Assessment of Adverse Events From the Patient Perspective in a Phase 3 Metastatic Castration-Resistant Prostate Cancer Clinical Trial

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IMPORTANCE Standard adverse event (AE) reporting in oncology clinical trials has historically relied on clinician grading, which prior research has shown can lead to underestimation of rates of symptomatic AEs. Industry sponsors are beginning to implement in trials the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which was developed to allow patients to self-report symptomatic AEs and improve the quality of symptomatic AE detection.

OBJECTIVES To evaluate the feasibility of implementing PRO-CTCAE in a prespecified correlative analysis of the phase 3 COMET-2 trial and enumerate statistically significant between-group differences in symptomatic AEs using PRO-CTCAE and the CTCAE.

DESIGN, SETTING, AND PARTICIPANTS This correlative study of 119 men in the randomized, double-blind, placebo-controlled phase 3 COMET-2 trial with metastatic castration-resistant prostate cancer who had undergone at least 2 prior lines of systemic treatment was conducted from March 2012 to July 2014. Participants completed PRO-CTCAE items using an automated telephone system from home prior to treatment and every 3 weeks during treatment. Statistical analysis was performed from May 2018 to June 2019.

MAIN OUTCOMES AND MEASURES The proportion of patients who completed expected PRO-CTCAE self-reports was computed as a measure of feasibility.

RESULTS Among the 119 men in the study (median age, 65 years [range, 44-80 years]), 534 of 587 (91.0%) expected PRO-CTCAE self-reports were completed, with consistently high rates of completion throughout participation. Rates of self-report adherence were similar between groups (cabozantinib s-maleate, 286 of 317 [90.2%]; and mitoxantrone hydrochloride-prednisone, 248 of 270 [91.9%]). Of 12 measured, patient-reported PRO-CTCAE symptomatic AEs, 4 reached statistical significance when comparing the proportion of patients with at least 1 postbaseline score greater than 0 between groups (differences ranged from 20.1% to 34.1% with higher proportions in the cabozantinib group; all $P < .05$), and use of a method for accounting for preexisting symptoms at baseline yielded 7 AEs with statistically significant differences between groups (differences ranged from 20.5% to 41.2% with higher proportions in the cabozantinib group; all $P < .05$). In the same analysis using investigator-reported CTCAE data, no statistically significant differences were found between groups for any symptomatic AEs.

CONCLUSIONS AND RELEVANCE PRO-CTCAE data collection was feasible and improved the accuracy of symptomatic AE detection in a phase 3 cancer trial. This analysis adds to mounting evidence of the feasibility and value of patient-reported AEs in oncology, which should be considered for inclusion in cancer trials that incorporate AE evaluation.

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Prior research reveals that investigators miss up to half of study participants' symptomatic adverse events (AEs) in drug development trials (eg, nausea or sensory neuropathy), leading to potential underestimations of harms.[1] To improve the quality of symptomatic AE detection in trials, the National Cancer Institute developed a patient-reported version of its standard AE lexicon, the Common Terminology Criteria for Adverse Events (CTCAE), which is called the Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE). Industry sponsors are now beginning to implement PRO-CTCAE across the continuum of trials including early-phase, phase 3, and postmarketing studies. The US Food and Drug Administration has encouraged adoption of this tool in oncology trials.[2]

The PRO-CTCAE is an item library that includes individual patient questions representing 78 unique symptomatic AEs.[3] Items are phrased in patient-friendly lay language (eg, "mouth or throat sores" for oral mucositis) and have undergone rigorous psychometric development and validation.[4,5] The PRO-CTCAE includes up to 3 discrete questions for each AE, separately representing the frequency, severity, and/or interference with daily activities of the event. Items may be downloaded for use in trials from the National Cancer Institute at http://healthcaredelivery.cancer.gov/pro-ctcae.

Investigators may select PRO-CTCAE items that are pertinent to a given trial context based on known and anticipated properties of study drugs.[6] These items can be administered to patients via paper or electronic forms at baseline, regularly during treatment, and after treatment (eg, weekly during active treatment and every 3 months during follow-up).

Key Points

Question Is implementation of the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) feasible in a phase 3 cancer trial, and how well can PRO-CTCAE be used to detect between-group differences in symptomatic adverse events relative to the Common Terminology Criteria for Adverse Events?

