Re: Tandem vs Single Autologous Hematopoietic Cell Transplantation for the Treatment of Multiple Myeloma: A Systematic Review and Meta-analysis

The conclusions of the meta-analysis by Kumar et al. (1) comparing single vs tandem transplantation in myeloma are compromised by serious errors and the retraction of a key study (2) included in the analysis.

The main conclusion of the meta-analysis is that tandem transplantation has no beneficial effect on overall survival (OS) or event-free survival (EFS) in myeloma. All except one of the studies included in the meta-analysis showed comparable outcomes with the two approaches or some advantage for tandem transplantation. In contrast, a study from Abdelkefi et al. (2) showed dramatic benefit of single transplantation over tandem.

When this study (2) was excluded from the meta-analysis to eliminate heterogeneity, EFS was statistically significantly better with tandem transplantation (1). The beneficial effect of tandem transplantation on OS also increased (improvement in the hazard ratio from 0.94 to 0.89) but did not reach the level of statistical significance (1). The authors dismissed the importance of EFS as an endpoint reasoning that the definition of EFS "may be entirely due to outcomes that are not important to patients" (1). However, they did not point out the fact that the availability of effective salvage therapy in myeloma has made it difficult to show differences in OS. Although transplantation is not equivalent to a novel drug, the Food and Drug Administration does accept improvement in EFS as a valid endpoint for approval of novel drugs in myeloma.

The biologically implausible findings of the study by Abdelkefi et al. (2) that contradicted previous findings have been pointed out (3). A careful review of the multiple online versions of the article (4, unpublished observations) and correspondence with the authors of the article and the editorial staff of Blood (unpublished data) uncovered inconsistencies and inaccuracies that cast doubt on the integrity of the study and resulted in retraction of the two articles describing the study (2,5). Retraction of this study alters the findings of the meta-analysis of Kumar et al. and invalidates the summary results and conclusions contained in the abstract.

In addition, there are serious errors involving data extraction by the authors from four of the six trials (2,6–8), which call into question the validity of the analysis. These errors have been summarized in Table 1. It is not possible to assess the accuracy of the data estimated from the remaining two trials, which are unpublished. Indeed, the response data in the meta-analysis (1), shown in figure 3 of the article, bear no resemblance whatsoever to the actual response rates in the published studies.

Although the authors make much of the statistically significant increase in treatment-related mortality with tandem transplantation, when the retracted study by Abdelkefi et al. is excluded and the denominator of patients in the single transplantation arm of the study by Sonneveld et al. (8) is corrected to 148 from 158 (Table 1), the risk ratio for treatment-related mortality becomes 1.60 (95% confidence interval = 0.98 to 2.62) and its statistical significance becomes borderline (P = .059).

There are errors suggesting a misunderstanding of different types of failure events and their interrelationship. For example, figure 2 in the meta-analysis shows the number of events in both arms of the study by Abdelkefi et al. to be higher for OS than for EFS—which is biologically impossible.

The authors also did not discuss the fact that the Fermand study (9) included randomization to CD34-selected vs unmanipulated stem cell transplantation. After finding that CD34 selection increased infectious complications and bearing in mind that the use of unmanipulated cells is the standard of care now, Fermand analyzed the outcome of single vs tandem transplantation in the subgroup of patients receiving unmanipulated grafts and found
OS better with tandem transplantation ($P = .04$). Median EFS was longer with tandem transplantation as well (36 vs 31 months) but was not statistically significant ($P = .11$).

Notwithstanding the fact that the best long-term survival data in myeloma have been seen in studies that have had tandem transplantation as their key component (10,11), the question of single vs tandem autotransplantation could still be considered open in some patient subpopulations. However, this meta-analysis is flawed and should not influence important treatment decisions, which can compromise patient welfare. Indeed, over a period of a month (July 2009), I have already seen two patients who have been counseled not to undergo tandem transplantation based on the results published by Kumar et al. I think it should be retracted.

**References**


**Notes**

Affiliation of author: Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL.

Correspondence to: Jayesh Mehta, MD, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, 676 N St Clair St, Ste 850, Chicago, IL 60611 (e-mail: j-mehta@northwestern.edu).

No conflict of interest information to disclose.

DOI: 10.1093/jnci/djp320

© The Author 2009. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.


**Table 1. Data errors in the meta-analysis.** The response rate data shown in figure 3 of the meta-analysis have not been included in the table because every single number is inaccurate*

<table>
<thead>
<tr>
<th>Study</th>
<th>OS</th>
<th>EFS</th>
<th>TRM</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelkefi et al. (2)</td>
<td>19 events in the tandem arm (not 34). 9 events in the single arm (not 15).</td>
<td>Accurate</td>
<td>Accurate</td>
<td>The number of events has been estimated when actual numbers are available in the article. The corrected OS figures reduce the difference between observed and expected events from 19 to 10, in favor of tandem transplantation.</td>
</tr>
<tr>
<td>Attal et al. (6)</td>
<td>Accurate</td>
<td>141 events in the tandem arm (not 132). 156 events in the single arm (not 149).</td>
<td>Accurate</td>
<td>The corrected EFS figures decrease the difference between observed and expected events from 17 to 15, in favor of single transplantation.</td>
</tr>
<tr>
<td>Cavo et al. (7)</td>
<td>Accurate</td>
<td>105 events in the tandem arm (not 102). 135 events in the single arm (not 124).</td>
<td>Accurate</td>
<td>The number of events has been estimated when actual numbers are available in the article. The corrected EFS figures increase the difference between observed and expected events from 22 to 30, in favor of tandem transplantation.</td>
</tr>
<tr>
<td>Sonneveld et al. (8)</td>
<td>Accurate</td>
<td>Denominator for the number of events in the single arm 148 (not 158).</td>
<td>Accurate</td>
<td>The corrected TRM figures reduce the magnitude of the difference seen between the two arms, in favor of tandem transplantation.</td>
</tr>
</tbody>
</table>

* EFS = event-free survival; OS = overall survival; TRM = treatment-related mortality.