ACTA ONCOLOGICA
2019, VOL. 58, NO. 5, 596–602
https://doi.org/10.1080/0284186X.2018.1560496

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The use of PRO in adverse event identification during cancer therapy – choosing the right questions to ask

Aase Nissen[a], Louise Bager[b] and Helle Pappot[a,b]

[a]Documentation and Quality, Danish Cancer Society, Copenhagen, Denmark; [b]Department of Oncology, The Finsen Centre, Rigshospitalet, Copenhagen, Denmark

ABSTRACT

Background: Adequate and timely monitoring of adverse events to cancer treatment is from our view dependent on a suitable Patient Reported Outcome (PRO) tool developed for the specific patient population based on cytostatic drugs included in the treatment. Therefore, a systematic method for construction of PRO questionnaires including selection of the appropriate questions is needed.

Purpose: The purpose of the present study was to develop and test a method of item selection for a PRO questionnaire to monitor adverse events in oncologic routine treatment of metastatic prostate cancer patients.

Patient and methods: Documentation on common symptomatic adverse events for the three drugs was collected from five different sources: 1) FDA product summary information; 2) EMA product summary information; 3) phase 3 Randomized Controlled Trials (RCT) leading to drug approval; 4) audit of the electronic patient files focusing on the oncologist's documentation of adverse events and 5) individual patient interview ($n = 16$) focusing on adverse events. The Patient Reported Outcome of Common Terminology Criteria for Adverse Events (PRO-CTCAE) was used as PRO item library. Selected symptoms were transformed into corresponding PRO-CTCAE questions. The questionnaire was tested by patients in a pilot test ($n = 12$). Patients for interviews and pilot testing were included by purposive sampling.

Results: A method for constructing a PRO questionnaire was developed, and a questionnaire of 25 PRO-CTCAE symptoms with 46 questions including an open write-in space for additional adverse events was constructed and tested.

Conclusion: This study demonstrates a systematic method to select questions on adverse events for a PRO questionnaire in a specific cancer population receiving oncologic treatment. The present study reveals that audit of patient files and patient interviews in our setting only add little to the information on adverse events obtained from FDA, EMA and RCT. The obtained questionnaire was found useful and acceptable by patients.

ARTICLE HISTORY
Received 23 July 2018
Accepted 4 December 2018

Introduction

Patient Reported Outcomes (PRO) has experienced increased focus in cancer care during recent years, and PRO has been included in research projects as an important source of information together with clinical investigations and objective test results [1]. The potential of PRO within the field of oncology seems of special importance since continuous monitoring of treatment results and timely handling of adverse events facilitates successful treatment of patients with numerous cycles of medical cancer treatment. Recent results have shown that an integration of PRO into care of patients with metastatic cancer during chemotherapy was associated with improved quality of life and increased survival [2]. Thus, it is important that a PRO tool for adequate and timely monitoring of adverse events experienced by the patient during chemotherapy can easily be constructed for a specific patient population [2]. By construction of a PRO questionnaire, it can be important to take in consideration, which cytostatic drugs are used in the treatment since adverse events can differ.

Clinicians can monitor patient's adverse events by Common Terminology Criteria for Adverse Events (CTCAE) [3]. Monitoring of patient experienced symptoms that indicate adverse events to medical cancer treatment is possible via the Patient Reported Outcome of Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument developed by National Cancer Institute (NCI) [3]. However, to our knowledge, no method has been published on how to select the right questions on adverse events for a PRO questionnaire in a specific cancer population during treatment.

The population of patients with metastatic prostate cancer is increasing in Denmark, as well as on an international level [4,5]. In addition, the treatment options for men with metastatic prostate cancer have increased within the last two decades from strictly hormone-therapy to several treatment

CONTACT Helle Pappot helle.pappot@regionh.dk Department of Oncology, The Finsen Centre, Rigshospitalet, 5073, Blegdamsvej 9, Copenhagen DK-2100, Denmark

lines including chemotherapy and other anti-cancer drugs administered intravenously, which have aided in improving the survival length for this patient population [6]. These developments suggest that more men each year will undergo treatment for metastatic prostate cancer, and that each patient will likely receive more treatment than those who have come before him. PRO could possibly be of special importance in this group to ensure proper handling of adverse events, fulfillment of planned treatment, good quality of life and prolonging of survival.

