Transplanted CD34\(^+\) Cell Dose Is Associated with Long-Term Platelet Count Recovery following Autologous Peripheral Blood Stem Cell Transplant in Patients with Non-Hodgkin Lymphoma or Multiple Myeloma

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Autologous hematopoietic stem cell transplantation (ASCT) is an established treatment for patients with hematologic malignancies, yet the impact of transplanted CD34\(^+\) cell dose on clinical outcomes is unresolved. We conducted post hoc analyses of transplanted CD34\(^+\) cell dose and hematopoietic recovery following ASCT in 438 patients with non-Hodgkin lymphoma (NHL) or multiple myeloma (MM), using data from 2 multicenter phase 3 clinical studies that compared plerixafor plus granulocyte colony-stimulating factor (G-CSF) versus placebo plus G-CSF as stem cell mobilization regimens. Days to engraftment and the proportion of patients who reached predetermined blood count thresholds were compared across 3 CD34\(^+\) cell dose levels: 2-4 \(\times 10^6\) cells/kg, 4-6 \(\times 10^6\) cells/kg, and >6 \(\times 10^6\) cells/kg, regardless of mobilization treatment. Short-term neutrophil and platelet engraftment times were similar regardless of cell dose. A significant linear trend was observed between transplanted CD34\(^+\) cell dose and the proportion of patients with platelet count \(\geq 150 \times 10^9/L\) at 100 days (\(P < .001\)), 6 months (\(P = .026\)), and 12 months (\(P = .020\)) in patients with NHL, and at 100 days in patients with MM (\(P = .004\)). A linear trend was also observed between transplanted cell dose and the proportion of patients with platelet count \(> 100 \times 10^9/L\) at 100 days (\(P < .001\)) and 6 months (\(P = .023\)) in patients with NHL. A higher cell dose was associated with a lower percentage of NHL patients requiring red blood cell transfusions (\(P = .006\)). Our analyses confirm previous findings that transplanted CD34\(^+\) cell dose may be associated with better long-term platelet recovery after ASCT.


KEY WORDS: Autologous peripheral blood stem cell transplantation, Cell dose, Platelet recovery, Plerixafor

INTRODUCTION

Autologous hematopoietic stem cell transplantation (ASCT) after high-dose chemotherapy has been shown to achieve better overall survival (OS) compared with conventional chemotherapy in randomized trials of patients with hematologic malignancies such as non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) [1-5]. This treatment strategy depends on successful collection of sufficient hematopoietic stem cells (HSCs). Approximately 20% of patients with NHL or MM fail to mobilize the minimum number of peripheral blood stem cells (PBSCs) required for transplantation (generally accepted as \(\geq 2 \times 10^6\) CD34\(^+\) cells/kg), with either cytokine alone or cytokine plus chemotherapy [6-11]. In patients with NHL, risk factors for poor HSC mobilization include age, prior therapy, mobilization regimen, and bone marrow involvement [6,9,12]. Factors that may affect mobilization in patients with MM include older age, prior melphalan exposure, extensive prior chemotherapy and/or radiotherapy, >4-6 cycles of lenalidomide [13], and prolonged disease duration. Multiple mobilization attempts may...
be needed for these patients and may be associated with adverse implications including increased toxicity or morbidity, delays in time to transplantation, and higher cost of care. Accumulating evidence suggests that among patients who are able to collect an adequate number of CD34+ cells and proceed to transplantation, higher transplanted cell doses, \( \geq 5 \times 10^6 \) CD34+ cells/kg, are associated with faster neutrophil recovery [14-16], higher median platelet counts or faster platelet recovery [16-18], improved disease-free survival (DFS) and OS [19,20], and reduced resource utilization and cost of care [21,22].

Plerixafor is a first-in-class small molecule drug that is indicated for HSC mobilization. It acts by reversibly inhibiting the binding of chemokine stromal cell-derived factor-1\( \alpha \) (SDF-1\( \alpha \)) to its receptor CXCR4, which is involved in the trafficking and homing of HSCs to the bone marrow [23-25]. Plerixafor was shown to mobilize CD34+ hematopoietic progenitor cells in healthy human subjects and patients with NHL and MM [26,27]. Two randomized, double-blind, placebo-controlled, phase 3 trials compared the efficacy and safety of plerixafor plus granulocyte colony-stimulating factor (G-CSF) versus placebo plus G-CSF in mobilization of PBSCs for ASCT in patients with NHL (Study 3101) and MM (Study 3102). Both studies showed that the combination of plerixafor plus G-CSF was well tolerated and enabled significantly more patients to collect the target number of CD34+ cells in fewer apheresis days, compared with patients treated with placebo plus G-CSF [28,29].

