To the editor:

Chemotherapy or allografting for young adults with high-risk ALL?

The recent paper by Goldstone et al.\(^1\) reported the results of a prospective clinical trial testing the role of allogeneic hematopoietic cell transplantation compared with chemotherapy in the treatment of acute lymphoblastic leukemia (ALL) in adults. Using an unbiased donor/no donor analysis, the study showed that allogeneic transplantation is beneficial in preventing relapse and improving the 5-year survival in Ph-negative ALL patients up to the age of 55. This study is likely to change current practice and introduce the use of allografting for adults with ALL in first remission.

The issues started to arise when subsets of patients were analyzed, and the authors concluded that high-risk patients did not significantly benefit from having a donor. The wrinkle in this paper lies in the definition of risk that included age greater than 35 years and high blast counts at diagnosis. Older age is a risk factor for leukemia relapse, but it is also an important risk factor for nonrelapse mortality after transplantation. High blast count at diagnosis is a risk factor for leukemia relapse. It is, therefore, important to assess whether patients younger than 35 years at transplantation but with high blast counts at diagnosis would do better with allografting than chemotherapy. The analysis should be unbiased donor/no donor analysis, the study showed that allogeneic transplantation but with high blast counts at diagnosis would do better with allografting than chemotherapy. The analysis should be presented as published in Rowe et al.,\(^2\) where patients are classified into 4 risk groups: younger than 35 years and low blast counts, younger than 35 years and high blast counts, older than 35 years and low blast counts, and older than 35 years and high blast counts.

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Conflict-of-interest disclosure: The author declares no competing financial interests.

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References


Response

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We thank the correspondent and agree that the issue is important. We enclose Table 1 of survival at 5 years in the subgroups requested by the correspondent, where standard risk (SR) and high risk (HR) refer to white cell count and lineage only.

The donor benefit is greater in young than old and in standard risk than in high risk. It may also be true that there is no benefit in the older high-risk patient. However, the differences in the magnitude of the donor versus no-donor effect in these subgroups are not statistically significant and could be due to chance. In particular, we do not see a difference by risk group in the older no-donor patient group. In summary, the subgroup analysis is consistent with the risk ratio being the same in all risk groups, but there are insufficient data to rule out a difference.

It is important to recall that the difference in survival benefits between younger (<35 years) and older (>35 years) patients who did and did not have a donor was related to increased treatment-related mortality (TRM). There was still a donor-attributable reduction in relapse risk for both groups but this did not translate into survival benefit due to increased TRM. Age over 35 years is the only factor that could be statistically shown to be independently responsible for the increased TRM in the high-risk group of patients. Thus, we would certainly recommend an allogeneic transplant for patients younger than 35, even with a high blast count.

This trial has taken 13 years to accrue the largest number of patients ever reported in a single study in adult ALL and yet the question posited by the correspondent still cannot be answered with certainty. It is now clear that only a meta-analysis will supply the appropriate statistical rigor to address this question. S.M.R. (one of the authors of this letter) is coordinating a meta-analysis at the Cancer Trials Support Unit (CTSU) in Oxford and the author of the letter and any other interested parties are invited to submit data to attempt to answer this and other important questions, which may otherwise go unaddressed. The fact that cytogenetic\(^3\) and molecular markers, as in AML, are likely to supersede high blast count, lineage, and age as the discriminating prognostic factors for relapse only adds complexity to the issue.

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Table 1. Five-year survival by age and risk group

<table>
<thead>
<tr>
<th>Survival at 5 years</th>
<th>No donor</th>
<th>Donor</th>
<th>Ratio of risks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age younger than 35 y, SR</td>
<td>52%</td>
<td>65%</td>
<td>0.73 (0.56-0.94)</td>
</tr>
<tr>
<td>Age older than 35 y, SR</td>
<td>33%</td>
<td>43%</td>
<td>0.86 (0.61-1.20)</td>
</tr>
<tr>
<td>Age younger than 35 y, HR</td>
<td>40%</td>
<td>51%</td>
<td>0.82 (0.55-1.20)</td>
</tr>
<tr>
<td>Age older than 35 y, HR</td>
<td>12.5%</td>
<td>14%</td>
<td>1.28 (0.76-2.15)</td>
</tr>
</tbody>
</table>

\(x^2\) for heterogeneity (3 df) = 3.66; \(P = .3\)

Overall ratio of risks, adjusted (95% CI) = 0.82 (0.69-0.98).

Reference

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