Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 5 Issue 1 January 2021

Research Article

Initiation of the Most Appropriate Adverse Event Treatment is More Likely to Occur if the 6 Steps of the TARGET Strategy are Taken

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Received: November 18, 2020

Published: January 21, 2021

Abstract

Purpose: A substantial number of patients on targeted anticancer therapy (TT) cannot complete their treatment as planned, due to severe or persistent adverse events (AEs) associated with these agents, which may affect clinical outcome. An effective approach to AEs is needed in order to help patients complete treatment as planned.

Objectives: The aim of this work was to identify a more detailed description of the AEs so that available treatment options can be provided leading to a decrease in dose modifications and continuing compliance with cancer care.

Methods: In part I, the medical records and clinical trial protocols of oncology patients on TT were searched. We explored terms used to describe AEs and documented missing information in a detailed AE diagnosis.

In part II, the core items identified in part I were applied on patients with AEs of TT and recorded if patients were able to complete treatment as planned.

Results: In part I we identified six core AE items, which were organized in six TARGET-steps: term, assess, report, grade, educate, and treat. In part II the AEs of 262 patients were approached according to the identified six TARGET-steps. At initiation, a total of 1.516 AEs was reported. The most frequent AEs patients and questioners' requested advice for in the study were dry skin, burning sensation, pruritis and dry oral cavity; 244 (16.1%), 201 (13.3%), 193 (12.7%) and 102 (6.7%) respectively. 98% of the AEs were decreased from moderate or severe to none or mild within 48 hours of AE treatment. No cancer treatment adjustments were performed.

Conclusion: Initiation of the most appropriate AE treatment is more likely to occur if the 6 steps of the TARGET strategy are taken.

Keywords: Targeted Therapy; Cancer; Adverse Event; TARGET; Treatment; Systematic Approach; Patient-Reported Outcome (PRO)

Introduction

Targeted Therapies

Currently, various types of cancer are treated with targeted anticancer therapy (TT). According to the National Cancer Institute [1], TTs include:

- Hormone therapies, e.g. tamoxifen, anastrozole, exemestane, letrozole, goserelin, leuprorelin, and triptorelin
- Signal transduction inhibitors, e.g. imatinib, erlotinib, sorafenib, sunitinib, everolimus, temsirolimus, and lapatinib

- Gene expression modulators, e.g. imatinib, nilotinib, and dasatinib
- Apoptosis inducers, e.g. erlotinib, and sorafenib
- Angiogenesis inhibitors, e.g. axitinib, bevacizumab, everolimus, pazopanib, regorafenib, sorafenib, and sunitinib
- Immunotherapies, e.g. ipilimumab, nivolumab, pembrolizumab, durvalumab, atezolizumab, and avelumab
- Monoclonal antibodies that deliver toxic molecules, e.g. trastuzumab, cetuximab, and panitumumab.

Adverse events

A downside of this kind of treatment is the occurrence of adverse events (AEs) due to inflammatory reactions in various tissues [2,3]. In most cases, the skin and mucosa are involved, such as a burning sensation, nail fold inflammation, blisters, calluses, extreme skin fissures, pustules, and mouth sores. These AEs can become very severe. The AEs are sometimes extremely visible and may be of esthetic concern or result in significant AEs. But sometimes they are not visible and can only be felt by the patient and therefore may be overlooked by the physician or nurse [4,5]. The consequence may be that the patient's quality of life and compliance with and continuing the cancer therapy may be reduced or stopped [6].

Clinician and patient reported outcome

The treatment of cancer in general and specifically of AEs requires close collaboration between the patient and the healthcare team. The healthcare provider (HCP) is naturally well versed in matters relating to the treatment and its AEs. However, the HCP is dependent on the patient and their social support system for insight into the patient's daily routine - how the patient is coping with his/her illness, how he/she is able to manage activities of daily living, how he/she is psychologically structured and in what frame of mind he/she is. This makes it clear that successful treatment will depend on the cooperation of both parties.

