Selection of Patient Reported Outcomes Questions Reflecting Symptoms for Patients with Metastatic Melanoma Receiving Immunotherapy

Tolstrup LK^{1,3,4} Bastholt L^{1,4} Dieperink KB^{1,3,4} Zwisler AD^{1,3,4} Pappot H²,

¹Department of Oncology, Odense University Hospital, DK and ²Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, DK and ³REHPA – The Danish Knowledge Center for Rehabilitation and Palliative Care, DK ⁴Institute of Clinical Research, University of Southern Denmark, Odense, DK

Background

- Toxicity-monitoring plays an important role in all cancer treatment, however, early recognition is vital for detecting and treating immune-related symptoms.
- Preparing a Patient Reported Outcomes (PRO) tool and including melanoma patients receiving immunotherapy in the reporting of symptoms, may optimize toxicity-monitoring.
- The objective of this study was to identify the symptoms and their equivalent questions to include from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) library for melanoma patients, receiving immunotherapy.

Methods and Materials

Literature Review
Three databases

Chart Audit
37 medical records

Product information
European Medicines
Agency

PubMed.gov

Embase®

CINAHL

Anti-PD1 (Pembrolizumab)
N = 23

Anti-CTLA-4 (Ipilimumab)
N = 3

Anti-PD1 and anti-CTLA-4 in sequence
N = 11

Anti-CTLA-4 (Ipilimumab) and anti-PD1 (Nivolumab) in combination

Perspectives

- One of the ways to detect AEs early may be to have the patients self-report the symptoms they experience
- When preparing a PRO-tool it is important that the preparatory work of selecting questions is done properly
- We have uncovered the most important and relevant symptoms and designed a PRO-questionnaire based on PRO-CTCAE
- The questionnaire is applied in an ongoing randomized clinical trial where melanoma patients in the intervention arm self-report their symptoms while on treatment with immunotherapy. Patients in the control have standard toxicity-monitoring
- We expect that the applied method can be used in relation to other patient groups when designing a PRO-questionnaire dealing with treatment-related symptoms

Results

Figure 1 Article selection flowchart. Articles on immune-related adverse events identified in melanoma patients treated with immunotherapy

Table 1 Characteristics of studies included to determine which AEs to include in the PRO-CTCAE for melanoma patients				
Trial	Design	Enrollment size (n)	Study drug	Dose (mg/kg)
Eggermont et al.	Adjuvant, Randomized phase 3	951	Ipilimumab	10
Hodi et al.	Phase 3 Randomized	676	Ipilimumab	3
Larkin et al.	Phase 3 randomized	945	Nivolumab or Nivolumab/Ipilimumab	3; 1+3; 3
Postow et al.	Double-blind Phase 2 – dose ranging	142	Ipilimumab or Ipilimumab/Nivolumab	3; 3+1
Ribas et al.	Phase 1b	655	Pembrolizumab	10; 2
Ribas et al.	Phase 2	540	Pembrolizumab	2; 10
Robert et al.	Randomized, phase 2	418	Nivolumab	3
Robert et al.	Phase 3	834	Pembrolizumab	10; 3
Weber et al.	Randomized, open-label phase 3	405	Nivolumab	3
Weber et al.	Randomized, open label, phase 2	140	Nivolumab	3; 3

Table 2 Adverse events included in the PRO-CTCAE for melanoma patients receiving immunotherapy based on findings in medical records, literature review and product information					
Frequency of Adverse Events	CTCAE terms	Literature review	Medical records	Product information	PRO-CTCAE symptom terms
Very common (may affect more than 1 in 10 people)	Vomiting	X		x	Vomiting
	Nausea	x	x	x	Nausea
	Anorexia	x	x	x	Decreased appetite
	Diarrhea	x	x	x	Diarrhea/Loose or watery stool
	Abdominal pain	x	x	x	Abdominal pain
	Constipation	x		x	Constipation
	Rash	x	x	x	Rash
	Pruritus	x	x	x	Itching
	Dyspnea	x			Shortness of breath
	Myalgia	x	x		Muscle pain
	Arthralgia	x	x	x	Joint pain
	Fatigue	x	x	x	Fatigue
	Injection site reaction			x	Pain and swelling at injection site
	Headache	x	x		Headache
	Chills	x	x		Chills
	Asthenia	x		x	
Common (may effect up to 1 in 10 people)	Mucositis (oral)	x	x	x	Mouth/throat sores
	Dry skin	x	x	x	Skin dryness
	Alopecia	x		x	Hair loss
	Blurred vision	x	x	x	Blurred vision
	Cough	x	x	x	Cough
	Dysgeusia	x	x	x	Taste changes
	Dizziness	x	x	x	Dizziness
	Edema	x		x	Swelling
	Pain	x		x	General pain
	Peripheral sensory neuropathy		x	x	Numbness & tingling
	Hot Flashes	x		x	Hot flashes
	Flu –like symptoms		x	x	
	Pain in extremity	x		x	
Uncommon/not present	Depression (2 items)		x		Discouraged
	Blood in stool				Sad

*Not PRO-CTCAE items, but covered by other items

Overall, the reported symptoms from the literature review aligned with those identified in the chart audit. The examination of the product information supported the findings from review and chart audit, revealing only one additional symptom.