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before HSCT and immunosuppression with MMF 30 mg/kg/d orally from day 0 to 27 and cyclophosphamide 12.5 mg/kg/d from day 0 to 2 in addition to TBI. The 40 patients were ineligible for conventional HSCT because of age or medical contraindications.

For comparison, data from a group of 67 patients given conventional myeloablative transplants for equivalent diseases during the same time interval were analyzed. Their conditioning regimens included combinations of busulfan and cyclophosphamide, busulfan and TBI, or cyclophosphamide and TBI. Busulfan was administered orally every 6 hours for 4 days before transplantation, with levels targeted from 600 to more than 900 ng/mL. Cyclophosphamide was administered for 2 days at 60 mg/kg/d. TBI was given over 3 or 4 days with total doses of 12 to 14.4 Gy. One patient with multiple myeloma received busulfan and 9 Gy total marrow irradiation. Two patients conditioned with busulfan and cyclophosphamide received additional therapy with 131I-labeled anti-CD45 antibody.

Splenomegaly, as defined either by imaging studies or through clinical palpation, was documented in 17.5% of nonmyeloablative and 23.9% of conventional HSCT patients. The disease diagnoses were not well balanced among the 2 patient groups. Most patients (77.5%) with nonmyeloablative grafts had B-cell malignancies, including multiple myeloma, chronic lymphocytic leukemia, and non-Hodgkin and Hodgkin lymphoma. By comparison, most conventional patients (83.5%) had acute leukemia, myelodysplastic syndrome, chronic myelogenous leukemia in chronic phase, or agnogenic myeloid metaplasia.

**Transplantation characteristics**

All patients were given PBSC grafts from genotypically HLA-identical siblings, collected after granulocyte colony-stimulating factor mobilization. None of the grafts were processed (ie, RBC- or plasma-depleted) before transplantation. The RBC content was less than 15 mL and the plasma volume less than 300 mL. The numbers of CD34+ cells transplanted and the numbers of ABO-incompatible transplants were not significantly different (P = .36) between nonmyeloablative and myeloablative recipients (Table 1).

**Transfusion policies**

Platelet support before transplantation was given when platelet counts were less than 10 × 10^9/L in the outpatient setting and less than 20 × 10^9/L in the inpatient setting or when patients had signs of bleeding. Patients received random donor platelets unless they developed refractoriness. Random platelets were either whole-blood pooled random platelets or random single-donor apheresis platelets. Before transplantation, all patients received leukocyte-reduced platelets. After transplantation, the leukocyte reduction was no longer required. Packed RBCs were transfused when hematocrits were less than 26% (0.26) or when patients were symptomatic. The numbers of patients who required pretransplantation platelet or RBC transfusions are shown in Table 1. In addition to the total numbers of transfusions, the transfusion requirements were adjusted to the average numbers of units transfused per day during the pretransplantation period.

Posttransplantation platelet and plasma transfusions were of recipient type, and all RBCs were transfused type O in patients with minor RBC incompatibilities (presence of isohemagglutinins in donors against RBC antigens of recipients). For patients with major incompatibilities (presence of isohemagglutinins in recipients against RBC antigens of donors) and bidirectional incompatibilities (bidirectional presence of isohemagglutinins), the first-choice blood groups were AB for posttransplantation platelet transfusions and plasma infusions, and all RBCs were type O. In case of ABO-incompatible platelet transfusions, the platelets were volume-reduced to minimize the amount of isohemagglutinins contained in the plasma. All patients received blood products of donor-type rhesus factor unless recipients had high anti-D titers.

**Statistical analysis**

Unadjusted comparisons of platelet and RBC transfusion requirements for the first 60 days after transplantation were made between recipients of nonmyeloablative transplants and recipients of conventional transplants using the Wilcoxon rank sum test. To account for potential differences in variables related to transfusion requirements, multiple linear regression models were fit with the rank of the numbers of transfusion units serving as outcome variables. Potential explanatory variables included advanced underlying disease, risk for transfusions, pretransplantation transfusion requirements, ABO compatibility, spleen size, age at transplantation, and posttransplantation graft-versus-host disease and cytomegalovirus antigenemia. Proportions of patients requiring transfusion support were compared between groups using the chi^2 test. P values from regression models were...
Results

