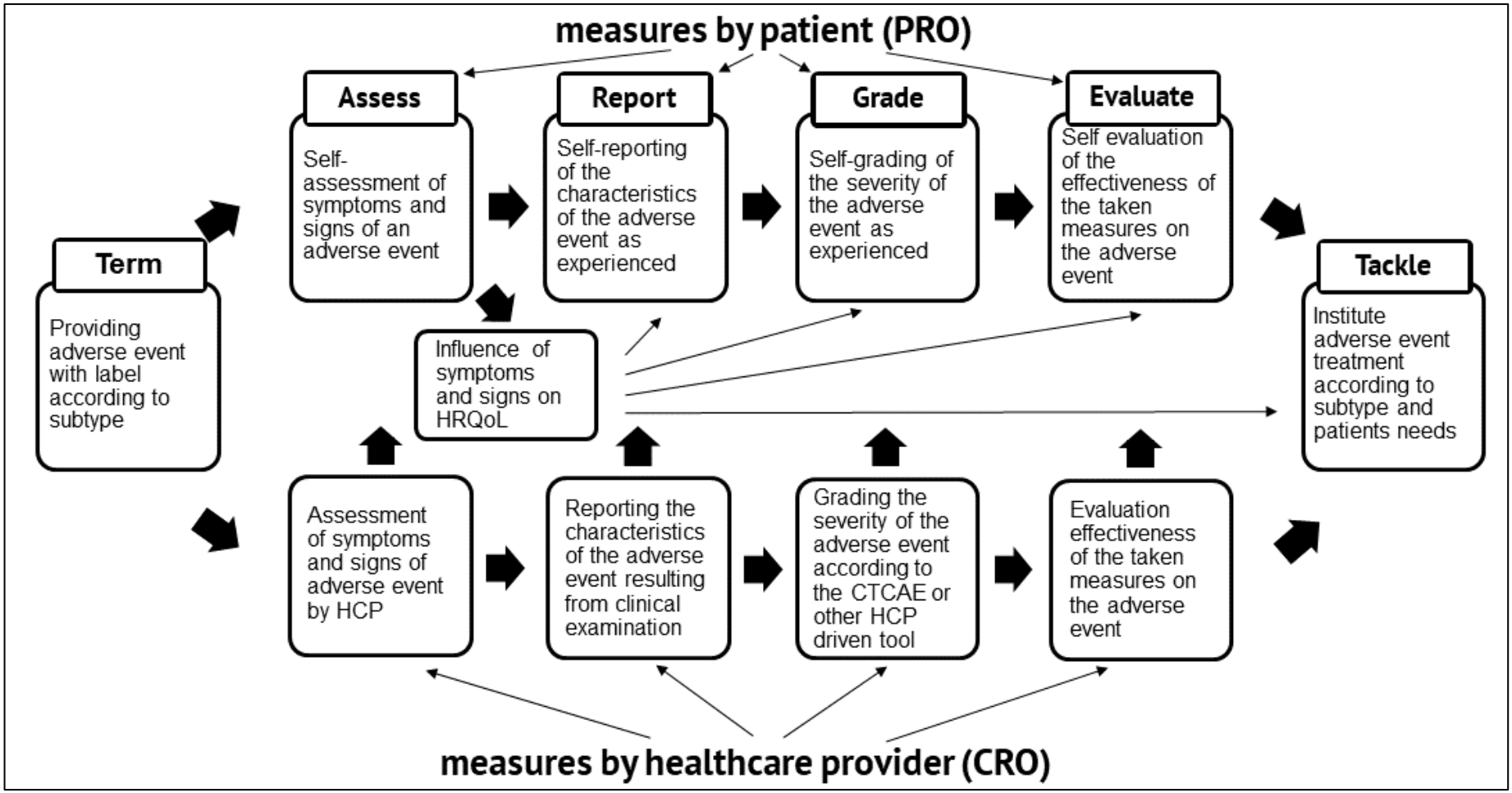
AEs = Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; HRQoL = Health Related Quality of Life; MOATT = MASCC Oral Agent Teaching Tool(11); Oral Care Protocol(15); mIAS scale = mTOR Inhibitor Associates Stomatitis(10); Derett-H = Dermatological Reactions Targeted Therapy-Healthcare Professionals(42); OMAS = Oral Mucositis Assessment Scale(14); WHO OTS = World Health Organization (WHO) Oral Toxicity Scale (OTS)(20, 21); Modified VHNSS2.0 = modified Vanderbilt Head and Neck Symptom Survey version 2.0(3); EA = Experimental Assessment(4); Derett-P = Dermatological Reactions Targeted Therapy-Patients(41); FACT-Egfri-18 = Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18(5); FAST-Egfri = Functional Assessment of Side Effects to Therapy-Epidermal Growth Factor Receptor Inhibitor(7); VHNSS2.0 = Vanderbilt Head and Neck Symptom Survey version 2.0(18); Bristol Stool Chart(2); SF-36 = Short Form Questionnaire(36); FACT-G = Functional Assessment of Cancer Therapy - General(8); Skindex-16 = Skin Index(17); MESTT = MASCC EGFRI Skin Toxicity Tool(46); CTCAE = Common Terminology Criteria for Adverse Events.(12); PRO-CTCAE = Patient-Reported Outcomes version of the CTCAE(13, 47)