In oncology healthcare it is common to register signs of AEs by observable measurements assessed by HCP's. 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 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 [7]. Publications by Basch., et al. [8,9] demonstrated that systematic collection of patient-reported symptoms and telephone-based symptom management resulted in both higher QoL and survival improvement. Their studies show that current care delivery systems fall short in identifying symptoms since AEs are mainly reported by HCP's.

Objectives

To decrease development of potentially severe AEs that might lead to treatment adjustments/interruptions, the patient needs to be educated about prophylactic measures at the initiation of treatment [17-20]. If the patient is educated to report the AE details correctly, unintended lifesaving or life prolonging treatment delays or interruptions may be avoided. Therefore, we searched for strategies that optimize the AE approach so patients can complete their lifesaving or life sustaining treatment as planned.

The primary objective of this work was to identify a more detailed description of the AEs so that available treatment options can be applied more specifically to the AEs. The secondary objective was to test the detailed description in daily practice.

Methods

We first identified in part I the critical items for an effective approach to AEs. After identifying the critical components for a systematic patient-driven AE approach, we examined these elements to determine if these components may be helpful in reducing the presence, severity, and control of AEs. Following identifying the critical AEs in part I, we applied the 6 steps identified in patients experiencing AEs from TT.

PART I: Identification of critical components for a systematic patient-driven AE approach

First, to identify a more detailed description of the AEs, questionnaires and case report forms from clinical TT trials were studied [10-18]. Second, for the identification of terms used in patient files the medical records of oncology patients on TT 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. Third, AE terms were identified in grading instruments [19-21].

PART II: Testing of the six core items found in part I

Patients, their support system, physicians, and nurses who consulted the researcher for an effective approach for severe or sus-

taining AEs from TT to support control of these AEs were considered eligible. Patients were ≥ 18 years of age; with a histologically proven cancer and experiencing AE(s) from any TT. The researcher could be consulted by telephone, video conferencing, email, WhatsApp or in person. The questioner needed to be willing to provide detailed information about the AEs according to the six core items, allowing the researcher to provide recommendations for the most appropriate AE treatment.

Results

PART I: The six core items of the TARGET strategy

The following critical components for a systematic, patient-driven TT-associated AE approach are identified: [22,23]

- Provide the AE with a detailed AE subtype label (inflammation, infection, calluses, skin fissures etc.)
- Assessment of the symptoms and signs (what is felt and what is seen) and the impact of the symptoms and signs on a patients' health-related quality of life (HRQoL)
- Reporting of in-depth characteristics of the symptoms and signs (how does it feel, where is it located, when does it bother the patient the most?)
- Determine the severity (how severe are the symptoms and signs according to the patient)
- Evaluation and education (did the patient follow the advice correctly and did it help?)
- Treatment of the symptoms and signs of the AE with the most appropriate and effective measures (at an early stage usually with over the counter drugs or household remedies).

Below the 6 critical steps are described in more detail.

Step 1: Terminology

Terminology is about labelling or designating concepts in the right context. It is important to define the terminology for all known AEs carefully, in order to be able to use the same vocabulary in discussion with others. Promoting consistency of the appropriate terminology of the AEs is important for documenting, treatment, and fewer misunderstandings in the communication between the HCP and the patient and among HCP's [24]. When for instance terms such as chemotherapy-associated hand-foot syndrome (HFS) and TT-associated hand-foot skin reaction (HFSR) are used consistently, it will be more likely to define the appropriate treatment option. On the other hand, when the assessment is based on the wrong AE diagnosis, it is unlikely to grade it correctly which can lead to the selection of an ineffective AE treatment strategy.

Therefore, patients and their social support system should be informed about the vocabulary used to denote an AE and which characteristics should be used to describe it. These may differ to those used in everyday conversation. When, for example, patients use the word diarrhea, they should know that the characteristic of diarrhea in this context is the watery component and that a loose stool in which the watery component is missing, is not diarrhea [23]. The consequence of misunderstandings of this kind in daily practice could be that they might be given a prescription of high dose loperamide, which is not an appropriate intervention for loose stool. In the worst-case scenario this can even lead to a TT dose modification. So, if patients are able to use the accurate terminology, they can actively support finding the right intervention for their AE(s).