Posttransplantation platelet transfusion requirements

Twenty-three percent of patients with nonmyeloablative HSCT required platelet transfusions compared with 100% of patients given conventional HSCT (P < .0001) (Figure 1). The overall numbers of platelet units transfused were also statistically significantly less after nonmyeloablative HSCT, with a median of 0 units (range, 0 to 214) compared with a median of 24 units (range, 4 to 358) after standard HSCT (unadjusted P < .0001). Figure 2 illustrates this comparison in more detail. This difference in numbers of units was maintained even after adjusting for risk for platelet transfusions, pretransplantation transfusion requirements, and ABO compatibility (adjusted P < .0001). Both the risk for platelet transfusions and risk for pretransplantation transfusion requirements were statistically significantly associated with numbers of units transfused (P = .01 for each). ABO compatibility was suggestively associated with transfusion requirements but was not statistically significantly associated. The multivariable regression model is summarized in Table 2. One nonmyeloablative transplant recipient became refractory to platelet transfusions after transplantation. Twenty-seven platelet transfusion products in 3 nonmyeloablative transplantation patients were volume-reduced compared with 80 transfusion products in 20 conventional transplantation patients.

Posttransplantation RBC transfusion requirements

Sixty-three percent of patients with nonmyeloablative HSCT required RBC transfusions compared with 96% of patients undergoing standard transplantation (P < .0001) (Figure 1). The numbers of RBC units transfused were also statistically significantly less for patients after nonmyeloablative HSCT, with a median of 2 units (range, 0 to 50) compared with a median of 6 units (range, 0 to 34) after standard HSCT (unadjusted P = .0002). Figure 3 illustrates this comparison in greater detail. As with platelet transfusions, the difference in RBC units remained statistically significant after adjusting for risk for RBC transfusions, pretransplantation RBC transfusion requirements, and ABO compatibility (adjusted P = .0004). Risk for RBC transfusions and risk for pretransplantation transfusion requirements were each statistically significantly associated with numbers of RBC units transfused (P = .0005 for each). Major ABO mismatches required more RBC units compared with compatible patients (P = .0001). The multivariable regression model is summarized in Table 3.

There was no suggestion of interactions between type of transplantation and any of the nontransplantation variables that were included in the regression models. In other words, the increased transfusion requirements seen with conventional PBSC grafts occurred at all levels of these other factors.

Neither development of acute graft-versus-host disease, seen in 55.0% of nonmyeloablative and 37.3% of conventional HSCT recipients; positive cytomegalovirus antigenemia or cytomegalovirus disease, seen in 15.0% of nonmyeloablative and 32.8% of conventional recipients before day 60; splenomegaly; nor increasing patient age were statistically significantly associated with increased posttransplantation transfusion requirements.

Table 2. Multivariable regression model for platelet transfusion requirements during the first 60 days after HSCT

<table>
<thead>
<tr>
<th>Transplant type</th>
<th>Median</th>
<th>Range</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmyeloablative (n = 40)</td>
<td>0</td>
<td>0-214</td>
<td>—</td>
</tr>
<tr>
<td>Conventional (n = 67)</td>
<td>24</td>
<td>4-358</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Risk for transfusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 65)</td>
<td>12</td>
<td>0-214</td>
<td>—</td>
</tr>
<tr>
<td>High (n = 42)</td>
<td>28</td>
<td>0-358</td>
<td>.01</td>
</tr>
<tr>
<td>ABO compatibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compatible (n = 61)</td>
<td>12</td>
<td>0-358</td>
<td>—</td>
</tr>
<tr>
<td>Major mismatch (n = 19)</td>
<td>24</td>
<td>0-214</td>
<td>.14</td>
</tr>
<tr>
<td>Minor/minor and major mismatches (n = 27)</td>
<td>18</td>
<td>0-172</td>
<td>.24</td>
</tr>
</tbody>
</table>

No. of pretransplantation platelet transfusions: continuous variable .01

Figure 2. Percentages of patients requiring platelet transfusions after nonmyeloablative (n = 40) versus conventional (n = 67) HSCT.

Figure 3. Percentages of patients requiring RBC transfusions after nonmyeloablative (n = 40) versus conventional (n = 67) HSCT.
Transfusion requirements of the patient subgroup receiving fludarabine as part of the nonmyeloablative conditioning regimen

The 10 patients conditioned with fludarabine and TBI were transfused with a median of 0 platelet units (range, 0 to 214) and a median of 5 RBC units (range, 0 to 22). The 30 patients given only TBI received a median of 0 platelet units (range, 0 to 172) and a median of 2 RBC units (range, 0 to 50), and these differences were not statistically significant (unadjusted \( P = .43 \) for platelets, \( P = .27 \) for RBCs).