outcomes. Patients report AE characteristics and severity, the effect of AE measures and the AE treatment they desire. Patients also report the impact of the AEs on their HRQoL. The HCP is supportive to the patient. At initiation of a new treatment, the patient may need guidance from the HCP in approaching AEs, since the HCP may be expected to be experienced and provide guidance & support where necessary. When a treatment becomes more chronic, a patient will may become more experienced and therefore less dependent on the HCP's support in measuring AEs. For obtaining some AE treatments, patients may be independent of the HCP, e.g.: obtaining hemorrhoid cream, foot salt, vinegar, insoles, and mouth rinses. Other treatments may require the HCP such as for receiving prescription when needed e.g.: antibiotics and corticosteroids. The concept is a co-care model while on chronic targeted therapy treatment, wherein the patient is leading the process and the HCP supports where appropriate.

By following the six steps described, terming, assessing, reporting, grading, evaluating, and treating AEs by their subtype, the scope of the AEs may become more apparent. For both the patient and the HCP, choosing the most appropriate treatment is facilitated by taking these six steps which provides a roadmap that supports the implementation of appropriate treatment options for AEs associated with targeted anticancer therapies.(3) The instruments that may be used to chart targeted therapy-associated AEs are shown in Figure 2. The top of the figure shows the instruments that may be used by the patient while the body of this figure shows the instruments that may be used by the HCP.

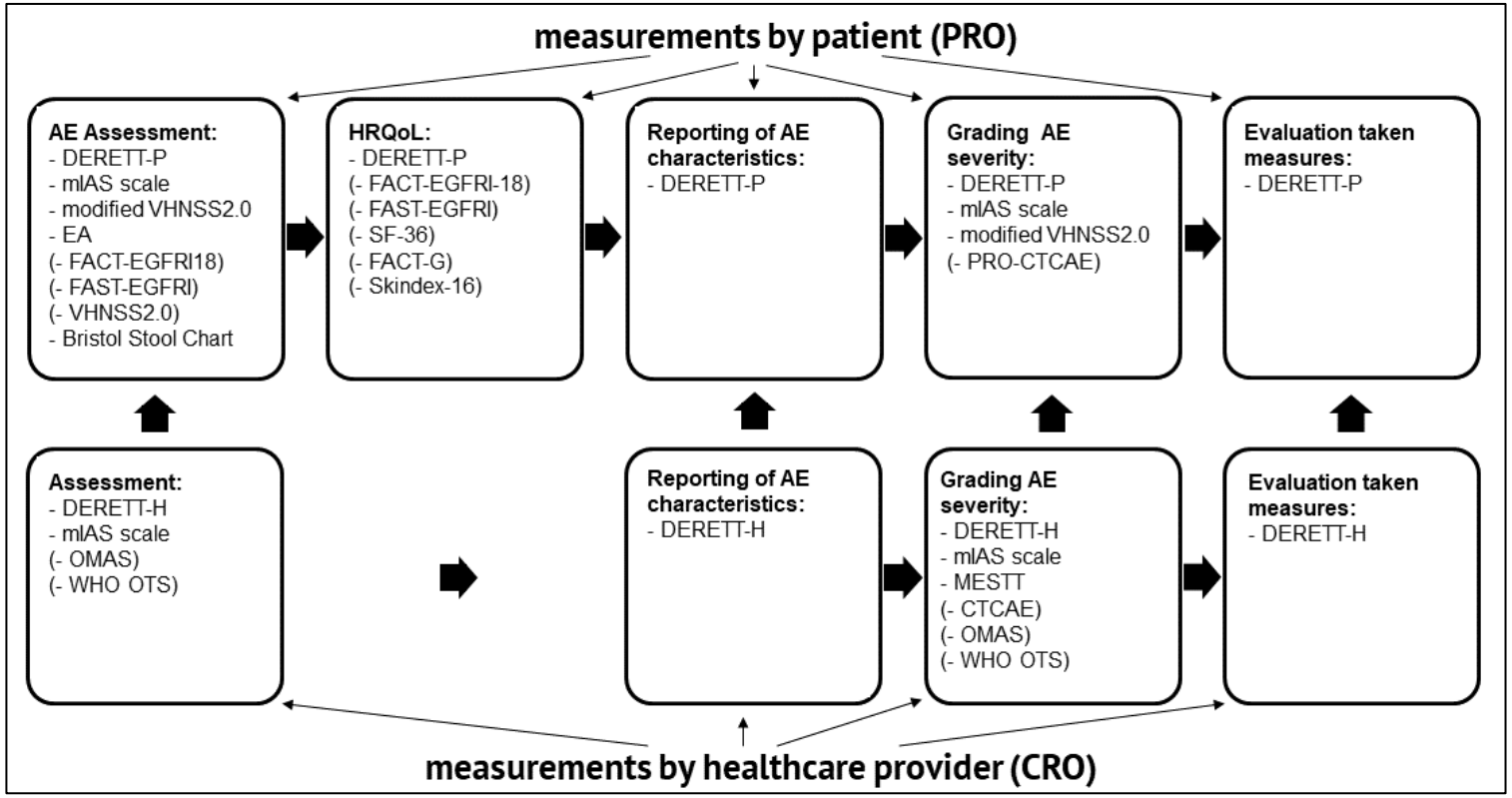
A growing number of patients with cancer will be treated with targeted agents, most frequently as outpatients and over a long time span. Targeted therapies are high cost medications.(48) The cost of targeted therapies is an important consideration, particularly when compared to some traditional chemotherapies. Additional treatment costs include the costs to get all stakeholders trained about effective AE management. Further costs are costs to treat AEs and costs for treatment modifications. This indicates a need for awareness and early recognition of AEs among the patients, oncologists, oncology nurses, dental professionals, dermatologists, pharmacologists, pharma representatives, and basic scientists but also among community HCPs, such as primary care doctors, primary care nurses, dental professionals, and allied health professionals. Scientific knowledge does not, by itself, result in widespread implementation and social impact. The research from the clinic must be translated into practical use. Valorisation is the impact that can be created through the transfer of scientific knowledge.(49) Examples include developing an assessment instrument or applying scientific knowledge to a system or process which can be disseminated through a training program. Some of our findings show high potential for valorisation.