Step 2: Assessment of symptoms and signs and their influence on HRQoL

Firstly, symptoms and signs need to be assessed, then their influence on HRQoL. Symptoms and signs can range from having "no influence at all" till "very much influence" on the QoL. Without this assessment a comprehensive grading of the AEs is not possible.

It is helpful if patients record their symptoms in a diary. The important points are; when did a symptom start; what impact did it have, what was used to try and treat it; was medical advice sought; what was recommended, and so on. Although the patient might have put a lot of time and effort into the diary it is often only briefly discussed by the clinician if the symptom is graded as 'just' mild or moderate. It is not general practice to ask a patient if a mild AE (according to the National Cancer Institute Common Criteria for Adverse Events (NCI-CTCAE) grading) [21] is causing discomfort severe enough to require a dose modification. But for the patient even mild or moderate AEs might in some cases have such an impact on the HRQoL that the patient would actually prefer a dose modification - especially if he has several symptoms. So, it is important for patients to know that in general the prescriber will modify the dose if one single severe AE occurs, while multiple mild or moderate AEs might not have the same consequence. Equally they should know that they can influence this decision by making it clear to the healthcare team whether they are prepared to tolerate the AE(s) which have occurred.

Wagner. et al. demonstrated that patients identify the physical discomfort of AEs as having the biggest impact on their HRQoL [25]. Especially pain, burning, and skin sensitivity have considerable impact. They experience worry, frustration, and depression because of their dermatological symptoms, and may withdraw from social activities. In general, younger patients tend to rate their HRQoL lower than older patients with the same AEs. The consequence is that younger patients are more likely to dropout because of the AEs [26]. Therefore, it is essential to understand which AEs are the most difficult to deal with in order to particularly address them in clinical trials. As survival times increase, it has become even more important to optimize treatment related QoL during treatment.

Step 3: Reporting of AE characteristics

A characteristic helps to identify, to differentiate, and to describe a feature more precisely [27]. It is a distinguishing mark or trait [27]. Characteristics provide more details than the symptoms and signs alone. It helps to distinguish symptoms which, taken together, lead to the AE diagnosis. Therefore, reporting of characteristics is a crucial step in the analysis and decision-making process. In addition, it helps in the appropriate grading of the severity.

The actually in-depth reporting may be performed mainly by the patient, since, compared with patients, physicians often underreport AEs [28]. Furthermore, the AE burden for patients who experience unaddressed symptoms cannot be underestimated when patients monitor their symptoms and signs by themselves [7]. Therefore, teaching the patient to accurately describe any symptoms (i.e. report by characteristics) and asking structured questions are essential for achieving a precise and comprehensive AE recording [23]. For example, when reporting papules; record onset, site, location, severity, and associated signs such as shape and color (brown, purple, pink or red) and if scales are present. Also record if open and/or scratched and if infected. In addition, clinical photographs, clinical testing/measurement (e.g. biopsies, swabs, etc.) by the HCP support the integral reporting of AE characteristics.

Furthermore, reporting of the characteristics enables identification of the symptoms of the AE on which the interventions had an effect. It also calls upon the symptoms that continues to require management. In addition to reporting of the characteristics, the affected areas should be drawn in a figure, to provide an overview where the symptoms appeared.

Step 4: Grading the AE severity

Grading of AEs attaches a severity label to the symptoms and signs and their impact on HRQoL. For HCPs involved in clinical trials, grading of AEs is a recurrent activity, since it is a key component of conducting research. For most oncological clinical trials, the NCI-CTCAE is used [21]. Nonetheless, the NCI-CTCAE is not actually a validated system but is rather based on expert opinions and con- sensus. Naturally, medical specialists prefer to prescribe a medication for which a high level of evidence is available - for a particular product in a particular setting. However, this non-validated grading system based on expert opinion consensus is widely accepted as providing a high level of evidence.

To avoid the use of the NCI-CTCAE, PRO's may be used instead. Most patients are capable of grading AEs by themselves [29,30]. To enable a patient to grade AEs it is useful to have a template or a form which will lead the patient through the grading process. An AE form should provide a space for the patient to record the manifestation and severity of symptoms and signs and the burden that goes along with these symptoms or signs. This will provide a detailed record for patients and HCPs alike.