The purpose of the present study was to develop and test a method of item selection for a PRO questionnaire to monitor adverse events in oncological routine treatment using metastatic prostate cancer as a test population.

Methods

Documentation on symptomatic adverse events that could be identified by the patient was collected from five different sources to get a complete picture of possible adverse events for each of the specific drugs.

FDA and EMA

Before marketing, drugs are approved by The Food and Drug Administration (FDA) in American countries and European Medicines Agency (EMA) in European countries. The documentation from these agencies contains information about adverse events discovered in clinical studies. Therefore, FDA and EMA product summary information of adverse events described as serious or very common (>10%) in single drug treatment were used for each drug [7–12].

Randomized controlled clinical trials

Common adverse events (>10%) found in the phase 3 Randomized Controlled Trials (RCT) leading to EMA approval were included for each drug [13–15].

Audit of patient files

A retrospective audit of the electronic patient files focusing on treating oncologist's documentation of adverse events was performed. Inclusion criteria for both the audit of patient files and individual interviews were patients diagnosed with metastatic prostate cancer, and who were treated with Alpharadin, Docetaxel or Cabazitaxel at the Oncology Clinic, Rigshospitalet, Copenhagen, Denmark. Patients for the audit were previously included in a feasibility study, $n = 54$, characteristics have previously been described [16]. In the audit of patient files, all adverse events mentioned at each treatment were noted and included in the study regardless of the frequency of the symptom.

Table 1. Characteristics of patients interviewed for adverse events (patient group 1) and patients who tested the questionnaire (patient group 2).

	Patient group 1 ($n = 14$)	Patient group 2 ($n = 12$)
Number		
Cabazitaxel	4	1
Docetaxel	7	7
Alpharadin	3	4
Age, years	72 (60–84)	71 (61–80)
Comorbidity		
Yes	5	8
No	9	4
Number of chemotherapy series		
2	1	3
3	2	1
4	3	1
5	3	1
>5	5	6
Dose reduction		
Yes	3	1
No	11	11
Education		
Skilled worker/short	5	7
Medium long	6	3
Long	3	1
Other	0	1
Marital status		
Married	14	11
Single	0	1

Patient interviews on adverse events

Inclusion criteria for patients included in the interviews (patient group 1, Table 1) were patients who had joined active cancer treatment, completed at least one cycle of medical treatment, and who were able to read and speak Danish and accept participation in the study. Patients for interviews were included by purposive sampling.

Individual patient interviews on adverse events experienced during their course of treatment were performed at the clinic when patients came for treatment. Patients were invited consecutively to participate. After agreeing to join the study, the research nurse interviewed the patients about their experience of adverse events. All adverse events mentioned by the patients were included regardless of frequency or severity.

Selecting adverse events for the questionnaire

The adverse events identified by each of the five methods were grouped in organ classes according to Medical Dictionary for Regulatory Activities – MedDRA [17]. In a consensus process, the research team comprising a pharmacist (AN), a research nurse (LB) and an oncologist (HP) agreed on the synonym classification of identical symptoms described in different wording (such as 'dyspnea' = 'shortness of breath' or 'appetite loss/decreased appetite' = 'anorexia') resulting in a list of equally worded symptoms from each of the five sources (Table 2). The consensus was based on the clinical description of the symptoms according to the Danish medical dictionary and the clinical experience from contact with the patients.

To select PRO items representing the most important symptoms relevant for continuous monitoring, two inclusion

Table 2. Adverse events for Cabazitaxel, Docetaxel and Alpharadin identified in different documentation (FDA and EMA summary, Clinical trials, patient files and patient interview).