FIGURE 1. Proposed new patient-driven co-care model of approaching adverse events



CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; CTCAE = Common Terminology Criteria for Adverse Events; HCP = healthcare provider

FIGURE 2. Instruments that may be used to chart targeted therapy-associated adverse events



AEs = Adverse Events; CRO = Clinician Rated Outcome; PRO = Patient Reported Outcome; HRQoL = Health Related Quality of Life; mIAS scale = mTOR Inhibitor Associates Stomatitis(10); Derett-H = Dermatological Reactions Targeted Therapy-Healthcare Professionals(42); OMAS = Oral Mucositis Assessment Scale(14); WHO OTS = World Health Organization (WHO) Oral Toxicity Scale (OTS)(20, 21); Modified VHNSS2.0 = modified Vanderbilt Head and Neck Symptom Survey version 2.0(3); EA = Experimental Assessment(4); Derett-P = Dermatological Reactions Targeted Therapy-Patients(41); FACT-Egfri-18 = Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18(5); FAST-EGFRI = Functional Assessment of Side Effects to Therapy-Epidermal Growth Factor Receptor Inhibitor(7); VHNSS2.0 = Vanderbilt Head and Neck Symptom Survey version 2.0(18); Bristol Stool Chart(2); SF-36 = Short Form Questionnaire(36); FACT-G = Functional Assessment of Cancer Therapy - General(8); Skindex-16 = Skin Index(17); MESTT = MASCC EGFRI Skin Toxicity Tool(46); CTCAE = Common Terminology Criteria for Adverse Events(12); PRO-CTCAE = Patient-Reported Outcomes version of the CTCAE(13, 47).

An assessment and grading instrument wherein the presence of AEs and their impact upon HRQoL are incorporated should be developed. As more and more patients will be treated with targeted therapies, alone or in combination with cytotoxic and immunomodulatory medications, it will become increasingly important to understand the multidimensional experiences of AEs. This is an important challenge for patients and HCPs in their effort to assess AEs. Therefore, in this thesis, in addition to assessing the symptoms and signs of the AEs, the influence of the AEs on the HRQoL are addressed and a conceptual co-care model of a patient-driven approach to AEs of targeted therapies is presented.

A continuing concern is the use of the CTCAE instrument since it is still commonly utilized in oncological clinical trials to assess adverse events of cancer treatment.(12) However, most CTCAE items are not specifically developed to grade the severity of targeted therapy-associated AEs and therefore the CTCAE is not recommended for direct application for assessment of targeted therapy-associated AEs. Development of a comprehensive grading system similar to the MESTT(9, 46) seems appropriate for staging the severity of targeted therapy-associated AEs by CRO. DERETT-H has mucocutaneous AE grading items incorporated as well.(42) Grading of the severity and impact of the AEs by the patients themselves as outlined in the AE co-care model may improve diagnosis and management of these specific reactions. For the mucocutaneous AEs DERETT-P seems suitable. For other AEs, a grading tool needs to be developed.

As outlined in chapter 7, the study participants felt the need to rate the experienced mucocutaneous AEs instead of the influence of the mucocutaneous AEs on their HRQoL. Therefore a combined assessment and grading instrument should be developed. When patients can separately rate the mucocutaneous AEs and their influence on their HRQoL, they may be able to better capture the effects upon HRQoL. AEs may be assessed in a three-part scale that may measure:

1. if an AE developed (appearance symptoms & signs)
2. the intensity/severity of the AE (grading)
3. if the patient is distressed/suffers from it (impact AE on HRQoL)

The proposed questionnaire is modeled in Table 3.

To be able to develop evidence based guidelines for the prevention and treatment of targeted therapy-associated AEs, more research in this area is needed. As outlined in chapters 2, 3 and 4 there is currently scant AE evidence upon which to build evidence-based guidelines. More evidence is needed since guidelines based on expert opinion are scientifically not ideal. However, until clinical trials establish evidence base clinical experience, expert opinion is the best available guidance.