An accurate assessment of the morbidity of the AE may allow the patient and HCP to make decisions on interventions including dose modifications or discontinuation which are based on correct information. This is important because those decisions may affect the clinical outcome.

Step 5: Education and evaluation

Education is indispensable throughout the entire treatment period. Before initiation of the TT, preventive measures should be presented and discussed. During treatment, the patient should be regularly re-educated depending on individual needs. Information should include the description, recognition and grading of common and potentially severe AEs associated with the treatment they are receiving. If the patient is educated to report AEs properly, unintended treatment delays or interruptions can be avoided. A patient should in particular receive detailed instructions on how to keep for instance the skin and mucosa in a healthy condition in order to prevent the onset or worsening of AEs. It is important that a patient knows why this is vital for success and why they play the key role in the procedure. Without accurate information it is highly unlikely that the patient will succeed in maintaining a healthy skin and mucosa. It is also important to allow the patient to decide for themselves how to integrate the care procedures into their daily routine taking into account their own preferences. If for example, a patient loves to take long, hot showers every day, it should be made clear that this is not good for the skin. However, it should be left up to the patient to decide whether to compensate by intensifying the skin care regimen or to take shorter and cooler showers. If the patient does not comply with the prescribed measures, it is less likely that the therapy of the AE will have the desired result. Therefore, it is important to educate patients very thoroughly on self-management.

It is crucial to evaluate already after 48 hours if the initiation of the AE interventions have resulted in the desired outcomes. Due to the inflammatory components, the AEs should start decreasing already within 12 hours after initiation of the AE treatment since when no response occurs within this timeframe, poor response can be expected after 48 hours. Before TT treatment adjustment, adjustment of AE treatment should be considered first [31].

Step 6: Treatment

TT-associated AEs may be addressed using preventive and/or reactive measures. By identifying strategies that minimize or decrease the AEs, the clinician will be able to improve the treatment for patients on TT and will maximize their benefits, leading to the highest possible HRQoL and treatment outcome. The patient plays a key role in all aspects of treatment and especially when it comes to treating AEs, since treatment frequently involves the use of creams, antiseptic soaks, general skin care, oral rinses, or other topical applications in the mouth. The patient should get information not only about the 'what', but also about the 'why' of an AE intervention, and be aware of the consequences if recommendations are not followed. They also need to know where to apply which product. A simple drawing can support the use of a product in the right place [23].

PART II: Testing of the theory on real patient situations

1.516 AEs from 262 patients were approached according to the identified six critical items noted in Part I. Patients were mainly from the Netherlands (81%). In addition, AEs from patients living in Belgium, Germany, Austria, Switzerland, Greece, Spain, Italy, Australia, and the US were approached according to the six critical items. Only 6% of the patients was seen in person (Table 1).

Patients' and questioners' demographic characteristics from part II are summarized in table 1. Most patients were male (148, 57%) with a median age of 69 years (range 19 - 81). Sunitinib was administered in the majority of patients (n = 37, 14%).

Table 2 lists the incidence of the AEs that questioners requested advice for. The most frequent AEs patients and questioners' requested advice for in the study were dry skin, burning sensation, pruritis and dry oral cavity; 244 (16.1%), 201 (13.3%), 193 (12.7%) and 102 (6.7%) respectively.

In this case series no patient discontinued the TT treatment due to AEs. Only one patient had sustaining AE after 14 days. The reason why we were not able to resolve the AE within that timeframe, was the dissemination, duration, and severity of the AE. The patient had infected papulopustular crusts on her scalp (Figure 1). While the patient stayed on her TT without any dose adjustments, the papulopustular rash inclusive crusts resolved completely after 2 months. No dose modification was performed.