Findings In this prespecified correlative analysis of the randomized COMET-2 trial of 119 patients with prostate cancer in which patients completed the PRO-CTCAE at baseline and every 3 weeks during treatment, 534 of 587 (91.0%) expected PRO-CTCAE self-reports were completed. The rates of 7 symptomatic adverse events were statistically significantly different between groups by PRO-CTCAE, while none were statistically significantly different by the Common Terminology Criteria for Adverse Events.

Meaning PRO-CTCAE data collection was feasible and improved the accuracy of symptomatic adverse event detection in this phase 3 cancer trial.

Methods

The PRO-CTCAE was implemented in a randomized, double-blind, placebo-controlled, phase 3 registration-track trial called COMET-2 comparing 60 mg of cabozantinib s-maleate once daily vs 12 mg/m^2 of mitoxantrone hydrochloride every 3 weeks plus 5 mg of oral prednisone twice daily in men with metastatic castration-resistant prostate cancer who had undergone at least 2 prior lines of systemic treatment (clinical results reported elsewhere).[7] This prespecified correlative analysis of the COMET-2 trial was conducted from March 2012 to July 2014. All patients provided written informed consent. The study was approved by the institutional review board or ethics committee at each center[7] and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.[8] An independent data monitoring committee monitored patient safety. The trial was discontinued early owing to negative overall survival results of a companion phase 3 trial (COMET-1), which compared cabozantinib vs placebo in this population.[9]

All patients enrolling in COMET-2 were trained to self-report PRO-CTCAE items with a 7-day recall period using an automated telephone system (ie, interactive voice response system). This system would call the patient every 3 weeks to self-report, with up to 2 reminder calls if a patient missed the initial call(s). The PRO-CTCAE items included 12 symptomatic AEs: insomnia, constipation, pain, fatigue, nausea, vomiting, diarrhea, rash, decreased appetite, numbness or tingling, mouth sores, and shortness of breath. Items were administered only during active treatment.

Statistical analysis was performed from May 2018 to June 2019. To assess feasibility of the PRO-CTCAE approach to AE reporting, the proportion of patients who completed expected PRO-CTCAE self-reports was computed. Scores on the PRO-CTCAE's 0 to 4 scale were compared between groups using the common standard approach that is typically applied to longitudinal CTCAE data in cancer trials. The maximum postbaseline score for each AE was tabulated per patient. Then, the proportion of participants by group with a maximum postbaseline score greater than 0, and subsequently for a score of 3 or more, was computed and compared between groups using Fisher exact tests. This analysis was repeated using a previously described baseline adjustment method,[6] computed per PRO-CTCAE item per patient as the maximum postbaseline score if that maximum score was worse than the patient's baseline score or a score of 0 if that maximum score was the same or better than the patient's baseline score. The method for comparing correlated receiver operating characteristic curves of DeLong et al[10] was used to assess whether maximum score with or without baseline adjustment (each dichotomized as a score of 0 vs ≥1) better differentiated between study groups by individual AE and overall.

Results

At the time of trial discontinuation, COMET-2 had enrolled 119 participants, of which 114 completed a baseline PRO-CTCAE questionnaire, 112 completed at least 1 follow-up PRO-CTCAE questionnaire, and 107 completed a baseline PRO-CTCAE questionnaire and at least 1 follow-up PRO-CTCAE questionnaire. PRO-CTCAE analysis included these 107 patients, all of whom received study treatment. Median age was 65 years (range, 44-80 years), 100 of 119 participants (84.0%) were white, 105 of 119 (88.2%) had a baseline Eastern Cooperative Oncology Group performance status of 0 to 1, and 72 of 119 (60.5%) had 5 or more prior lines of systemic treatment for castration-resistant metastatic prostate cancer.

