Should HLA-Identical Sibling Bone Marrow Transplants for Leukemia Be Restricted to Large Centers?

By Mary M. Horowitz, Donna Przepiorka, Richard E. Champlin, Robert Peter Gale, Alois Gratwohl, Roger H. Herzig, H. Grant Prentice, Alfred A. Rimm, Olle Ringdén, and Mortimer M. Bortin

There is substantial evidence that the volume of medical procedures in a hospital has an inverse relationship with mortality. We analyzed data for 1313 recipients of HLA-identical sibling bone marrow transplants for early leukemia (acute leukemia in first remission or chronic myelogenous leukemia in first chronic phase) to determine whether transplant outcome differed in small and large centers. Transplants were performed in 86 bone marrow transplant centers active between the years 1983 and 1988, which participated in the International Bone Marrow Transplant Registry. Twenty-one (24%) centers performed five or fewer allogeneic transplants per year during the study period; five (6%) performed more than 40 per year. After adjustment for differences in patient and disease characteristics, the relative risks of treatment-related mortality (1.53, \( P < .01 \)) and treatment failure (1.38, \( P < .04 \)) were higher among patients who received transplants at centers doing five or fewer transplants per year than among those at larger centers. Among patients receiving transplants in centers performing more than five transplants a year, there was no statistically significant correlation between number of transplants and outcome.

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MATERIALS AND METHODS

Participating centers. Two hundred eighty-two centers reported performing one or more allogeneic bone marrow transplants between 1983 and 1987 in two IBMTR surveys of bone marrow transplant activity worldwide.\(^{10,11}\) One hundred forty-one centers started performing bone marrow transplants sometime between 1983 and 1987; these were excluded from consideration to avoid confusing center size with effects caused by program initiation. One hundred and six (75%) of the 141 teams active during the entire study period participated in the IBMTR; 86 of these reported data for patients with the eligibility criteria described below and were included in this study.

Patients. This analysis included 1,313 recipients of HLA-identical sibling transplants for acute myelogenous leukemia (AML) in first remission (n = 574), acute lymphoblastic leukemia (ALL) in first remission (n = 275), or chronic myelogenous leukemia (CML) in first chronic phase (n = 464). Median age was 26 years (range, 1 to 59 years). Nine hundred forty-eight (72%) patients received total body radiation and cyclophosphamide for conditioning; 232 (18%) received total body irradiation, cyclophosphamide, and other drugs; 44 (6%) received total body irradiation and drugs other than cyclophosphamide; and 49 (4%) received busulfan and cyclophosphamide without radiation. Four hundred twenty-one (32%) patients received methotrexate to prevent graft-versus-host disease; 663 (51%) received cyclosporine; and 229 (17%) received both. Recipients of T-cell–depleted transplants were not included in this study.

Statistical methods. Centers were grouped according to the average annual number of allogeneic bone marrow transplants performed for any disease between 1983 and 1987 as reported in two worldwide surveys conducted by the IBMTR in 1985 and 1988 (Table 1).\(^{10,11}\) Patients receiving transplants in centers of various size were compared for their probabilities of leukemia relapse, treatment-related mortality (death, from any cause, in patients in
Table 1. Number of Centers and Patients Studied

<table>
<thead>
<tr>
<th>Group</th>
<th>Center Size*</th>
<th>No. of Centers</th>
<th>No. of Patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-5</td>
<td>21 (24)</td>
<td>95 (7)</td>
</tr>
<tr>
<td>2</td>
<td>6-10</td>
<td>14 (16)</td>
<td>134 (10)</td>
</tr>
<tr>
<td>3</td>
<td>11-15</td>
<td>18 (19)</td>
<td>285 (22)</td>
</tr>
<tr>
<td>4</td>
<td>16-20</td>
<td>9 (10)</td>
<td>162 (12)</td>
</tr>
<tr>
<td>5</td>
<td>21-30</td>
<td>14 (16)</td>
<td>213 (16)</td>
</tr>
<tr>
<td>6</td>
<td>31-40</td>
<td>7 (8)</td>
<td>146 (11)</td>
</tr>
<tr>
<td>7</td>
<td>&gt; 40</td>
<td>5 (6)</td>
<td>278 (21)</td>
</tr>
</tbody>
</table>

Percentages given in parentheses.
*Center size equals average number of allogeneic transplants performed per year, 1983-1987.
†Refers to total number of patients receiving non-T-cell–depleted HLA-identical sibling transplants for early leukemia during the study period.