By empowering patients to be more involved in their treatment and in the approach of targeted therapy-associated AEs, the entire interdisciplinary team may help patients maintain their HRQoL, promote treatment adherence, and support completion of

TABLE 3. 3-part adverse event assessment and grading instrument

	Was, or is, this symptom or sign present?	Complete only when marked 'yes', so when you **EXPERIENCED** the mentioned symptoms or signs	
		On a scale from 0 – 10, what was the **SEVERITY** of these symptoms or signs at their worst, according to you?	On a scale from 0 – 10, how much did these symptoms or signs **INTERFERE** with your usual activities?
symptoms & signs	Yes/No	0 = not at all; 10 = very severe	0 = not at all; 10 = very much
symptom 1	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
symptom 2	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
symptom 3	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 1	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 2	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10
sign 3 etc.	☐Y ☐N	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10	0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Y = yes; N = no

cancer treatment as planned. Well-designed trials with appropriate terminology, assessment and grading instruments wherein the AE treatment response is the primary outcome measure can bring the evidence desired by patients, HCPs, pharmaceutical companies and the society at large, to bring more HRQoL, enhanced treatment outcome and to conserve resources.

For the generation of a patient-driven AE conceptual co-care model, the critical items are derived from questionnaires and case report forms used in clinical targeted therapy trials.(6, 32, 33, 50-55) For the identification of terms used in patient files the medical records of oncology patients on targeted agents in the Waterland Hospital in Purmerend, The Netherlands were searched systematically from March 2009 until March 2014. Terminology used to describe AEs and recorded missing information has been evaluated in detailed AE diagnoses. Terms were identified in prior grading instruments.(9, 12, 46) The identified components for a systematic, patient-driven targeted therapy-associated AE approach can be summarized in 6 steps:(1, 3)

1. Terming – the establishment of the diagnosis of the AE by subtype
2. Assessing – the identification of symptoms and signs of the AEs and the impact of such an event on a patients' HRQoL
3. Reporting – the collection and reporting of in-depth characteristics of the AEs
4. Grading – the classification of the severity of the AEs
5. Evaluating – the exploration of the taken measures and discussion about the treatments to be initiated
6. Treating – the institution of the most appropriate and effective AE treatment.

The AE management skill is an important competency since there can much be achieved by individuals. However, competencies in AE management alone will not make a sustainable difference for society at large. Competencies in several distinct core areas may improve cancer treatment outcomes. Recommendations include developing:

1. explorative AE trials in a structured way in early phase drug development (phase I and II),
2. long-term advisory boards, steering committees, summits, and roundtables,
3. interdisciplinary teams with key disciplines involved,
4. thorough training of pharma, pharmacists, HCPs and patients,
5. patient centered drug launches, and
6. easy, understandable patient information written in the same format as the HCP information.

These seven measures may promote adherence to the cancer medication, resulting in improved patient outcome.

The work in this thesis lead to recommendations to develop collaboration with patients. The conceptual co-care model of a patient-driven approach to AEs of targeted agents in oncology may be complemented with a 3-part adverse event assessment and grading instrument, evidence based AE treatment guidelines, and obligated educational programs on the AE core competencies, and applied.

References

1. Boers-Doets CB. The TARGET System: Six practical steps from diagnosis to management of adverse events of targeted therapy. Abstracts of the 2015 International MASCC/ISOO Symposium. Support Care Cancer. 2015;23 (Suppl 1):S1–S388(1):70-1.
2. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4.
3. Boers-Doets CB. The Target System - Approach to assessment, grading, and management of dermatological & mucosal side effects of targeted anticancer therapies. Wormer: Impaqtt; 2014.
4. Ferrari V, Sgotti D, Amoroso V, Valcamonico F, Grisanti S, Consoli F, et al. Oral mucositis a side effect in Tyrosin-Kinase Inhibitor Therapy (Sunitinib): the role of assessment of symptoms in evaluation of toxicity. Eur J Cancer Supp. 2009;7(2):195-6.
5. Wagner LI, Rosenbaum SE, Gandhi M, Webster K, Aneja MS, Cella D, et al. Development of a functional assessment of chronic illness therapy questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors: FACT-EGFRI. J Clin Oncol. 2010;28(15 suppl; abstr 9046).
6. Wagner LI, Berg SR, Gandhi M, Hlubocky FJ, Webster K, Aneja M, et al. The development of a Functional Assessment of Cancer Therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors (FACT-EGFRI-18). Support Care Cancer. 2013;21(4):1033-41.
7. Wagner LI, Lai SE, Aneja M, LoRusso P, Perez-Soler R, O'Brien B, et al. Development of a functional assessment of side-effects to therapy (FAST) questionnaire to assess dermatology-related quality of life in patients treated with EGFR inhibitors (EGFRI): The FAST-EGFRI. J Clin Oncol (Meeting Abstracts). 2007;25(18 Suppl):19532.
8. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.
9. Lacouture ME, Maitland ML, Segaert S, Setser A, Baran R, Fox LP, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer. 2010;18(4):509-22.
10. Boers-Doets CB, Lalla RV. The mIAS Scale: A Scale to Measure mTOR Inhibitor-associated Stomatitis. Support Care Cancer. 2013;21(S1):S140-S.
11. Group MES. MASCC Oral Agent Teaching Tool© (MOATT) 2013 [updated 2013. Available from: https://www.mascc.org/MOATT.
12. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) 2018 [updated 03/01/2018. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