Table. Rates of PRO-CTCAE Scores Greater Than 0 and 3 or More Between Study Groups During Active Treatment, Without or With Adjustment for Baseline Scores

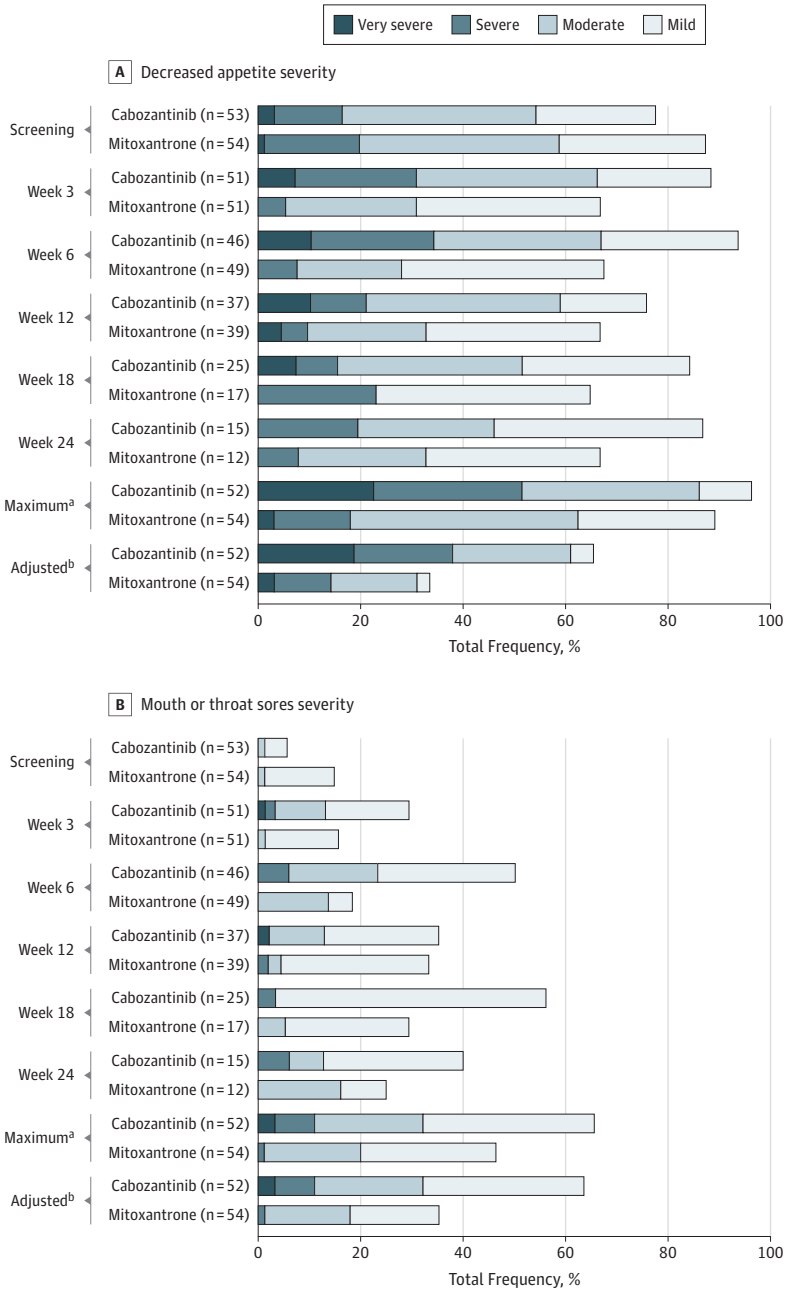
PRO-CTCAE Item[a]	No.		Without Baseline Adjustment						With Baseline Adjustment					
			Score >0			Score ≥3			Score >0			Score ≥3		
	Cabozantinib	Mitoxantrone-Prednisone	Cabozantinib, No. (%)	Mitoxantrone-Prednisone, No. (%)	*P* Value[b]	Cabozantinib, No. (%)	Mitoxantrone-Prednisone, No. (%)	*P* Value[b]	Cabozantinib, No. (%)	Mitoxantrone-Prednisone, No. (%)	*P* Value[b]	Cabozantinib, No. (%)	Mitoxantrone-Prednisone, No. (%)	*P* Value[b]
Constipation														
Severity	53	54	50 (94.3)	47 (87.0)	.32	19 (35.8)	11 (20.4)	.09	25 (47.2)	16 (29.6)	.08	14 (26.4)	7 (13.0)	.09
Decreased appetite														
Severity	52	54	50 (96.1)	48 (88.9)	.27	27 (51.9)	10 (18.5)	<.001	34 (65.4)	18 (33.3)	.002	20 (38.5)	8 (14.8)	.008
Interference	52	54	48 (92.3)	39 (72.2)	.01	23 (44.2)	11 (20.4)	.01	34 (65.4)	19 (35.2)	.003	18 (34.6)	9 (16.7)	.04
Diarrhea														
Frequency	52	54	48 (92.3)	34 (63.0)	<.001	23 (44.2)	6 (11.1)	<.001	42 (80.8)	26 (48.1)	<.001	23 (44.2)	6 (11.1)	<.001
Fatigue														
Severity	53	54	53 (100)	54 (100)	NA	39 (73.6)	32 (59.3)	.15	24 (45.3)	17 (31.5)	.17	19 (35.8)	14 (25.9)	.30
Interference	53	54	53 (100)	54 (100)	NA	40 (75.5)	35 (64.8)	.29	27 (50.9)	19 (35.2)	.12	23 (43.4)	17 (31.5)	.23
Insomnia														
Severity	53	54	44 (83.0)	47 (87.0)	.60	10 (18.9)	8 (14.8)	.61	20 (37.7)	22 (40.7)	.84	7 (13.2)	7 (13.0)	>.99
Interference	53	54	36 (67.9)	41 (75.9)	.40	10 (18.9)	10 (18.5)	>.99	15 (28.3)	22 (40.7)	.22	5 (9.4)	7 (13.0)	.76
