

A Qualitative Study Examining PRO-CTCAE Coverage of Treatment-Emergent Adverse Events Reported by Patients with Multiple Myeloma

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Discussion



The PRO-CTCAE covered most TEAEs found in this study, including GI symptoms, which were among the most bothersome types of symptoms reported by participants. In relation to steroid-related TEAEs, sleep disturbance was the most common and most bothersome and is covered in the PRO-CTCAE. However, there were some key gaps in PRO-CTCAE coverage: excessive energy, bitter/metallic taste, taste sensitivity, irritability, hunger/increased appetite. While PRO-CTCAE item 7 asks about difficulty tasting, it does not specifically address bad tastes or being overly sensitive. Muscle weakness and brittle nails were also not fully covered by the PRO-CTCAE.



Conclusions

People with MM report bothersome TEAEs linked to MM therapies including steroids, some of which are not measured by the PRO-CTCAE. Additional assessment instruments may be needed to cover specific gaps in the PRO-CTCAE item library to appropriately measure treatment-related symptoms in trials of MM therapy.

Introduction

Background

Patient-reported treatment-emergent adverse events (TEAEs) are becoming more relevant, not just for patients and practitioners, but also for regulatory agencies.¹ The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a validated tool for reporting TEAEs experienced by patients in cancer clinical trials, but more research is needed on the suitability of the PRO-CTCAE for assessing treatment-related symptoms for multiple myeloma (MM) therapies. Conventional therapies for MM rely on high doses of steroids which are associated with metabolic toxicities, thus it is especially important to understand TEAEs associated with steroids.

Objective

Evaluate whether the PRO-CTCAE system comprehensively measures TEAEs identified by MM patients, including TEAEs associated with steroids.

Results

Concept saturation, the point at which new concepts ceased to appear in interviews, occurred at interview 11, with most concepts identified during the first 8 interviews.

The most commonly-reported TEAEs were:

- Gastrointestinal (nausea, diarrhea/constipation, appetite or taste changes)
- Changes in energy level (fatigue, excessive energy)
- Cognitive (brain fog, difficulty concentrating, memory problems)
- Pain (muscle cramps, joint pain, headache)
- Neuropathy
- Changes in skin, nails, or hair (rash, bruising, brittle nails, hair loss)
- Mood symptoms (anxiety, irritability)
- Sleep problems
- Muscle weakness

Participants commonly described gastrointestinal symptoms as the most bothersome or least tolerable TEAE.

Participants also reported less-common symptoms, including dizziness, blurry vision, chills/flushing/sweating, racing heart, respiratory problems, fever, infections, urinary problems, and sexual problems.

TEAEs reported in association with steroids included:

- Excessive energy that disrupted sleep or functioning
- Irritability
- Taste changes (e.g., bitter/metallic taste)*
- Increased appetite and unwanted weight gain

*Note that taste changes were commonly mentioned both in association with steroids and with other treatments.

The study included 16 participants (see Table 1 for participant demographics). All participants had received steroids with either their current or a past line of treatment. Seven participants (44%) were on their first line of therapy. Six (38%) had relapsed/refractory MM and three (19%) had ceased at least one prior treatment due to TEAEs.

Most of the TEAEs reported by participants were covered in the PRO-CTCAE. Table 2 shows the TEAEs that were reported in interviews (not directly associated with steroids) and are covered in the PRO-CTCAE. Table 3 shows the steroid related TEAEs reported in interviews and covered in the PRO-CTCAE.

Some concepts from the PRO-CTCAE were not reported in MM interviews, these concepts are shown in Table 4.

Table 1. Participant Demographic Characteristics

Characteristic	N (%)
Age	
40-49	1 (6%)
50-59	7 (44%)
60-69	6 (38%)
70-79	2 (13%)
Sex	
Male	6 (38%)
Female	10 (63%)
Race	
White	11 (69%)
Black	4 (25%)
Mixed Race	1 (6%)
Ethnicity	
Hispanic	2 (13%)
Non-Hispanic	14 (88%)

Table 2. MM TEAEs not Directly Associated with Steroids Reported in Interviews and Covered in the PRO-CTCAE