13. Hay JL, Atkinson TM, Reeve BB, Mitchell SA, Mendoza TR, Willis G, et al. Cognitive interviewing of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Qual Life Res. 2014;23(1):257-69.
14. Sonis ST, Eilers JP, Epstein JB, LeVeque FG, Liggett WH, Jr., Mulagha MT, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer. 1999;85(10):2103-13.
15. Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2015;26 Suppl 5:v139-51.
16. Newnham EA, Harwood KE, Page AC. Evaluating the clinical significance of responses by psychiatric inpatients to the mental health subscales of the SF-36. J Affect Disord. 2007;98(1-2):91-7.
17. Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. J Cutan Med Surg. 2001;5(2):105-10.
18. Cooperstein E, Epstein JB, Murphy BA, Dietrich MS, Gilbert J. Vanderbilt Head and Neck Symptom Survey Version 2.0 (VHNSS 2.0): A tool for the study of long-term oral health consequences of therapy for head and neck cancer (HNC). ASCO Meeting Abstracts. 2010;28(15_suppl):9055.
19. Cooperstein E, Gilbert J, Epstein JB, Dietrich MS, Bond SM, Ridner SH, et al. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck. 2012;34(6):797-804.
20. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22 Suppl 6:vi78-84.
21. Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, Kolnick L, et al. Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. CA Cancer J Clin. 2012;62(6):400-22.
22. Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. Future Oncol. 2013;9(12):1883-92.
23. Bellmunt J, Szczylik C, Feingold J, Strahs A, Berkenblit A. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol. 2008;19(8):1387-92.
24. Merck. Ridaforolimus: Data on file. 2012.
25. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: A narrative literature review. Oral Oncol. 2011;47(6):441-8.
26. Li E, Trovato JA. New developments in management of oral mucositis in patients with head and neck cancer or receiving targeted anticancer therapies. Am J Health Syst Pharm. 2012;69(12):1031-7.

27. Pilotte AP, Hohos MB, Polson KM, Huftalen TM, Treister N. Managing stomatitis in patients treated with Mammalian target of rapamycin inhibitors. Clin J Oncol Nurs. 2011;15(5):E83-E9.
28. de Oliveira MA, Martins F, Wang Q, Sonis S, Demetri G, George S, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol. 2011;47(10):998-1003.
29. Messadi DV, Younai F. Aphthous ulcers. Dermatol Ther. 2010;23(3):281-90.
30. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer. 2007;109(5):820-31.
31. Al-Dasooqi N, Gibson RJ, Bowen JM, Keefe DM. Matrix metalloproteinases: key regulators in the pathogenesis of chemotherapy-induced mucositis? Cancer Chemother Pharmacol. 2009;64(1):1-9.
32. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, et al. Skin Toxicity Evaluation Protocol With Panitumumab (STEPP), a Phase II, Open-Label, Randomized Trial Evaluating the Impact of a Pre-Emptive Skin Treatment Regimen on Skin Toxicities and Quality of Life in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2010;28(8):1351-7.
33. Coleman S, Jatoi A. STEPP for the EGFR inhibitor-induced rash--definitely a step in the right direction. Curr Oncol Rep. 2010;12(4):223-5.
34. Lee EH, Chun M, Kang S, Lee HJ. Validation of the Functional Assessment of Cancer Therapy-General (FACT-G) scale for measuring the health-related quality of life in Korean women with breast cancer. Jpn J Clin Oncol. 2004;34(7):393-9.
35. Overcash J, Extermann M, Parr J, Perry J, Balducci L. Validity and reliability of the FACT-G scale for use in the older person with cancer. Am J Clin Oncol. 2001;24(6):591-6.
36. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055-68.
37. Gandhi M, Oishi K, Zubal B, Lacouture ME. Unanticipated toxicities from anticancer therapies: survivors' perspectives. Support Care Cancer. 2010;18(11):1461-8.
38. Frith H, Harcourt D, Fussell A. Anticipating an altered appearance: women undergoing chemotherapy treatment for breast cancer. Eur J Oncol Nurs. 2007;11(5):385-91.
39. Haley AC, Calahan C, Gandhi M, West DP, Rademaker A, Lacouture ME. Skin care management in cancer patients: an evaluation of quality of life and tolerability. Support Care Cancer. 2011;19(4):545-54.
40. Siminoff LA. Improving communication with cancer patients. Oncology (Williston Park). 1992;6(10):83-7.