Characteristics	Mean (range)	N
Questioner		
Patient themselves		27 (10.3%)
Patients support system		71 (27.0%)
Nurse		146 (55.7%)
Physician		18 (6.8%)
Country of Questioner		
The Netherlands		211 (80.5%)
Outside The Netherlands		51 (19.5%)
Consultation		
By telephone		40 (15.3%)
By video conferencing		7 (2.7%)
By email		122 (46.6%)
By whatsapp		77 (29.4%)
In person		16 (6.1%)
Age	69 (19-81)	
Gender		
Male		148 (56.5%)
Female		114 (43.5%)
ECOG PS; rating (0-4)		
0		54 (20.6%)
1		181 (69.0%)
2		27 (10.3%)
Targeted therapy		
Afatinib		9 (3.4%)
Axitinib		5 (1.9%)
Cetuximab		23 (8.8%
Dacomitinib		3 (1.5%)
Erlotinib		15 (5.7%)
Everolimus		24 (9.2%)
Gefitinib		7 (2.7%)
Imatinib		5 (1.9%)
Ipilimumab		3 (1.5%)
Lapatinib		9 (3.4%)
Nilotinib		1 (0.4%)
Nivolumab		8 (3.1%)
Osimertinib		1 (0.4%)
Panitumumab		32 (12.2%)
Pazopanib		12 (4.6%)
Pembrolizumab		4 (1.5%)
Regorafenib		23 (8.8%)
Ridaforolimus		4 (1.5%)
Sorafenib		21 (8.0%)
Sunitinib		37 (14.1%)
Temsirolimus		5 (1.9%)
Trametinib		4 (1.5%)
Vemurafenib		7 (2.7%)

Table 1: Demographic and clinical characteristics (N = 262).

ECOG PS = Eastern Cooperative Oncology Group Performance Status.

	At initiation (all grades)	After 48 hours	After 96 hours	After 14 days
Skin				
Dry skin	244 (16.1%)	0	0	0
Burning sensation	201 (13.3%)	2 (0.1%)	0	0
Eczema	3 (0.2%)	3 (0.2%)	2 (0.1%)	0
Pruritus	193 (12.7%)	0	0	0
Maculopapular rash	67 (5.0%)	0	0	0
Papulopustular rash without infection	93 (6.1%)	2 (0.1%)	0	0
Papulopustular rash with infection	54 (3.6%)	0	0	0
Scalp rash	9 (0.6%)	9 (0.6%)	4 (0.3%)	1 (0.06%)
Stool				
Loose stool	83 (5.5%)	0	0	0
Colitis	3 (0.2%)	0	0	0
Hand and Feet				
HFSR with erythema	47 (3.1%)	0	0	0
HFSR with calluses	41 (2.7%)	0	0	0
HFSR with blisters	23 (1.5%)	0	0	0
fissures fingers & toes	87 (5.7%)	3 (0.2%)	0	0
Paronychia	56 (3.7%)	1 (0.06%)	0	0
Oral cavity and lips				
Dry oral cavity	102 (6.7%)	0	0	0
Burning sensation tongue	22 (1.5%)	0	0	0
Aphthous ulcerations (mIAS)	31 (2.0%)	0	0	0
Fissures Lips	9 (0.6%)	0	0	0
Eyes				
Dry eyes	84 (5.5%)	0	0	0
Teary eyes	13 (0.9%)	0	0	0
Miscellaneous				
Interstitial lung disease (ILD)	4 (0.3%)	4 (0.3%)	2 (0.1%)	0
Hypertension	13 (0.9%)	11 (0.7%)	10 (0.7%)	0
Nasal vestibulitis	34 (2.2%)	0	0	0
Total number of AEs	1.516 (100%)	35 (2.3%)	18 (1.2%)	1 (0.06%)

Table 2: Adverse Event Severity before and after initiation of the most appropriate AE treatment (N = 262).

HFSR hand-foot skin reaction; AEs adverse events.

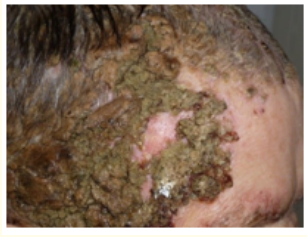

Figure 1: Scalp of a patient on erlotinib with extended pustules covered with crusts.