Mouth or throat sores														
Severity	52	54	34 (65.4)	25 (46.3)	.05	6 (11.5)	1 (1.9)	.06	33 (63.5)	19 (35.2)	.006	6 (11.5)	1 (1.9)	.06
Nausea														
Frequency	52	54	49 (94.2)	38 (70.4)	.002	25 (48.1)	11 (20.4)	.004	35 (67.3)	20 (37.0)	.002	23 (44.2)	10 (18.5)	.006
Severity	52	54	49 (94.2)	36 (66.7)	<.001	21 (40.4)	9 (16.7)	.009	39 (75.0)	20 (37.0)	<.001	20 (38.5)	8 (14.8)	.008
Numbness or tingling in hands or feet														
Severity	52	54	44 (84.6)	40 (74.1)	.23	16 (30.8)	7 (13.0)	.03	28 (53.8)	18 (33.3)	.049	12 (23.1)	4 (7.4)	.03
Interference	52	54	34 (65.4)	26 (48.1)	.08	11 (21.2)	5 (9.3)	.11	24 (46.2)	16 (29.6)	.11	7 (13.5)	4 (7.4)	.35
Pain														
Frequency	53	54	53 (100)	54 (100)	NA	44 (83.0)	44 (81.5)	>.99	10 (18.9)	11 (20.4)	>.99	10 (18.9)	11 (20.4)	>.99
Severity	53	54	53 (100)	54 (100)	NA	32 (60.4)	36 (66.7)	.55	10 (18.9)	17 (31.5)	.18	10 (18.9)	16 (29.6)	.26
Interference	53	54	53 (100)	54 (100)	NA	26 (49.1)	33 (61.1)	.25	12 (22.6)	16 (29.6)	.51	9 (17.0)	13 (24.1)	.47
Rash														
Presence	52	54	16 (30.8)	11 (20.4)	.27	NA	NA	NA	13 (25.0)	11 (20.4)	.65	NA	NA	NA
Shortness of breath														
Severity	50	54	40 (80.0)	43 (79.6)	>.99	8 (16.0)	9 (16.7)	>.99	29 (58.0)	21 (38.9)	.08	7 (14.0)	7 (13.0)	>.99
Interference	50	54	36 (72.0)	37 (68.5)	.83	12 (24.0)	12 (22.2)	>.99	29 (58.0)	20 (37.0)	.049	10 (20.0)	9 (16.7)	.80
Vomiting														
Frequency	52	54	40 (76.9)	26 (48.1)	.003	6 (11.5)	4 (7.4)	.52	33 (63.5)	18 (33.3)	.003	6 (11.5)	4 (7.4)	.52
Severity	52	54	37 (71.2)	20 (37.0)	<.001	11 (21.2)	4 (7.4)	.05	33 (63.5)	12 (22.2)	<.001	11 (21.1)	4 (7.4)	.05