41. Clabbers JMK, Boers-Doets CB, Gelderblom H, Stijnen T, Lacouture ME, van der Hoeven KJM, et al. Xerosis and pruritus as major EGFRI-associated adverse events. Support Care Cancer. 2016;24(2):513-21.
42. Boers-Doets CB, Kaptein AA, Brakenhoff JA, Nortier JW, Gelderblom H. Doelgerichte therapie geassocieerde mucocutane bijwerkingen - de BeCet en de COMTT studie [Targeted therapy associated mucocutaneous reactions - the BeCet and the COMTT study]. Ned Tijd Oncol. 2013;10(8):343-7.
43. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273(1):59-65.
44. Cella DF. Quality of life: concepts and definition. J Pain Symptom Manage. 1994;9(3):186-92.
45. Chren MM, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol. 1996;107(5):707-13.
46. Chan A, Tan EH. How well does the MESTT correlate with CTCAE scale for the grading of dermatological toxicities associated with oral tyrosine kinase inhibitors? Support Care Cancer. 2011;19(10):1667-74.
47. National Cancer Institute. Patient-Reported Outcomes version of the CTCAE 2013 [Available from: https://healthcaredelivery.cancer.gov/pro-ctcae/.
48. The Economist. The costly war on cancer - New cancer drugs are technically impressive. But must they cost so much? 2011 [Available from: https://www.economist.com/business/2011/05/26/the-costly-war-on-cancer.
49. Netherlands Proteomic Centre. What is valorisation? [Online Article]. 2018 [Available from: http://www.netherlandsproteomicscentre.nl/npc/valorisation/what-is-valorisation.html.
50. Wong SF, Lindgren A, Mummaneni M, Byun T, Vasko C, Arenos R, et al. A prospective crossover pilot study to evaluate the use of a topical wound gel in patients with cutaneous toxicity caused by epidermal growth factor receptor inhibitors. J Support Oncol. 2010;8(5):202-8.
51. Purdy-Lloyd K, Wong S, Chen T, Mumaneni M, Quist R, Vasko C. A pilot crossover study to evaluate the use of Regencare topical gel in patients with cutaneous toxicity caused by epidermal growth factor receptor (HER1/EGFR) inhibitors. Oncology Nursing Forum 2007 Jan; 34(1): 216-7. 2007(1):216-7.
52. Gowland P, Vlamakis J, Koch J, Lloyd K, Spaulding JB. Evaluation of REGENECARE topical gel for treatment of adverse rash symptoms associated with EGFR inhibitor drugs. Oncol Nurs Forum. 2008;35(3):536-7.
53. Tejpar S, Peeters M, Humblet Y, Gelderblom H, Vermorken J, Viret F, et al. Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. ASCO Meeting Abstracts. 2007;25(18_suppl):4037.

54. Boers-Doets CB, Lacouture ME. Dermatologic Events in Oncology: How to Measure the Impact of Dermatologic and Mucosal AEs on Symptom Burden and Quality of Life. ASCO Post. 2013;4(20):70-1.
55. Berthelet E, Truong PT, Musso K, Grant V, Kwan W, Moravan V, et al. Preliminary reliability and validity testing of a new Skin Toxicity Assessment Tool (STAT) in breast cancer patients undergoing radiotherapy. Am J Clin Oncol. 2004;27(6):626-31.

09 | Samenvatting (Summary in Dutch)

Context

Targeted anti-kankertherapieën blijken effectief te zijn in het behandelen van veel soorten van kanker bij zowel volwassenen als bij kinderen. Naast de toename van het aantal targeted anti-kankertherapieën is er ook sprake van een bredere indicatie, waardoor een groeiend aantal patiënten met kanker in aanmerking komt voor deze behandelingen. De duur van de behandelingen die overwegend poliklinisch of in de thuissituatie plaatsvinden kan variëren van enkele maanden tot jaren. Targeted therapieën worden toegepast als monotherapie, maar worden ook ingezet als een combinatiebehandeling met o.a. cytotoxische chemotherapie en/of bestralingstherapie.

Onderzoek en praktijk laten echter ook zien dat bijwerkingen als gevolg van deze behandelingen ervoor kunnen zorgen dat, ondanks de effectieve werking tegen kanker, de therapie tijdelijk wordt onderbroken, een dosisreductie wordt toegepast of de behandeling vroegtijdig geheel wordt gestaakt. Het bijwerkingenprofiel bij targeted therapieën is multidimensionaal met een wisselende mate van invloed op kwaliteit van leven. Veel bijwerkingen zijn overwegend symptomatisch. Hierdoor kunnen deze bijwerkingen alleen door de patiënt zelf waargenomen en gemeten worden, terwijl het behandelteam verantwoordelijk is voor een adequate vastlegging ervan. De hieruit voortvloeiende interventies sluiten niet altijd naadloos aan bij de behoeften van de patiënt. Deze discongruentie laat zien dat er behoefte is aan een integrale patiëntgestuurde benadering van bijwerkingen.

Vraagstelling

De centrale vraag van dit proefschrift is of er methodieken en instrumenten beschikbaar zijn die als basis kunnen dienen voor de totstandkoming van een integrale patiëntgestuurde benadering van targeted therapie-geassocieerde bijwerkingen.

Bevindingen

Het onderzoek identificeerde drie concrete bevindingen:

1. Huidige bijwerkingen-inventarisatielijsten zijn van beperkte waarde voor de diagnostisering, rapportage, gradering en evaluatie van targeted therapie-geassocieerde huid- en slijmvliesreacties. In het algemeen wordt het patiëntenperspectief nauwelijks meegenomen.
2. Er is momenteel beperkt wetenschappelijke bijwerkingenkennis beschikbaar om evidence-based behandelingsrichtlijnen op te stellen.
3. De gegenereerde wetenschappelijke bijwerkingenkennis die beschikbaar gekomen is, is niet breed ingebed in de klinische en onderzoekspraktijk.

Conclusies

Het signaleren en beoordelen van de bijwerkingen door middel van patiënt-gerapporteerde uitkomsten en de behandeling van bijwerkingen zijn algemeen geaccepteerde pijlers in de zorg bij anti-kankerbehandelingen.