Discussion

We found six critical steps that may be helpful in identifying the most appropriate AE treatments. In only one situation did it take longer than 14 days to achieve control of the AE (the erlotinib patient with scalp crusts). From the 1.516 AEs approached according to the six critical items, no AE required a TT treatment adjustment. This finding is remarkable, since in the literature we find differing impacts and outcomes. In table 3 we listed the TTs the patients in this case series were treated with. The table displays the dose reductions or interruption and discontinuation of TT due to AEs as mentioned in the literature. Despite many attempts to manage AEs effectively, about 36-55% of patients received a dose reduction or dose interruption due to severe or persistent AEs (Table 3). However, with the application of the six critical TARGET steps (terming, assessing, reporting, grading, evaluating, and treating AEs), the 36-55% mentioned in the literature is much higher than the 0% in our case series. Furthermore, the case series suggests that AE management can be provided remotely.

There are several limitations to this study. First, the participants were mainly from The Netherlands and mainly Caucasian (96%). Second, not all the available AEs known and TT available were studied and most AEs studied were mucocutaneous AEs. However, the findings support an approach to management of

mucocutaneous AEs in TT. Third, the success of AE management is not only dependent on finding the most appropriate AE treatment. When patients need a prescription drug, like a corticosteroid or an antibiotic, the HCP needs to provide a management with the most appropriate medication, vehicle of delivery and dose. Otherwise, the AE treatment may fail, and TT adjustments are still required. Fourth, the researcher had in the majority of cases no direct contact with the patient. This may have influenced the AE duration.

Targeted Therapy	Dose interruptions/delay	Dose reduction	Discontinuation of TT due to AEs	Reference
Afatinib	NR	42%	6%	Park K. 2016 [32]
Axitinib	77%*	31%	4%	Rini BI. 2011 [33]
Cetuximab	NR	28.8%	76%	Ocean AJ. 2010 [34]
Dacomitinib	56%	32%	6%	Lavacchi D. 2019 [35]
Erlotinib	NR	40%	11%	Pennell NA. 2019 [36]
Everolimus (Ev)+ exemestane (Ex)	62%		26% (Ev); 9% (Ex)	Rugo HS. 2016 [37]
Gefitinib 500 mg/d	45.8%	23.2%	NR	Giaccone G. 2004 [38]
Imatinib 600 mg/d	NR	59%	NR	Hamdan MY. 2007 [39]
Ipilimumab	NR	NR	41.7%	Weber J. 2017 [40]
Lapatinib		15%	19%	Goss PE. 2013 [41]
Nilotinib	NR	15%	NR	Blay J-Y. 2015 [42]
Nivolumab	NR	NR	7.7%	Weber J. 2017 [40]
Osimertinib	NR	19.4%	27.8%	Nakao A. [43]
Panitumumab	35%	NR	12%	Freeman DJ. 2009 [44]
Pazopanib	58%	39%	14%	Sutter S. 2012 [45]
Pembrolizumab + ipilimumab	NR	NR	30%	Carlino MS. 2020 [46]
Regorafenib	43.8%		24%	Krishnamoorthy SK. 2015 [47]
Ridaforolimus	56%	70%	14%	Sutter S. 2012 [45]
Sorafenib (HCC)	44%	26%	NR	Escudier B. 2007 [48]
Sorafenib (RCC)	80%*	52%	8%	Rini BI. 2011 [33]
Sunitinib	NR	50%	19%	Motzer RJ. 2009 [49]
Temsirolimus	NR	43%	16%	Dreyling M. 2015 [50]
Trametinib + dabrafenib	55%	33%	13%	Robert C. 2015 [51]
Vemurafenib	56%	39%	12%	Robert C. 2015 [51]
Average	55%	36.5%	18.9%	

Table 3: Dose reductions or interruption and discontinuation of TT due to AEs as mentioned in the literature.

TT: Targeted Therapy; AEs: Adverse Events; NT: Not Reported; *due to missed dose or toxic effects; HCC: Hepatocellular Carcinoma; RCC: Renal Cell Carcinoma.