Item #	PRO-CTCAE Item Concept	Item #	PRO-CTCAE Item Concept
1	Dry mouth	25	Skin dryness
2	Difficulty swallowing	26	Acne or pimples on the face or chest
3	Mouth or throat sores	27	Hair loss
8	Decreased appetite	28	Itchy skin
11	Heartburn	29	Hives (itchy red bumps on the skin)
12	Increased passing of gas (flatulence)	31	Lose any fingernails or toenails
13	Bloating of the abdomen (belly)	32	Ridges or bumps on fingernails or toenails
15	Constipation	33	Change in color of fingernails or toenails
16	Loose or watery stools (diarrhea)	50	Aching muscles
17	Pain in the abdomen (belly)	51	Aching joints
17c	Activity interference from abdomen pain	63	Urinate frequently
18	Lose control of bowel movements	68	Decreased sexual interest
19	Shortness of breath	73	Bruise easily (black and blue marks)
20	Cough	74	Shivering or shaking chills
21	Wheezing	78	Nosebleeds
22	Arm or leg swelling	79	Pain, swelling, redness of a site of drug injection or IV
24	Rash	80	Body odor

Table 3. Steroid Related Symptoms Reported in Interviews and Covered in the PRO-CTCAE

Item #	PRO-CTCAE Item Concept
7	Problems with tasting food or drink
9	Nausea
10	Vomiting
14	Hiccups
23	Pounding or racing heart (palpitations)
39	Numbness or tingling in your hands or feet
40	Dizziness
41	Blurry vision
46	Problems with concentration
47	Problems with memory
48	Pain
49	Headache
52	Insomnia (including difficulty falling asleep, staying asleep, or waking up early)
53	Fatigue, tiredness, or lack of energy
54	Anxiety
56	Sad or unhappy feelings
75	Unexpected/excessive sweating during the day/nighttime
77	Hot flashes/flushes

Table 4. PRO-CTCAE Concepts not Reported in MM Interviews

PRO-CTCAE Item Concepts NOT reported in interviews			
• Skin cracking at the corners of mouth	• Skin burns from radiation	• Irregular menstrual periods	• Difficulty getting or keeping an erection
• Voice changes	• Unusual darkening of the skin	• Missed an expected menstrual period	• Ejaculation problems
• Hoarse voice	• Stretch marks	• Unusual vaginal discharge	• Took too long to climax
• Wheezing	• Flashing lights in front of your eyes	• Vaginal dryness	• Unable to have an orgasm
• Interference with activities from arm or leg swelling	• Spots or lines (floaters) that drift in front of your eyes	• Pain or burning with urination	• Pain during vaginal sex
• Hand-foot syndrome	• Watery eyes (tearing)	• Sudden urge to urinate	• Breast area enlargement or tenderness
• Increased skin sensitivity to sunlight	• Ringing in your ears	• Urine color change	• Unexpected decrease in sweating
• Bed sores	• Feel that nothing could cheer you up	• Loss of control of urine (leakage)	

A few TEAEs reported by MM patients were not in the PRO-CTCAE. Table 5 below shows concepts reported by MM patients but not found in the PRO-CTCAE, with representative quotations.

Table 5. Representative Quotations: Symptoms not Covered in the PRO-CTCAE

Concept	N	Representative quotation
Taste Changes	11	The dex causes changes in taste. . . Bitter. It's almost like if you had bitter taste. Almost like if you – I don't know, I always put salt on my grapefruit to kind of mask the grapefruit taste, but imagine if you did not put any salt or any sugar on your grapefruit, it's kind of like that kind of a taste. (US13)
Excess Energy	9	"More energy than you ever could imagine. But that crashes and then you can't sleep. We call it devil dex." (US01)
Muscle Weakness	9	"So weak. I can't lift anything. Yes, I can't make my bed." (US17)
Brittle Nails	8	"They have more defined ridges than they used to, and they're not very strong. It's hard to grow them without breaking." (US03)
Increased Appetite	7	"My appetite – I felt like I was the Incredible Hulk, you know, with the amount of food that I would eat. My wife and I, we'd go out and eat, and we'd have breakfast. Instead of getting one plate, I would get two plates, and it really packed on the pounds for me. It changed the perceptions of me. It just had my body feeling like I was working on overdrive all the time." (US15)
Irritability	6	"[I'd] get agitated so what I had to do was tell everybody, "Okay, it's my dex day." Like, you need to warn friends and family." (US14)
Weight Gain	6	"I still have the weight gain from being on the dex. As soon as I started this new treatment, even at a lower dose of dex, I immediately put on like eight pounds." (US19)

References

1. U.S. Food and Drug Administration. (2024). Core Patient-Reported Outcomes in Cancer Clinical Trials; Guidance for Industry; Availability, 89 FR 83884. October 18, 2024.

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