Table 2. Relative Risk (RR) of Adverse Outcomes According to Center Size

<table>
<thead>
<tr>
<th>Center Size†</th>
<th>N</th>
<th>Relapse</th>
<th>RR*</th>
<th>P†</th>
<th>Treatment-Related Mortality</th>
<th>RR*</th>
<th>P†</th>
<th>Treatment Failure</th>
<th>RR*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>95</td>
<td>0.84</td>
<td>.7</td>
<td>.04</td>
<td>0.94</td>
<td>.7</td>
<td>.99</td>
<td>1.37</td>
<td>.07</td>
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<tr>
<td>6-10</td>
<td>134</td>
<td>1.47</td>
<td>.2</td>
<td>&lt; .01</td>
<td>0.90</td>
<td>.5</td>
<td>&lt; .03</td>
<td>1.08</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>285</td>
<td>1.30</td>
<td>.3</td>
<td>.09</td>
<td>0.99</td>
<td>.9</td>
<td>&lt; .01</td>
<td>1.08</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>162</td>
<td>0.98</td>
<td>.9</td>
<td>.11</td>
<td>1.09</td>
<td>.6</td>
<td>.07</td>
<td>0.97</td>
<td>.8</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>213</td>
<td>0.51</td>
<td>.09</td>
<td>1.09</td>
<td>0.97</td>
<td>.6</td>
<td>.07</td>
<td>0.97</td>
<td>.8</td>
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<td>1.15</td>
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<td>.09</td>
<td>0.94</td>
<td>.9</td>
<td>&lt; .01</td>
<td>1.00</td>
<td>&lt; .01</td>
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</tr>
<tr>
<td>&gt; 40</td>
<td>278</td>
<td>1.06</td>
<td>.06</td>
<td>1.00</td>
<td>1.00</td>
<td>.06</td>
<td>&lt; .01</td>
<td>1.00</td>
<td>&lt; .01</td>
<td></td>
</tr>
</tbody>
</table>

*Derived from multivariate analyses adjusting for disease, age, interval between diagnosis and transplant, organ impairment pretransplant, and year of transplant.
†Center size = average number of allogeneic transplants performed per year, 1983-1987.
‡For comparison of each group with the reference group (patients receiving transplants in centers performing > 40 transplants a year).
§Reference group.
and conditioning regimen in the regression equations did not alter the relative risks of treatment-related mortality, relapse, or treatment failure. Incidence and case-fatality rates of acute and chronic graft-versus-host disease and interstitial pneumonia were similar as were causes of death in small and large centers.

**DISCUSSION**

Allogeneic bone marrow transplants are effective in treating leukemia. Five-year leukemia-free survival is between 40% and 70% for patients with early disease.\(^{18-22}\) Determinants of outcome include patient-, disease-, and treatment-related variables. An important question is whether center size influences outcome independent of these considerations.

Allogeneic bone marrow transplantation requires sophisticated medical facilities and highly trained personnel. It is possible that teams performing many transplants might have better results than those performing fewer transplants. Previous studies report improved outcome of surgical procedures such as renal transplants, coronary artery bypass grafting, and cholecystectomy, in centers where many such procedures are performed.\(^{18-22}\) Other therapies do not show such a correlation.\(^{1-4,9}\) Luft et al\(^{1}\) categorized procedures into three groups based on observed associations between procedure volume and outcome: (1) procedures in which there is no relationship; (2) procedures in which outcome improves in a continuous fashion with increasing volume; and (3) procedures in which outcome improves to a maximum value at some identifiable volume. In this study, allogeneic bone marrow transplantation appears to fall within the third group, although the effect of volume was modest.

We found that the 2-year probability of leukemia-free survival was 10% to 15% lower among patients transplanted in centers doing five or fewer transplants a year than in patients transplanted in larger centers; this difference was of borderline statistical significance. Lower leukemia-free survival resulted from significantly increased treatment-related mortality in the first 6 months posttransplant. Among patients receiving transplants in centers performing more than five transplants a year, there was no association between increasing center size and outcome.

It is possible that differences in outcome between large and small centers could result from differences in the type of patients. Because disease and disease state are the most important determinants of transplant outcome,\(^{18-22}\) we restricted this study to patients with early leukemia. Whether the results apply to patients with more advanced disease is unknown. We also used multivariate statistical techniques to adjust for age and other patient-related factors that might influence outcome. A previous study examining the relationship between transplant volume and outcome failed to show a relationship.\(^{23}\) That study included patients with both early and advanced leukemia. It also considered total rather than annual numbers of transplants. This approach would not distinguish small centers active for a long period from large centers more recently active. In the present study, all centers were active for the entire study period.

Patients receiving transplants in small and large centers had similar patient and disease characteristics. Although transplant regimens differed significantly, they did not account for the different outcomes observed. It was not possible from the data available to identify precisely the reason for different outcomes in small versus large centers. Institutional characteristics, like physician and nurse training or experience and technical facilities, may be important. Insufficient information was available to address these issues.

A plateau in the association between procedure volume and outcome was reached at a relatively low volume, five transplants a year. This may be because center size has only a minor impact on transplant outcome compared with problems like graft-versus-host disease, interstitial pneumonia, and leukemia relapse. There is no evidence that the incidence of these problems was affected by center size.

Whether or not center size affects transplant outcome is important for health care policy. A strong relationship might suggest a policy of limiting transplants to larger centers. Other advantages of this recommendation might be decreased cost and facilitation of large clinical trials. Disadvantages might include limiting access to transplant for patients unable to travel to referral centers and separating patients from family and other support systems. The relationship between center size and outcome identified in this study was modest both in absolute effect and statistical significance. This and the lack of data regarding other institutional characteristics influencing transplant outcome dictate caution and further study before mandating such a policy.

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