Conclusions

Our study suggests that the six critical steps of the TARGET-strategy is helpful in managing AEs resulting from TTs. In general, both patients and consultant perceived high efficacy of the TARGET strategy. Fortunately, the AEs patients faced, decreased with help of the TARGET strategy in 98% of the cases within 48 hours till grade 0-1, leading to completion of lifesaving or life prolonging cancer treatment full dose on time. For a patient-driven approach to

AEs, the TARGET strategy requires testing by patients themselves without interference of a healthcare professional.

Acknowledgements

We thank all patients who participated in the TARGET registry study.

Funding

This work was sponsored by the Impaqtt Foundation, Wormer, The Netherlands.

Availability of Data and Material

Part I of this work is in part published in the dissertation 'Towards a patient-driven approach to adverse events of targeted agents in oncology' from the first author. The authors confirm they have full control of all primary data and agree to allow the journal to review their data if requested. The datasets generated and/or analyzed during the current study are not publicly available as sharing is not explicitly covered by patient consent.

Author Contributions

Commissioned by the Impaqtt Foundation, Christine Boers-Doets designed and wrote the study protocol, collected, and analyzed the data, and wrote the manuscript. Joel Epstein participated in study design, review of data and preparation of this manuscript.

Bibliography

1. National Cancer Institute. Targeted Cancer Therapies (2020).

2. Carrozzo M., *et al*. "Oral Mucosal Injury Caused by Targeted Cancer Therapies". *Journal of the National Cancer Institute* 53 (2019).

3. Pastore S., *et al*. "The epidermal growth factor receptor system in skin repair and inflammation". *Journal of Investigative Dermatology* 128.6 (2008): 1365-1374.

4. Wilson IB and Cleary PD. "Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes". *Journal of the American Medical Association* 273.1 (1995): 59-65.

5. Ferrari V., *et al*. "Oral mucositis a side effect in Tyrosin-Kinase Inhibitor Therapy (Sunitinib): the role of assessment of symptoms in evaluation of toxicity". *EJC Supplements* 7.2 (2009): 195-196.

6. Lee WJ., *et al*. "Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib". *British Journal of Dermatology* 161.5 (2009): 1045-1051.

7. Rocque G. "What Is the Role of Symptom Management and Patient-Reported Outcomes in Adherence to Aromatase Inhibitors?" *Journal of Clinical Oncology* 36.4 (2018): 308-309.

8. Basch E., *et al*. "Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment". *Journal of the American Medical Association* 318.2 (2017): 197-198.

9. Basch E., *et al*. "Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial". *Journal of Clinical Oncology* 34.6 (2016): 557-565.

10. Wong SF., *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". *The Journal of Supportive Oncology* 8.5 (2010): 202-208.

11. Purdy-Lloyd K., *et al*. "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* 34.1 (2007): 216-217.

12. Gowland P., *et al*. "Evaluation of REGENECARE topical gel for treatment of adverse rash symptoms associated with EGFR inhibitor drugs". *Oncology Nursing Forum* 35.3 (2008): 536-537.

13. Tejpar S., *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* 25 (2007): 4037

14. Lacouture ME., *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". *Journal of Clinical Oncology* 28.8 (2010): 1351-1357.

15. Coleman S and Jatoi A. "STEPP for the EGFR inhibitor-induced rash--definitely a step in the right direction". *Current Oncology Report* 12.4 (2010): 223-225.

16. Boers-Doets CB and 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* 4.20 (2013): 70-71.

17. Wagner LI., *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* 21.4 (2013): 1033-1041.

18. Berthelet E., *et al*. "Preliminary reliability and validity testing of a new Skin Toxicity Assessment Tool (STAT) in breast cancer patients undergoing radiotherapy". *American Journal of Clinical Oncology* 27.6 (2004): 626-631.

19. Chan A and 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* 19.10 (2011): 1667-1674.

20. Lacouture ME., *et al*. "A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group". *Support Care Cancer* 18.4 (2010): 509-522.

21. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) (2018).

22. 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* 23 (2015): S1-S388.

23. Boers-Doets CB. "The Target System - Approach to assessment, grading, and management of dermatological and mucosal side effects of targeted anticancer therapies". Impaqtt, Wormer (2014).

24. Temmerman R. "Towards New Ways of Terminology Description. The sociocognitive approach". John Benjamins Publishing Company, Amsterdam/Philadelphia (2000).

