Reply to T. Kaneko et al

We thank Kaneko et al[1] for their interest related to our recently published article in the *Journal of Clinical Oncology*.[2] We appreciate the opportunity to provide clarifications for the issues and questions they raised. The definition of tolerability of cancer treatment has expanded to now include recommendations that assess patient experience as reported directly from the patient.[3] Patient-reported outcomes (eg, symptoms) are defined by the US Food and Drug Administration[4] as measures of a patient's health status as reported directly from the patient without added interpretation by a clinician or anyone else. Kaneko et al[1] commented on the credibility of patient responses to Patient-Reported Outcome (PRO) version of Common Terminology Criteria for Adverse Events (CTCAE), given the presence of impairment in cognition or psychological status on geriatric assessment (GA) screening. Older adults with GA impairments are often asked to report symptoms in research and in clinical care.[5] It is important not to equate cognitive impairment with an inability to self-report symptoms. Furthermore, an abnormal GA screening score often does not equate to a formal diagnosis of dementia.[6] In the GAP70+ study,[7] the vast majority (> 96%) of individuals did not have severe cognitive impairment. Similarly, having a positive screen for anxiety or depression (the measurements collected in GAP70+) on GA does not negate the ability to self-report symptoms. We agree with the authors'[1] point that short-term memory difficulties may affect 7-day recall for PRO-CTCAE and thus we acknowledged the timing of data collection as a limitation. Older adults may need support completing PROs; our team found in a similar population from the same oncology sites that 28% of patients received assistance by having the questions read to them and/or writing down the answers.[8]

The second comment addresses comparison of PRO-CTCAE with CTCAE and favors additional analysis reporting on each PRO-CTCAE. To date, our team has reported direct comparisons of PRO-CTCAE to CTCAE for two items, neuropathy[9] and pain.[10] Comparisons of CTCAE/PRO-CTCAE individual items has also been reported by others.[11] Although we acknowledge that the direct comparative analysis for all PRO-CTCAE items would provide interesting information, these analysis are outside the scope of this manuscript. The GAP70+ was a trial of a behavioral intervention (GA with tailored management recommendations) specifically designed to address toxicity. The primary study findings showed that the GA intervention decreased overall toxicity captured via clinician-reported CTCAE.[7] This manuscript was a parallel analysis to examine the role of GA for improving patient-reported symptomatic toxicity. One of the novel contributions of the report was to codify overall symptomatic toxicity. Both overall CTCAE and PRO-CTCAE were composite outcomes and thus direct comparison would not be meaningful, as each composite outcome is comprised using different events. In the Discussion section, we highlighted that the significance of findings was greater for CTCAE. This outcome is not surprising given that PRO-CTCAE was specifically designed to capture different but complementary information on tolerability.

Regarding the comment about sample heterogeneity, we refer Kaneko et al[1] to Appendix Figure A2,[2] which provides a visualization of the stratified analysis conducted by cancer type and whether prior chemotherapy had been received. The pattern of results, for all diagnoses, consistently indicated higher severity for symptomatic toxicity in the usual care arm, as compared with GA intervention. We also note that although heterogeneity in diagnosis and treatment was present, the sample in the GAP70+ study was homogeneous in terms of being of older age, having aging-related impairments, having incurable cancer, and initiating a new systemic regimen with at least a 50% risk for serious CTCAE. This particular sample was specifically sought to evaluate the intervention.

We agree with the authors[1] that GA, when followed by GA-guided management, is an important tool for decision making and additionally for guiding supportive care recommendations. The GAP70+ study enrolled an at-risk and understudied population of older adults with advanced cancer.[7] The primary results of the GAP70+ trial demonstrated that GA-intervention reduced clinician-rated toxicity. Our paper[2] provides a similar assessment of the overall incidence of reporting a grade 2 or 3 newly developed or worsening symptomatic toxicity in a population of older adults with advanced cancer initiating a new toxic treatment regimen. Additionally, the results provide critical data on the experience of symptomatic toxicities, which were highly prevalent in this sample, reinforcing the importance of integrating best care practices for symptom assessment and management concurrently with treatment and GA-guided aging-related care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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