De toepassing van goed gedefinieerde bijwerkingenterminologie, in combinatie met de ontwikkeling van geschikte bijwerkingeneducatie-, diagnostisering-, rapportage-, gradering- en evaluatie-instrumenten, is nodig om een gedetailleerd beeld van het bijwerkingenprofiel van de patiënt te krijgen. Daarnaast draagt deze aanpak bij aan een effectieve inzet van financiële middelen doordat intensieve, tijdrovende en langdurige behandelingen van bijwerkingen vermeden kunnen worden.

Bij een systematische benadering van deze bijwerkingen is het van belang dat alle belanghebbenden bij de behandeling betrokken worden, zodat de targeted anti-kankertherapie zo effectief mogelijk voortgezet kan worden. Belanghebbenden zijn o.a. de patiënt, diens naasten, medisch specialisten, verpleegkundigen, data managers, huidspecialisten, oncologisch voetzorgverleners, apothekers, laboranten, farmaceuten, verzekeraars, overheid en goedkeuringsinstanties.

Implicaties voor onderzoek en dagelijkse praktijk

Een integrale patiëntgestuurde benadering van targeted therapie-geassocieerde bijwerkingen dient systematisch plaats te vinden vanuit een geïntegreerd, interdisciplinair teammodel van zorg. Het in dit proefschrift voorgestelde co-care model biedt hiervoor een kader waarin de drie bevindingen in dit proefschrift ingebed kunnen worden:

1. De ontwikkeling van een gecombineerd driedelig patiënt-gerapporteerd beoordelings- en graderingsinstrument dat zowel de symptomen en de kenmerken als het effect van een bijwerking op de kwaliteit van leven in kaart brengt.
2. Het genereren van evidence-based behandelingsrichtlijnen gericht op bijwerkingen van targeted therapie.
3. Het ontwikkelen van verplichte trainingsprogramma's voor zorgverleners is geïndiceerd. In het bijzonder voor de professionals die in de dagelijkse praktijk direct betrokken zijn bij klinisch onderzoek en zorg rondom de patiënt die behandeld wordt met een targeted therapie.

De drie bevindingen binnen het conceptueel co-care model van een patiëntgestuurde benadering van targeted therapie-geassocieerde bijwerkingen biedt handvatten om de kwaliteit van leven en het effect van de targeted anti-kankertherapie te vergroten en de kosten van de bijwerkingenbehandeling te verlagen.

10 | About the author

Curriculum Vitae

Christine Boers-Doets was born April 19th 1968 in Rheinberg, Germany. She currently lives with her husband Edwin and her three children Esmée, Danique, and Loran, in Wormer, The Netherlands.

After finishing secondary school at the Realschule in Rheinkamp, Germany, she moved to the Netherlands to complete class 4 & 5 of the HAVO in Venray. After finishing secondary school, she studied nursing at the HBO-V in Eindhoven and completed this education in 1992 in Alkmaar, The Netherlands. She received her bachelor degree in 1988 and her nursing degree in 1992. Besides being full-time employed as a nurse at the St Lucas Hospital in Amsterdam, The Netherlands, she finished her master degree in Health Sciences from 1993 to 1997 at the University of Utrecht. From 1997 till 2012 Christine has worked as clinical nurse specialist and research coordinator at the Waterland Hospital in Purmerend, The Netherlands.

In 2012 she founded the Impaqtt Foundation to be able to complete her research program with special attention to finalizing the COMTT and the BeCet trial on the one hand and raising awareness and funding for more next generation patient-driven studies and patient support projects on the other hand. In 2013 she founded her own company *Cancer*Med. She is an active member of MASCC, the Multinational Association of Supportive Care in Cancer. With her research, teaching, and mentoring she supports pharmaceutical companies, policymakers, universities, hospitals, homecare organizations, footcare specialists, and patient advocacies on how to help patients conquer cancer. Targeted anticancer therapies, inclusive endocrine therapies and immuno-oncology, have her upmost attention.

Besides being fulltime employed, Christine started her PhD journey in 2006 at the Radboud University Nijmegen, The Netherlands. In 2008, the Leiden University Medical Center (LUMC), The Netherlands became involved. In 2010, she moved her PhD project entirely to the LUMC, where she completed her PhD in 2019.

List of publications

Ouwerkerk J, **Boers-Doets CB**: Best practices in the management of toxicities related to anti-EGFR agents for metastatic colorectal cancer. *Eur J Oncol Nurs*. 2010;14(4):337-49. Epub 2010 May 23

Balagula Y, Garbe C, Myskowski PL, Hauschild A, Rapoport BL, **Boers-Doets CB**, Lacouture ME. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. *Int J Dermatol.* 2011 Feb;50(2):129-46. doi: 10.1111/j.1365-4632.2010.04791.x.

Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, Epstein JB, Eaby-Sandy B, Murphy BA; MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer*. 2011 Aug;19(8):1079-95. doi: 10.1007/s00520-011-1197-6. Epub 2011 Jun 1.

Boers-Doets CB, Epstein JB, Raber-Durlacher JE, Ouwerkerk J, Logan RM, Brakenhoff JA, Lacouture ME, Gelderblom H. Oral AEs associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. *Oncologist.* 2012;17(1):135-44. doi: 10.1634/theoncologist.2011-0111. Epub 2011 Dec 29.