SYMPTOM REGISTRATION		FDA Freq ≥ 10 %			EMA Freq ≥ 10 %			Clinical trials Freq ≥ 10 %			Patient files			Patient interviews		
MedDRA SYSTEM ORGAN CLASS	SYMPTOM	C	D	X	C	D	X	C	D	X	C	D	X	C	D	X
Metabolism and nutrition disorders	**Appetite loss/decreased**	x			x	x			x		x	x	x		x	x
	Dysguesia	x			x	x			x		x	x	x		x	
Nervous system disorders	**Neuropathy**	x	x			x			x		x	x		x		
	Trouble Sleeping										x	x			x	x
	Memory Impairment														x	
	Tremor														x	
	Dizziness										x	x	x	x		
Eye disorders	Eye disorders										x					
	Lacrimation disorder								x		x	x	x			
Respiratory, thoracic and mediastinal disorders	**Cough**	x			x							x	x	x		
	Dyspnea	x			x	x		x	x		x	x	x		x	
	Dysphonia											x				
	Rhinitis														x	
Cardiac disorders	Chest pain												x			
Gastrointestinal disorders	**Vomiting**	x	x	x	x	x	x	x	x		x	x	x			x
	Nausea	x	x	x	x	x	x	x	x	x	x	x	x	x		
	Diarrhea	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
	Dyspepsia	x										x		x		
	Abdominal pain	x			x			x					x		x	
	Stomatitis		x			x			x			x			x	
	Constipation	x			x			x			x	x	x	x	x	
	Dry Mouth											x			x	
Skin and subcutaneous tissue disorders	**Rash**		x			x						x			x	
	Dry Skin													x	x	
	Acne											x				
	Nail and nail bed conditions		x			x			x		x	x	x			
	Alopecia	x	x		x	x			x		x	x		x	x	
	Increased sweating														x	
Vascular disorders	Flushing										x			x	x	
Musculoskeletal and connective tissue disorders	**Back Pain**	x			x			x								
	Arthralgia	x			x			x		x	x	x	x		x	
	Myalgia		x			x			x	x		x	x		x	
General disorders and administration site conditions	**Fatigue**	x			x	x		x	x		x	x	x	x	x	x
	Fever and chills	x	x		x			x			x	x	x	x	x	
	Asthenia	x	x		x	x		x				x		x	x	
	Pain					x					x					
	Oedema		x	x		x			x			x	x		x	
	Mucosal findings abnormal										x	x		x	x	
	Peripheral coldness														x	
	Epistaxis											x				
Ear and labyrinth disorders	Tinnitus														x	
Renal and urinary disorders	Urinary retention										x					
	Urinary incontinence														x	
Psychiatric disorders	Trouble thinking or concentrating														x	
	Confused state														x	
	Depression											x				
Total number of symptoms		17	12	4	15	16	3	11	14	4	21	29	18	14	29	4

C: Cabazitaxel; D: Docetaxel; X: Alpharadin.
Grey background: Symptoms selected for the PRO questionnaire.
Bold font: Identified by criteria 1 and corresponding PRO-CTCAE item.
Bold italic font: Identified by criteria 2 and corresponding PRO-CTCAE item.

criteria were created. For selection, at least one criterion should be fulfilled within the scope of any of the drugs:

1. Symptoms mentioned in at least 2 of the 5 sources and at least one of them being FDA product summary or EMA leaflet
2. Symptoms mentioned by both oncologists (audit of patient file) and patients (individual interview)

For each of the symptoms identified by this method, the corresponding symptom and items from the PRO-CTCAE item library were used, if present. PRO-CTCAE items are defined as questions describing presence, amount, frequency, severity and/or interference with daily activities of a symptom. If no PRO-CTCAE symptom matched an identified symptom, it was decided by the research group whether the symptom could be partly covered by an existing PRO-CTCAE symptom, required a separate question from another PRO tool, or if it could be covered by an open write-in space in the PRO tool. The specific phrasing of the questions directed to the patients for each symptom originates from the Danish translation of PRO-CTCAE [18]. The feasibility of Danish PRO-CTCAE has been investigated previously among prostate cancer patients [16].

Pilot test of the PRO-CTCAE questionnaire

A pilot test of the PRO-CTCAE questionnaire (i.e., the list of symptoms constructed from these criteria) was conducted according to design, number and relevance of the questions and overall satisfaction in patients with metastatic prostate cancer until saturation was met (patient group 2, Table 1). The patient interviews were conducted in the same way as the patient interview on adverse events. Patients for pilot testing were included by purposive sampling. After agreeing to join the study, the patients were given a paper version of the PRO-CTCAE questionnaire to read on their own. Then the research nurse interviewed the patients about their experience of completing the questionnaire. The focus of the interview was the questionnaires' ability to cover the patients' adverse events, the total number of questions and the patients' experience of the questions' relevance.

