Importance of Assessing Patient-Reported Outcomes With Salvage Autologous Transplantation in Relapsed Multiple Myeloma

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The inclusion of patient-reported outcomes (PROs) in clinical trials provides unique information about the impact of an intervention from the patient's perspective and complements the classic trial end points of survival, disease status, and treatment adverse events. Historically, the assessment of quality of life (QOL) using PROs in clinical trials was not standardized and lacked consistent reporting, which made results difficult to interpret. Recently, increased rigor has helped ensure that the value of the additional time invested by both participants and study personnel is realized and that results can inform treatment of future patients. Methodologic recommendations contained in two recent guidelines that describe best practices for the inclusion of PROs in clinical trial protocols, and their resulting publications, have been helpful.^{1,2} Better data have been used to stratify disease risk, assess toxicity, predict outcomes (eg, function, QOL, and survival) and monitor symptoms within the clinical trials context.

In the article that accompanies this editorial, Ahmedzai et al³ report the PRO differences between patients with relapsed multiple myeloma after first autologous transplantation who were randomly assigned to either salvage autologous stem-cell transplantation (sASCT) or nontransplantation weekly oral cyclophosphamide therapy. The investigators should be commended for following many best practices in PRO research: using well-validated, informative instruments; performing baseline assessments before random assignment; obtaining reasonable compliance with assessments; performing careful statistical analysis with interpretation anchored to clinically meaningful differences; and finally, adhering to the CONSORT-PRO extension consensus guidelines.¹ Historically, myeloma investigators have been leaders in assessing PROs alongside clinical trials of both ASCT and maintenance therapy, perhaps because treatments are not viewed as curative, so symptom burden and QOL seem more relevant.^{4,5} For example, some recent data suggest that QOL is unaffected by ongoing maintenance.⁶

The primary results of the trial have already been reported and showed longer time to progression (TTP) and better overall survival (OS) with sASCT than with

oral weekly cyclophosphamide.⁷ This paper by Ahmedzai et al³ answers the corollary question of whether the advantages seen in the sASCT arm were minimized or enhanced by QOL considerations. To answer this question, the investigators compared the patient experience in each treatment arm and focused on QOL, treatment adverse effects, and pain up to 2 years after random assignment. After analysis was adjusted for PROs collected just before random assignment, the sASCT arm had worse global health and role functioning at 100 days after random assignment, worse treatment adverse effects at 100 days and 6 months after random assignment, and higher pain interference from 6 months through 2 years; there were no statistically significant differences at other time points or for other end points. The results suggest that sASCT improves TTP and OS, but these improvements might come at some small but measurable decrement in short- and long-term QOL compared with weekly oral cyclophosphamide.

This study illustrates two main issues that highlight the challenges of performing PRO research. First, although the response rates after random assignment were quite good given the multicenter design, the study still lacked data on 40% (69 of 171) of consented patients before random assignment. This is a critical time point to miss, because one needs these scores to prove that the arms were similar in QOL at the time of random assignment and to establish the baseline for future comparisons. Although the authors performed many analyses to understand this deficit and concluded that data were missing at random, we are left to wonder about the comparability of the groups and unmeasured differences. Second, it was unexpected and unfortunate that the group randomly assigned to sASCT had worse health before random assignment (with no clear reason despite extensive additional analyses by the authors), not just in global health but also in several other QOL and symptom areas. This concerning observation, compounded by the amount of missing data at the time point before random assignment and the cessation of PRO data collection upon relapse, complicates interpretation of the results.

ASSOCIATED CONTENT

See accompanying article on page 1617

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Additional limitations of the study interpretation are related in part to the generalizability of the therapies given to patients at relapse. In the United States, weekly cyclophosphamide is not used as a standard therapy for relapse in multiple myeloma. Furthermore, since the time of this study, several additional novel therapies with different adverse effect profiles have become available. Second, the methods of PRO research also have advanced. This study collected PROs on paper, either at the treating center or by return of post. The use of paper-based surveys has been associated with significant amounts of missing data, logistic challenges, and respondent burden. It is likely, or even probable, that a similar study launched today would make use of available electronic platforms that may reduce respondent and logistic burden by using automated reminders and multiple options for patients (eg, tablets, cell phones, computers).

Many aspects of the results are not surprising but are reassuring to see in the context of a randomized trial. Patient-reported scores initially worsened in the sASCT arm but then recovered. We should question an instrument's sensitivity if it cannot detect worse QOL in patients receiving high-dose chemotherapy and autologous transplantation compared with nontransplantation therapies. According to prior work, we also expected that these adverse effects would resolve by 6 to 12 months, as they did.⁸ Nor are we surprised that patients who reported fewer adverse effects had longer TTP and better OS after transplantation,

because reported symptoms could reflect past treatment and current disease status. What is surprising is the finding that patients undergoing sASCT had more pain interference for up to 2 years after random assignment, as measured by the Brief Pain Inventory. The interference scale of the Brief Pain Inventory asks about how much a patient's pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a 0 to 10 scale. This observation is unexplained but hints at lingering adverse effects long after the acute sASCT period has passed. The article provides some hypotheses, and more work is needed to explore this finding. Reassuringly, the disease symptoms subscale of the QLQ-MY20 also primarily measures pain, and no differences between the groups were detected in these scores.

A challenge faced by all researchers who measure PROs is how to make these data interpretable to both clinicians and patients.⁹ Numerous PRO measures exist, all with varying criteria to assess statistically and clinically relevant differences. Although the authors clearly pointed out in the text when these differences were found and interpreted them as trivial, small, or medium, making these differences clear with footnotes, other enhancements to tables, or illustrations may assist reader understanding. Similarly, patient-friendly summaries or other consumable aids to patient understanding would help ensure that the results can be used to enhance informed patient decision making in the future.

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