25. Wagner LI and Lacouture ME. "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 (2007): 34-36.

26. Joshi SS., *et al*. "Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life". *Cancer* 116.16 (2010): 3916-3923.

27. The Free Dictionary. Characteristics (2014).

28. Di Maio M., *et al*. "Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials". *Journal of Clinical Oncology* 33.8 (2015): 910-915.

29. National Cancer Institute. Patient-Reported Outcomes version of the CTCAE (2013).

30. Hay JL., *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)". *Quality of Life Research* 23 (2014): 257-269.

31. Boers-Doets CB. "Oral Drugs: Challenges for the Oncology Nurse". *The Breast* 36 (2017): S24.

32. Park K., *et al*. "Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial". *Lancet Oncology* 17.5 (2016): 577-589.

33. Rini BI., *et al*. "Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial". *Lancet* 378.9807 (2011): 1931-1939.

34. Ocean AJ., *et al*. "Cetuximab is associated with excessive toxicity when combined with bevacizumab Plus mFOLFOX6 in metastatic colorectal carcinoma". *Clinical Colorectal Cancer* 9.5 (2010): 290-296.

35. Lavacchi D., *et al*. "Clinical evaluation of dacomitinib for the treatment of metastatic non-small cell lung cancer (NSCLC): current perspectives". *Drug Design, Development and Therapy* 13 (2019): 3187-3198.

36. Pennell NA., *et al*. "SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer". *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 37.2 (2019): 97-104.

37. Rugo HS. "Dosing and Safety Implications for Oncologists When Administering Everolimus to Patients With Hormone Receptor-Positive Breast Cancer". *Clinical Breast Cancer* 16.1 (2016): 18-22.

38. Giaccone G., *et al*. "Gefitinib in Combination With Gemcitabine and Cisplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 1". *Journal of Clinical Oncology* 22.5 (2004): 777-784.

39. Hamdan MY., *et al*. "Discontinuation and dose modification of imatinib in clinical practice". *Journal of Clinical Oncology* 25 (2007): 7045-7045.

40. Weber J., *et al*. "Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma". *The New England Journal of Medicine* 377.19 (2007): 1824-1835.

41. Goss PE., *et al*. "Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial". *The Lancet Oncology* 14.1 (2013): 88-96.

42. Blay J-Y., *et al*. "Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial". *The Lancet Oncology* 16.5 (2015): 550-560.

43. Nakao A., *et al*. "Final Results from a Phase II Trial of Osimertinib for Elderly Patients with Epidermal Growth Factor Receptor t790m-Positive Non-Small Cell Lung Cancer That Progressed during Previous Treatment". *Journal of Clinical Medicine* 9.6 (2020): 1762.

44. Freeman DJ. "Safety and Efficacy of Panitumumab in the Treatment of Metastatic Colorectal Cancer". *Clinical Medicine Therapeutics* 1 (2009): CMT.S2039.

45. Sutter S. "FDA Panel to Assess Ridaforolimus, Pazopanib for Sarcoma". MDEdge (2012).

46. Carlino MS., *et al*. "Long-term Follow-up of Standard-Dose Pembrolizumab Plus Reduced-Dose Ipilimumab in Patients with Advanced Melanoma: KEYNOTE-029 Part 1B". *Clinical Cancer Research* 26.19 (2020): 5086-5091.

47. Krishnamoorthy SK., *et al*. "Management of regorafenib-related toxicities: a review". *Therapeutic Advances in Gastroenterology* 8.5 (2015): 285-297.

48. Escudier B., *et al*. "Sorafenib in advanced clear-cell renal-cell carcinoma". *The New England Journal of Medicine* 356.2 (2007): 125-134.

49. Motzer RJ., *et al*. "Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma". *Journal of Clinical Oncology* 27.22 (2009): 3584-3590.

50. Dreyling M., *et al*. "Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study". *Lancet* 387.10020 (2016): 770-778.

51. Robert C., *et al*. "Improved overall survival in melanoma with combined dabrafenib and trametinib". *The New England Journal of Medicine* 372.1 (2015): 30-39.