The study was approved by the Danish Data Protection Agency (case no. 2012-58-0004). In Denmark, questionnaire and interview-based studies are exempt from the approval of the national ethical review board. Informed consent was obtained from all included patients.

Results

The documents from FDA, EMA and the clinical trials were reviewed separately by two researchers. Their findings for each of the three drugs were agreed on in a consensus process. The audit was conducted on 52 patient files of patients of average age 69 (51–88), who were treated at the clinic during the period from September 2014 to May 2015. In total, 299 treatment series were reviewed. The mean number of treatment series was 5.8 (range 4–6). Fourteen individual semi-structured patient interviews on adverse events in patient group 1 were conducted in May to June 2017. The patient characteristics are presented in Table 1.

In total, 46 adverse events were identified and 27 of those fulfilled our criteria for inclusion in a monitoring questionnaire (Table 2). Four common symptoms 'Trouble sleeping', 'Dizziness', 'Dry mouth' and 'Mucosal findings abnormal' were identified by criteria 2 (mentioned by both oncologists and patients).

Table 3 shows the identified symptoms and the matching PRO-CTCAE symptoms. Four symptoms 'Dyspepsia', 'Stomatitis', 'Back pain' and 'Asthenia' had no direct matching symptom in the PRO-CTCAE. However, the symptoms 'Dyspepsia' was considered partly covered by the PRO-CTCAE symptom 'Abdominal pain' and 'Stomatitis' partly covered by the symptom 'Mouth/throat sores'. 'Back pain' could be covered by the less specific PRO-CTCAE 'Pain' and 'Asthenia' was considered covered by the PRO-CTCAE 'Fatigue', which also include lack of energy. The symptom 'Rash' expressed allergic reaction in the documentation from FDA and EMA, and it was covered by three symptoms from PRO-CTCAE; 'Rash', 'Itching skin' and 'Hives', and it was considered also to cover the symptom 'Hand and foot syndrome' as this symptom was described also to be present on the body. Thus, the matching process resulted in a questionnaire of 25 PRO-CTCAE symptoms consisting of 46 PRO-CTCAE items. Finally, a blank write-in space was added to cover the rest of the identified symptoms without a direct matching PRO-CTCAE symptom as well as other symptoms.

The pilot test of the PRO-CTCAE questionnaire was conducted in 12 patients in patient group 2 in July 2017. Patient characteristics are presented in Table 1. The number of questions was accepted by all patients, although a few patients expressed, that it should not be any higher. All participants considered both main- and sub-questions to cover the range of symptoms they had experienced and that they knew they were at risk of. Furthermore, all questions were found to correspond to their experiences of symptoms from cancer treatment and disease. The questionnaire had room for write-in of additional symptoms. Only one patient added two symptoms: 'Increased sweating' and 'Floaters in the eyes'. One patient treated with Alpharadin was confused and concerned by the experience of the questionnaire, as he could not recognize the range of symptoms and feared he would experience these symptoms later.

Discussion

In this study, we developed, tested and now suggest a method for selection of appropriate questions to ask patients during cancer treatment. This method aimed at discovering patients' experienced adverse events, as this is a prerequisite for offering adequate adverse event handling and facilitating the tolerability of a full treatment schedule. In clinical trials, one of the aims is to discover the adverse event profile for a specific drug, which is included in the marketing approval documentation. However, these studies are performed on selected patient populations, and often post-marketing

Table 3. Matching of identified adverse events symptoms and PRO-CTCAE symptoms and the corresponding items escribing presence, amount, frequency, severity and/or interference with daily activities of a symptom.

