Clinician vs Patient Reporting of Baseline and Postbaseline Symptoms for Adverse Event Assessment in Cancer Clinical Trials

Many patients enter cancer clinical trials with baseline symptoms.[1] Notably, the current clinician reporting mechanism for symptomatic adverse events (AEs) via the Common Terminology Criteria for Adverse Events (CTCAE)[2] does not formally distinguish between symptoms present at baseline vs those that develop during a trial. Therefore, AE estimation in clinical trials may include symptoms that predate trial entry. This raises concern that the cumulative incidence of patient-reported AEs may be high, particularly if preexisting symptoms related to other causes (eg, comorbidities, prior treatment) are attributed to study drugs.

Just as patients are better positioned to detect symptomatic AEs during a trial,[3-5] we hypothesized that they are also better at reporting baseline symptoms. As such, we anticipated that patient reporting would facilitate better understanding of pretrial symptoms. Moreover, if baseline symptom information were available, we might be able to adjust AE analyses to remove preexisting symptoms from tabulations, thereby enabling a focus on symptomatic AEs that are incident during the clinical trial.

Methods | To test these suppositions, we completed a retrospective analysis (NCCTG N0591/Alliance) of legacy clinical trials from the National Cancer Institute (NCI)-supported National Clinical Trials Network group the Alliance for Clinical Trials in Oncology that included clinician reporting of AEs (via CTCAE) and patient reporting of analogous symptoms (via patient-reported outcome [PRO] questionnaires) at baseline and throughout the clinical trial. Because this was a retrospective analysis, institutional review board approval was not obtained for this specific study, and all data collection for the included trials was approved by their respective institutional review boards, with informed consent provided by enrolled patients.

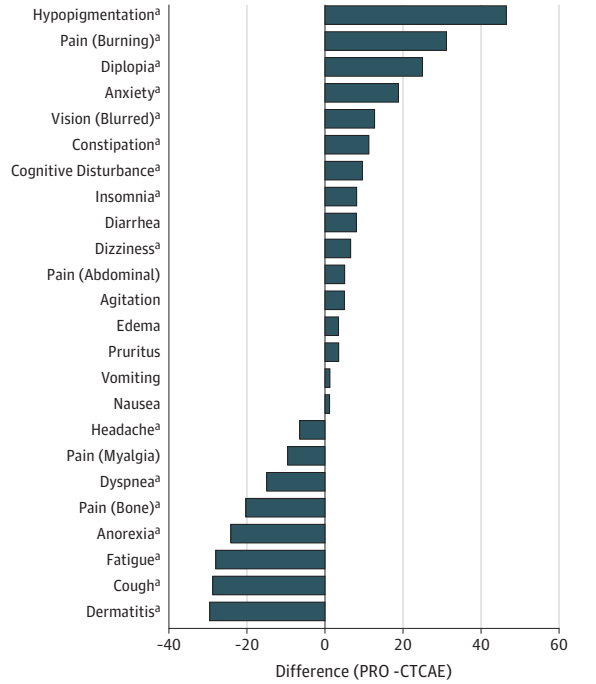
For clinician-reported CTCAE symptoms, the incidence of baseline grade of 1 or greater was compared using McNemar's test[6] with the maximum CTCAE grade postbaseline (ie, none

Table. Differences in Baseline and Worst Postbaseline Symptom Rates Between Patient and Clinician Reports