Discussion

The use of conventional high-dose cytotoxic conditioning regimens before allogeneic HSCT eliminates recipient marrow function. To reduce toxicities to nonhematopoietic organs, those regimens are generally administered over 5 to 7 days. At the time of allograft infusions, peripheral blood granulocyte counts are low or absent, and platelet counts have declined. Typically, conventional allogeneic PBSCT recipients remain neutropenic (granulocytes < 500/\( \mu \)L) for a median of 16 days (range, 11-29 days) and thrombocytopenic (platelets < 20 \( \times 10^3/\mu \)L [<20 000/\( \mu \)L]) for a median of 13 days (range, 5-41 days).\(^{10}\)

Recovery of RBC production and RBC transfusion independence are usually later, with medians of 60 to 70 days. Because of the profound and prolonged pancytopenia, virtually all conventional allograft recipients required both multiple platelet and RBC transfusions, and the current control group was no exception.

By comparison, only 23% of current nonmyeloablative recipients required platelet transfusions and 63% needed RBC transfusions. Furthermore, the numbers of platelet and RBC units transfused were significantly reduced. To account for the fact that clinical practice requires platelet transfusions for inpatients when counts decline below 20 \( \times 10^3/\mu \)L (20 000/\( \mu \)L) and for outpatients when counts decline below 10 \( \times 10^3/\mu \)L (10 000/\( \mu \)L), we made the theoretical assumption that all outpatients with platelet counts ranging from 10 \( \times 10^3/\mu \)L to 20 \( \times 10^3/\mu \)L received 6 units of platelets. Even with this assumption, the average number of platelet transfusions was still significantly lower among nonmyeloablative compared with myeloablative HSCT recipients (\( P = .0001 \)). Also, the proportion of patients given platelet transfusions remained statistically significantly lower among nonmyeloablative compared with myeloablative HSCT (\( P < .0001 \)).

There are at least 3 possible reasons for the decreased transfusion requirements. First, the single dose of 2 Gy TBI delivered at the low exposure rate of 0.07 Gy/min, while causing moderate pancytopenia, did not lead to irreversible marrow damage as conclusively documented in canine studies.\(^{11}\)

The declines in peripheral blood counts in dogs given 2 Gy TBI and no subsequent marrow grafts were slow, and granulocyte and platelet nadirs were not reached until 14 to 20 days after TBI. Virtually all dogs showed prompt and complete hematopoietic recoveries within a few weeks of irradiation. In line with these experimental observations, the median granulocyte nadir in a group of 45 nonmyeloablative patients comparable to the current study was 750/\( \mu \)L and the platelet nadir 75 \( \times 10^3/\mu \)L (75 000/\( \mu \)L).\(^{8}\)

Second, the low-dose conditioning regimen was delivered just hours before HSCT. This led to a considerable reduction of the period of pancytopenia compared with the conventional 7 days of high-dose conditioning therapy with busulfan and cyclophosphamide. The addition of 3 doses of fludarabine to the 2 Gy TBI, while extending the regimen by several days, increased the transfusion requirement.

Third, other factors that might lead to increased transfusion needs in conventionally conditioned patients, such as gastrointestinal damage, veno-occlusive disease of the liver, hemorrhagic cystitis, and bacterial sepsis, were either completely absent or significantly reduced (bacterial sepsis) in current nonmyeloablative patients.

Not surprisingly, both transfusion needs before transplantation and major ABO incompatibility between donors and recipients resulted in increased platelet and/or RBC transfusions in all affected patients regardless of the HSCT regimen used. With the relatively small numbers of patients studied, it is as yet unclear whether ABO-incompatible nonmyeloablative recipients will require extended RBC transfusion support compared with conventional HSCT recipients, owing to the theoretical possibility that host and donor isohemagglutinins might be slower to disappear than after a myeloablative HSCT.

Finally, graft-versus-host disease,\(^12\) splenomegaly,\(^13,14\) cytomegalovirus infection\(^15\) or its treatment with ganciclovir,\(^16\) or infection prophylaxis with trimethoprim-sulfamethoxazole\(^17\) have all been reported to affect the tempo of hematopoietic recovery and transfusion needs after conventional HSCT. Whether any of these factors will play a role in nonmyeloablative HSCT can be answered only with the study of larger numbers of transplanted patients.

A number of other nonmyeloablative HSCT regimens have been described, all based on combinations of chemotherapeutic drugs.\(^7,18-22\) Although much is known about transfusions following myeloablative transplants,\(^23,24\) careful studies of posttransplantation transfusion requirements have as yet not been reported for any of the nonmyeloablative chemotherapy regimens.

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References


Decreased transfusion requirements for patients receiving nonmyeloablative compared with conventional peripheral blood stem cell transplants from HLA-identical siblings

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