Identified symptom	Matching PRO-CTCAE symptom	PRO-CTCAE Items	Comment
Appetite loss/decreased	Decreased appetite	2: Severity and interference with daily life	
Dysguesia	Taste change	1: Severity	
Neuropathy	Numbness and tingling	2: Severity and interference with daily life	
Trouble Sleeping	Insomnia	2: Severity and interference with daily life	
Dizziness	Dizziness	2: Severity and interference with daily life	
Cough	Cough	2: Severity and interference with daily life	
Dyspnea	Shortness of breath	2: Severity and interference with daily life	
Vomiting	Vomiting	2: How often and severity	
Nausea	Nausea	2: How often and severity	
Diarrhea	Diarrhea/Diarrhoea	1: How often	
Dyspepsia			Partly covered by PRO-CTCAE 'Abdominal pain'
Abdominal pain	Abdominal pain	3: How often, severity and interference with daily life	
Stomatitis			Partly covered by the PRO-CTCAE symptom 'Mouth/throat sores'
Constipation	Constipation	1: Severity	
Dry Mouth	Dry mouth	1: Severity	
Rash	Rash	1: Presence	The symptom is covered by three PRO-CTCAE symptoms
	Itching	1: Severity	
	Hives	1: Presence	
Nail and nail bed conditions	Nail discoloration	1: Presence	Partly covered by the PRO-CTCAE symptom
Alopecia	Hair loss	1: Amount	
Back Pain			Partly covered by the PRO-CTCAE symptom 'General pain'
Arthralgia	Joint pain	3: How often, severity and interference with daily life	
Myalgia	Muscle pain	3: How often, severity and interference with daily life	
Fatigue	Fatigue	2: Severity and interference with daily life	
Fever and chills	Chills	2: How often, severity	
Asthenia			Partly covered by the PRO-CTCAE symptom 'Fatigue'
Pain	General pain	3: How often, severity and interference with daily life	
Oedema	Swelling	3: How often, severity and interference with daily life	
Mucosal findings abnormal	Mouth/throat sores	2: Severity and interference with daily life	Partly covered by the PRO-CTCAE symptom
Total: 27 symptoms	Total: 25 symptoms	Total: 46 items	

surveillance must be initiated to monitor the adverse event profile throughout the routine use of the drug. Therefore, we considered it of importance to additionally include information on the adverse events noted by the treating oncologists and patients during active cancer treatment, when developing an adequate questionnaire for the monitoring of adverse events

The study was inspired by the EORTC guidelines for the development of a PRO questionnaire for Quality of Life as described by Johnson et al. [18] and included information from public documentation (FDA and EMA) and clinical trials of the drugs used in metastatic prostate cancer treatment alongside information from oncologists and patients on experienced adverse events throughout routine clinical treatment. We believe that the systematic selection of questions for PRO-questionnaires is of importance for future studies and that our method has the advantage of including experience from daily practice and patient involvement, which may better mimic real-world practice.

Information from the oncologists and patients had the drawback that it included all adverse events and symptoms mentioned by the patient regardless the frequency and severity of those during a longer treatment phase in comparison to the information from the official documents, which only included common adverse events experienced by more than 10 % of the patients. If serious adverse events that were not included in the official documents would be discovered in the qualitative information from oncologists and patients, it would indicate the need for including this type of information in developing a questionnaire to adequately monitor adverse events during routine cancer treatment.

However, as shown in Table 3 our study showed good harmony between the identified adverse event profiles discovered by official documents and the information from oncologists and patients. Although the terminology of symptoms differed between both the official documents and the additional sources, it was possible to identify meaningful synonym groups of symptoms. The additional four symptoms mentioned in Table 2 as identified by the oncologists and patients were common oncological adverse events. A limitation of the present study was, that it could not evaluate the frequency or severity of these specific symptoms. No rare adverse events were discovered by adding results from oncologists or patients.

In developing the questionnaire, we chose to use the official phrasing of patient questions for specific toxicity symptoms in PRO-CTCAE, if possible. Few of the identified adverse

events were not covered by a PRO-CTCAE symptom, and as it is a comprehensive task to develop new patient questions, it was decided to test a model of questionnaire including only the PRO-CTCAE symptoms and an additional open write-in space to cover adverse events that was only partly or not covered by the PRO-CTCAE symptoms. The pilot test confirmed that the questionnaire was well accepted by the patients regarding the number of questions, and that it covered the experienced adverse events. However, the chosen number of questions may have both and advantages and limitations; a low number of questions may improve compliance and adherence while an increased number can comprise the complete patient experience.