	Baseline, %				Worst Postbaseline, %			
Symptom	PRO	CTCAE	% Difference	*P* Value	PRO	CTCAE	% Difference	*P* Value
Agitation	62.6	13.9	48.7	<.001	61.0	29.3	31.7	<.001
Anorexia	75.0	44.8	30.2	<.001	83.6	100	−16.4	<.001
Anxiety	58.4	25.9	32.5	<.001	73.6	28.2	45.4	<.001
Cognitive disturbance	45.1	5.1	40.0	<.001	70.7	26.0	44.7	<.001
Constipation	36.6	12.0	24.6	<.001	68.5	33.7	34.8	<.001
Cough	92.9	38.1	54.8	<.001	75.0	100	−25.0	<.001
Dermatitis	4.2	1.2	3.0	.059	65.3	81.4	−16.1	<.001
Diarrhea	64.0	4.0	60.0	<.001	77.8	100	−22.2	<.001
Diplopia	8.5	0.6	7.9	<.001	39.8	3.3	36.5	<.001
Dizziness	35.1	15.1	20.0	<.001	59.9	31.2	28.7	<.001
Dyspnea	26.2	23.4	2.8	.45	46.9	60.8	−13.9	.002
Edema	19.6	7.9	11.7	<.001	43.4	32.7	10.7	<.001
Fatigue	93.3	43.1	50.2	<.001	98.9	96.7	2.2	.10
Headache	50.2	21.1	29.1	<.001	64.9	42.8	22.1	<.001
Hypopigmentation	3.6	1.2	2.4	.157	69.5	9.0	60.5	<.001
Insomnia	58.0	37.0	21.0	<.001	78.5	68.4	10.1	.02
Nausea	45.7	22.4	23.3	<.001	69.1	49.9	19.2	<.001
Pain								
Abdominal	31.1	15.0	16.1	<.001	43.5	28.8	14.7	<.001
Bone	61.5	7.7	53.8	<.001	66.7	54.9	11.8	.05
Burning	21.1	0.6	20.5	<.001	86.2	46.1	40.1	<.001
Myalgia	54.0	20.0	34.0	<.001	66.0	54.7	11.3	.18
Pruritus	42.8	3.0	39.8	<.001	88.6	73.1	15.5	<.001
Vision (blurred)	8.5	4.5	4.0	.11	39.8	18.8	21.0	<.001
Vomiting	29.5	13.6	15.9	<.001	37.8	26.6	11.2	<.001

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; PRO, patient-reported outcome.

Figure. Differences Between Rates of Patient and Clinician Reports of Adverse Events After Adjustment for Baseline Symptoms From Worst Postbaseline Symptoms



CTCAE Indicates Common Terminology Criteria for Adverse Events; PRO, patient-reported outcome. Positive differences indicate higher rates of patient reports, negative differences indicate higher rates of clinician reports.

[a] Statistically significant difference $P < .05$.

vs grade ≥1), as well as with worsened CTCAE grade postbaseline (ie, no worsening vs worsening by ≥1 grade). For patient-reported measures, the incidence of baseline score of greater than 1 was compared with maximum score postbaseline (ie, score of 0 vs score ≥1), as well as with worsened score postbaseline (ie, no worsening vs worsening by ≥1 point for 0-4/0-5 scales or ≥2 points for 0-10 scales). All P values were 2-sided and considered statistically significant if $P < .05$, with no adjustments made for multiple comparisons.

Results | Twenty-six clinical trials (1996-2015) were identified (n = 2608; mean [SD] age, 60.1 [12.2] years; 1611 [61.8%] women; 2492 [93.1%] white), with 24 distinct AEs captured via 23 PRO questionnaires, including the Brief Fatigue Inventory, Functional Assessment of Anorexia/Cachexia Therapy, Functional Assessment of Cancer Therapy-General, Linear Analogue Self Assessment, Lung Cancer Symptom Scale, Pittsburgh Sleep Quality Index, Profile of Mood States, SF-36, Symptom Distress Scale, Symptom Experience Diary, and UNISCALE. At baseline, symptom reporting was significantly more prevalent for patients vs clinicians (20/24, 83%) (**Table**).

When examining worst postbaseline symptom rates without using baseline adjustment, 21 of 24 (88%) were significantly different between patients and clinicians, with 16 of 21 (76%) having a higher rate by patient reporting. In contrast, the **Figure** displays differences between patient and clinician symptom reporting rates after adjusting for baseline symptoms. Across clinical trials, 16 of 24 (67%) symptoms were significantly different between patients and clinicians; but only 9 of 16 (56%) had a significantly higher rate via patient report.

Discussion | At time of clinical trial enrollment, patients may have elevated symptoms that are unrelated and potentially misattributed to investigational treatments if not detected and adjusted for in analyses. This study found that clinical investigators detect fewer baseline symptoms compared with patients. Moreover, we tested a method to adjust for baseline symptoms when tabulating incident symptoms during clinical trials, to avoid misattribution. We found that without using this method, patients report more symptoms than clinicians about three-quarters of the time, whereas with this method this is reduced to about half. The lack of sample ethnic/racial diversity may limit result generalizability. Nevertheless, use of the baseline adjustment method can provide clinicians, patients, pharmaceutical sponsors, and drug trialists with greater confidence about the meaningfulness of symptom and tolerability data in clinical trials, particularly for patient-reported data.

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