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CORRESPONDENCE

Total Therapy 2 in Treatment of Multiple Myeloma: Questions About Gene Expression Profiling and Treatment-Related Mortality

TO THE EDITOR: In a report presenting the reiterative outcome of patients with multiple myeloma who were treated as part of the Total Therapy 2 study performed at the University of Arkansas for Medical Sciences (Total Therapy II: Study for Multiple Myeloma Evaluating Anti-Angiogenesis With Thalidomide and Post-Transplant Consolidation Chemotherapy),[1] the authors suggest that stability of patient characteristics during the accrual period underpins the robustness of the results and the prognostic factors found. This is only partly accurate; completeness of analysis and data presentation are at least as important in determining validity. Unfortunately, incompleteness in these areas undermines the report as it stands.

One major weakness is that the influence of specific cytogenetic abnormalities has not been shown individually, and all abnormalities have been grouped together (present/absent). The prognostic implications of various karyotype abnormalities differ. For example, t(4;14), del(17p), and 1q21 abnormalities are adverse, whereas hyperdiploidy and t(11;14) are favorable. It is not logical for all of these karyotype abnormalities to be grouped together. It is possible that the only reason that gene expression profiling (GEP), which apparently identifies a small subgroup of patients with high-risk disease,[2] seems to influence outcome in the series of patients enrolled onto this Total Therapy 2 study by Barlogie et al[1] is because the effect of individual cytogenetic abnormalities has not been considered. Can the authors show the individual influence of karyotype abnormalities known to be favorable or adverse? This would allow accurate evaluation of the contribution of GEP, if any, to prognosis. Such transparency is especially important if the suggestion by Barlogie et al that the test be widely used, presumably in a proprietary/commercial setting on the basis of intellectual property undisclosed in any published article,[2] is to be followed. The GEP data, although academically interesting, cannot be considered practically relevant unless these data are shown to add materially to established prognostic factors.

Another weakness is the lack of direct information on fatal treatment-related toxicity in any of the published articles that report on the Total Therapy 2 trial. Figure 2B in the article by Barlogie et al[1] shows that a total of 287 patients have died, and Figure 2D shows that 159 patients have died after experiencing disease progression. This suggests that 128 of 668 patients (19%) died as a result of nonrelapse causes. If true, this indicates that the treatment approach is prohibitively toxic. If the 19% estimate that I derived on the basis of available data is incorrect, the entire analysis and data set need to be revisited for possible inaccuracies, not only for this article but for all publications pertaining to the Total Therapy 2 trial.

Because of the complexity of the data and the piecemeal presentation of the study outcomes in several different manuscripts published during the last several years, Barlogie et al should make deidentified primary data, including detailed karyotype information, available to interested readers in an appropriate form so that the contribution of GEP in multiple myeloma and the extent of treatment-related mortality associated with the approach used in the Total Therapy 2 trial can be evaluated independently.

Jayesh Mehta

The Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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