Abbreviations: NA, not applicable; PRO-CTCAE, Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

[a] Not all symptoms in the PRO-CTCAE include frequency, severity, and interference; depending on the symptom, anywhere between 1 and 3 attributes are elicited; for details, see https://healthcaredelivery.cancer.gov/pro-ctcae/. Rash is assessed for presence only on a binary 0 or 1 scale.

[b] Determined by use of the Fisher exact test.

Figure. Distribution of PRO-CTCAE Scores at Successive Time Points During Active Therapy and Maximum Postbaseline Score Without and With Baseline Adjustment, by Study Arm



See eFigure in the Supplement for all Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items.

[a] Maximum score reported after baseline per patient.

[b] Maximum score reported after baseline per patient when including only scores that were worse than the patient's baseline score.

There were 587 time points at which a PRO-CTCAE self-report was expected, of which 534 reports (91.0%) were completed, with consistently high rates of completion throughout participation. Rates were similar between groups (cabozantinib, 286 of 317 [90.2%]; mitoxantrone-prednisone, 248 of 270 [91.9%]) (eTable 1 in the Supplement).

Baseline PRO-CTCAE scores were balanced between groups (eTable 2 in the Supplement). In comparing the proportion of participants with PRO-CTCAE scores greater than 0 without baseline adjustment to account for pretreatment symptoms, there were 4 AEs with statistically significant differences between groups (anorexia, diarrhea, nausea, and vomiting), whereas use of baseline adjustment yielded 7 AEs with statistically significant differences between groups (anorexia, diarrhea, dyspnea, mucositis, nausea, neuropathy, and vomiting) (**Table**). Higher rates were observed in the cabozantinib group for all of these AEs. In the primary reporting of safety data using the CTCAE, no statistically significant differences were found between groups for any symptomatic AEs. Similar results were observed in an analysis restricting AEs to scores of grades of 3 or more.

The **Figure** and the eFigure in the Supplement show the distribution of PRO-CTCAE responses for each week of active therapy

through week 24, after which there were fewer than 10 patients still participating per group. The Figure also displays the maximum postbaseline score without and with baseline adjustment. In AEs with high baseline rates (eg, decreased appetite in Figure, A), adjustment for baseline was substantially associated with summary rates, whereas in AEs with low baseline rates (eg, mouth or throat sores in Figure, B), adjustment for baseline was not substantially associated with summary rates. In receiver operating characteristic curve comparisons, baseline adjustment better differentiated between treatment groups for decreased appetite severity (difference in area under the receiver operating characteristic curve [ΔAUC], 0.12; 95% CI, 0.03-0.12; $P = .008$) and shortness of breath severity (ΔAUC, 0.09; 95% CI, 0.01-0.18; $P = .04$) and interference with daily activities (ΔAUC, 0.09; 95% CI, 0.01-0.17; $P = .03$) (median ΔAUC across the 21 items, 0.04; range, −0.03 to 0.12), leading to a significant overall association (ΔAUC, 0.03; 95% CI, 0.01-0.05; $P = .004$). Overall, higher rates and magnitudes of each symptomatic AE were seen in the cabozantinib group.

Discussion

This study demonstrates that remote electronic collection of PRO-CTCAE data every 3 weeks from patients is feasible with high completion rates even in a heavily pretreated population with end-stage metastatic disease. Moreover, when evaluating tolerability, AEs are better differentiated between study groups with the PRO-CTCAE than the CTCAE, likely owing to the greater accuracy of patient reporting for symptomatic AEs compared with the current standard of clinician reporting. Overall, patient self-reporting provides a depiction of the patient's experience of treatment that differs from traditional CTCAE data. Because many patients enter clinical trials with baseline symptoms, adjustment for these in analysis of symptomatic AEs is desirable and was successfully applied in this analysis and should be considered for future evaluations of PRO-CTCAE to ensure appropriate attribution to study drugs.

Limitations

This study is limited by its relatively small sample size in a single disease with a relatively young median participant age of 65 years. However, it is not that dissimilar from other cancer clinical trials and offers an example of the implementation of PRO-CTCAE that can be used in the conduct of future studies.

Conclusions

PRO-CTCAE data collection was feasible and improved the accuracy of symptomatic AE detection in a phase 3 cancer trial. This analysis adds to mounting evidence of the feasibility and value of patient-reported AEs in oncology, which should be considered for inclusion in cancer trials that incorporate AE evaluation.

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Concept and design: Dueck, Scher, Bennett, Schwab, Weitzman, Basch.
Acquisition, analysis, or interpretation of data: Dueck, Mazza, Thanarajasingam, Schwab, Rogak, Basch.
Drafting of the manuscript: Dueck, Thanarajasingam, Rogak, Basch.
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