The study showed that the number and character of adverse events were different for the three drugs, and that Alpharadin had the lowest number of adverse events. In developing a monitoring tool for a specific disease, it is preferable to use one model covering all drugs used in the treatment of the specific diagnose, as the patients often shift treatment regimen during their treatment. Shifting questionnaires according to the drug in actual treatment would be confusing for the patients, inadequate for the discovery of adverse events from a previously used drug, inconvenient for the health professionals, and capable of increasing the risk of using the wrong questionnaire. For the clinician, it is an advantage that as many as possible of the adverse events, that will require a clinical action are caught. Therefore, we made one questionnaire covering all identified questions included in PRO-CTCAE, resulting in 25 symptoms covered by 46 questions. A comprehensive questionnaire might be a challenge for the patients to answer, but in our pilot test the symptoms were considered relevant to the patients and the number of questions was accepted. Further, patients get familiar with the questions during their treatment, if asked at each cycle of chemotherapy.

Conclusion

To our knowledge, this is the first description of a method of systematic selection of questions on adverse events for a PRO questionnaire in a specific cancer population receiving oncological treatment. The present study reveals that audit of patient files and patient interviews only add little to the information on adverse events obtained from FDA, EMA and RCT. However, we recommend inclusion of a pilot test of every PRO questionnaire constructed according to our method, to test the appropriateness of the identified symptoms, the number of questions and any if additional symptoms need to be included. To our opinion, this method will contribute to both a practically useful and clinically valid construction of PRO questionnaires for use during oncological treatment.

Ethical approval

Due to Danish regulations, no ethical approval was needed for the present study.

Acknowledgments

We acknowledge the Danish prostate cancer patients, who participated in this research project.

Disclosure statement

AN and LB has no conflicts of interest to declare. HP has participated in an advisory board for MSD, received research grants from MSD, Pfizer, Janssen, Sanofi, Abbvie and Roche.

Funding

The study was funded by the Danish Cancer Society.

References

[1] LeBlanc TW, Abernethy AP. Patient-reported outcomes in cancer care – hearing the patient voice at greater volume. Nat Rev Clin Oncol. 2017;14:763–772.

[2] Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197–198.

[3] Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JNCI J Natl Cancer Inst. 2014;106. DOI:10.1093/jnci/dju244.

[4] World Health Organization; GLOBOCAN. Cancer fact sheets: prostate cancer; 2012 [accessed 2017 Dec 19]. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/prostate-new.asp

[5] Association of the Nordic Cancer Registries. NORDCAN, Kraeftstatistik: Nøgletal og figurer; 2016 [cited 2017 Dec 19]. Available from: http://www-dep.iarc.fr/NORDCAN/DK/StatsFact.asp?cancer=261&country=208

[6] Professionals S-O. Prostate Cancer. Uroweb; 2014 [accessed 2017 Dec 19]. Available from: http://uroweb.org/guideline/prostate-cancer/

[7] U.S. Food & Drug Administration. Highlights of prescribing information. Xofigo; 2013 [cited 2017 Dec 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203971lbl.pdf

[8] U.S. Food & Drug Administration. Highlights of prescribing information. Jevtana; 2010 [cited 2017 Dec 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201023lbl.pdf

[9] U.S. Food & Drug Administration. Highlights of prescribing information. Taxotere; 2010 [cited 2017 Dec 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020449s059lbl.pdf

[10] European Medicines Agency. EPAR product information; 2017 [cited 2017 Dec 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002018/WC500104764.pdf

[11] European Medicines Agency. EPAR product information. Xofigo; 2016 [cited 2017 Dec 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002653/WC500156172.pdf

[12] European Medicines Agency. EPAR product information. Taxotere; 2017 [cited 2017 Dec 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000073/WC500035264.pdf

[13] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502–1512.

[14] de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic

castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376: 1147–1154.

[15] Parker CC, Pascoe S, Chodacki A, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol. 2013;63:189–197.

[16] Baeksted C, Pappot H, Nissen A, et al. Feasibility and acceptability of electronic symptom surveillance with clinician feedback using the Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events (PRO-CTCAE) in Danish prostate cancer patients. J Patient Rep Outcomes. 2017;1:1.

[17] Baeksted C, Nissen A, Pappot H, et al. Danish translation and linguistic validation of the US National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). J Pain Symptom Manage. 2016; 52:292–297.

[18] Johnson C, Aaronson N, Blazeby JM, et al. Guidelines for developing questionnaire modules. Eortc Quality of Life GROUP; 2011.