Edmonds K, Hull D, Spencer-Shaw A, Koldenhof J, Chrysou M, **Boers-Doets C**, Molassiotis A: Strategies for assessing and managing the AEs of sorafenib and other targeted therapies in the treatment of renal cell and hepatocellular carcinoma: Recommendations from a European nursing task group. *Eur J Oncol Nurs.* 2012 Apr;16(2):172-84. Epub 2011 Jun 8.

Boers-Doets CB, Gelderblom H, Lacouture ME, Bredle JM, Epstein JB, Schrama NA, Gall H, Ouwerkerk J, Brakenhoff JA, Nortier JW, Kaptein AA. Translation and linguistic validation of the FACT-EGFRI-18 quality of life instrument from English into Dutch. *Eur J Oncol Nurs*. 2013 Dec;17(6):802-7. doi: 10.1016/j.ejon.2013.03.004. Epub 2013 Apr 6.

Boers-Doets CB, Gelderblom H, Lacouture ME, Epstein JB, Nortier JW, Kaptein AA. Experiences with the FACT-EGFRI-18 instrument in EGFRI-associated mucocutaneous AEs. *Support Care Cancer.* 2013 Jul;21(7):1919-26. doi: 10.1007/s00520-013-1752-4. Epub 2013 Feb 17.

Wong RK, Bensadoun RJ, **Boers-Doets CB**, Bryce J, Chan A, Epstein JB, Eaby-Sandy B, Lacouture ME. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group. *Support Care Cancer*. 2013 Oct;21(10):2933-48. doi: 10.1007/s00520-013-1896-2. Epub 2013 Aug 14.

Elting LS, Chang YC, Parelkar P, **Boers-Doets CB**, Michelet M, Hita G, Rouleau T, Cooksley C, Halm J, Vithala M, Bossi P, Escalante C, Brennan MT; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Risk of oral and gastrointestinal mucosal injury among patients receiving selected targeted agents: a meta-analysis. *Support*

Care Cancer. 2013 Nov;21(11):3243-54. doi: 10.1007/s00520-013-1821-8. Epub 2013 May 2.

Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, Lalla RV, Logan RM, van Erp NP, Gelderblom H. Mammalian target of rapamycin inhibitor-associated stomatitis. *Future Oncol*. 2013 Dec;9(12):1883-92. doi: 10.2217/fon.13.141.

De Wit M, **Boers-Doets CB**, Saettini A, Vermeersch K, de Juan CR, Ouwerkerk J, Raynard SS, Bazin A, Cremolini C. Prevention and management of AEs related to regorafenib. *Support Care Cancer*. 2014 Mar;22(3):837-46. doi: 10.1007/s00520-013-2085-z. Epub 2013 Dec 14.

Bryce J, **Boers-Doets CB**. Non-rash dermatologic AEs related to targeted therapies. *Semin Oncol Nurs*. 2014 Aug;30(3):155-68. doi: 10.1016/j.soncn.2014.05.003.

Clabbers JM, **Boers-Doets CB**, Gelderblom H, Stijnen T, Lacouture ME, van der Hoeven KJ, Kaptein AA. Xerosis and pruritus as major EGFRI-associated AEs. *Support Care Cancer*. 2016 Feb;24(2):513-521. doi: 10.1007/s00520-015-2781-y. Epub 2015 Jun 27.

Ruiz JN, Belum VR, **Boers-Doets CB**, Kamboj M, Babady NE, Tang YW, Valdez TA, Lacouture ME. Nasal vestibulitis due to targeted therapies in cancer patients. *Support Care Cancer*. 2015 Aug;23(8):2391-8. doi: 10.1007/s00520-014-2580-x. Epub 2015 Jan 22.

Chan A, Cameron MC, Garden B, **Boers-Doets CB**, Schindler K, Epstein JB, Choi J, Beamer L, Roeland E, Russi EG, Bensadoun RJ, Teo YL, Chan RJ, Shih V, Bryce J, Raber-Durlacher J, Gerber PA, Freytes CO, Rapoport B, LeBoeuf N, Sibaud V, Lacouture ME. A systematic review of patient-reported outcome instruments of dermatologic AEs associated with targeted cancer therapies. *Support Care Cancer*. 2015 Aug;23(8):2231-44. doi: 10.1007/s00520-014-2564-x. Epub 2015 Jan 7.

Peterson DE, **Boers-Doets CB**, Bensadoun RJ, Herrstedt J; ESMO Guidelines Committee. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2015 Sep;26 Suppl 5:v139-51. doi: 10.1093/annonc/mdv202. Epub 2015 Jul 4.

Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, Harbeck N, Aguilar Lopez B, Barrios CH, Bergh J, Biganzoli L, **Boers-Doets CB**, Cardoso MJ, Carey LA, Cortés J, Curigliano G, Diéras V, El Saghir NS, Eniu A, Fallowfield L, Francis PA, Gelmon K, Johnston SRD, Kaufman B, Koppikar S, Krop IE, Mayer M, Nakigudde G, Offersen BV, Ohno S, Pagani O, Paluch-Shimon S, Penault-Llorca F, Prat A, Rugo HS, Sledge GW, Spence D, Thomssen C, Vorobiof DA, Xu B, Norton L, Winer EP. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol*. 2018 Aug 1;29(8):1634-1657. doi: 10.1093/annonc/mdy192.

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