To further validate the importance of CD34+ cell dose on hematopoietic recovery, we conducted post hoc analyses of pooled disease-specific data from studies 3101 and 3102, aiming to examine the relationship between transplanted CD34+ cell dose and posttransplantation recovery of neutrophils, platelets, red blood cells, and lymphocytes; transfusion requirements; and survival, irrespective of the mobilization regimen.

**PATIENTS AND METHODS**

**Study Design and Patient Population**

This was a post hoc analysis of posttransplant outcomes in patients with NHL or MM stratified by transplanted CD34+ cell dose from 2 phase 3, multicenter, randomized, double-blind, placebo-controlled studies comparing the safety and efficacy of plerixafor plus G-CSF versus placebo plus G-CSF for the mobilization of CD34+ HSCs for autologous transplantation (Study 3101, NCT00103610, and Study 3102, NCT00103662). For each study, regardless of the mobilization regimen employed, transplanted CD34+ cell dose levels were categorized as 2-4 \( \times 10^6 \) cells/kg, 4-6 \( \times 10^6 \) cells/kg, and \( \geq 6 \times 10^6 \) cells/kg. These categories were chosen based on clinical judgment and to evaluate the usefulness of a infusion cell dose beyond what most consider optimum (5 \( \times 10^6 \) CD34/kg). Patients who underwent transplantation after a single mobilization attempt and had data available with regard to the number of cells infused were included in this analysis; patients undergoing tandem transplantation and rescue patients were excluded. There were 5 patients overall (in 3101 and 3102) who were transfused with <2 \( \times 10^6 \) CD34+ cells/kg. Because the cell dose transplanted was very close to 2 \( \times 10^6 \) cells/kg, these patients were included in the 2-4 category.

Detailed information about the study design and preliminary safety and efficacy outcomes were described in previous publications [28,29]. Briefly, patients with biopsy-confirmed diagnoses were eligible for enrollment in Study 3101 if they had NHL or in Study 3102 if they had MM. Diagnoses were confirmed by biopsy prior to first mobilization. Other inclusion criteria common to the 2 studies included the following: age 18 to 78 years, disease status of being in first or second remission (complete or partial response), eligibility for autologous HSCT, \( \geq 4 \) weeks since last cycle of chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate blood cell counts, and adequate organ function. Patients were excluded from the 2 studies if they had a comorbid condition rendering them at high risk for complications, failed previous HSC collections or collection attempts, prior autologous or allogeneic transplantation, received radiation therapy to the pelvis, and anticipated posttransplantation chemotherapy and/or radiation therapy below the diaphragm. Exclusion criteria specific to Study 3101 included >20% bone marrow involvement and prior radioimmunotherapy with ibritumomab tiuxetan (Zevalin) or tositumomab (Bexxar); exclusion criteria specific to Study 3102 included use of bone-seeking radionuclides; >2 cycles of alkylating agent combinations; and use of thalidomide, lenalidomide, dexamethasone, and/or bortezomib within 7 days prior to first dose of G-CSF.

**Study Treatment**

Randomized patients received G-CSF 10 \( \mu \)g/kg subcutaneously daily in the morning for up to 8 days. Beginning on day 4, patients received either plerixafor 0.24 \( \mu \)g/kg or placebo subcutaneously daily in the evening for up to 4 days. Apheresis (3.0 blood volume \( \pm 10\% \)) began on the morning of day 5 and continued daily for up to 4 days or until sufficient CD34+ cells were collected (\( \geq 5 \times 10^6 \) cells/kg for patients with NHL and \( \geq 6 \times 10^6 \) cells/kg for patients with MM). Apheresis products were processed and stored according to local practice guidelines. Patients who failed to collect either \( \geq 0.8 \times 10^6 \) cells/kg after 2 apheresis days...
or ≥2 × 10^6 cells/kg after 4 apheresis days had the option to enter an open-label rescue procedure in which they would receive a course of G-CSF and plerixafor as described above.

Transplantation and Engraftment

Within 5 weeks of last apheresis, patients received high-dose chemotherapy (with or without total-body irradiation [TBI] for patients with MM) and underwent transplantation using collected CD34^+ cells according to local practice guidelines. G-CSF (5 μg/kg) was started on day 5 or day 6 after stem cell transplantation (SCT) and continued until absolute neutrophil count (ANC) was ≥0.5 × 10^9/L for 3 days or ≥1.0 × 10^9/L for 1 day. Patients were followed for up to 12 months to monitor engraftment and graft durability. The number of CD34^+ cells transplanted and blood cell counts (ANC, lymphocyte, platelet, and red blood cell [RBC]) at 100 days, 6 months, and 12 months was determined by a central laboratory. Neutrophil engraftment was defined as neutrophil count ≥0.5 × 10^9/L for 3 days or ≥1.0 × 10^9/L for 1 day. Platelet engraftment was defined as platelet count ≥20 × 10^9/L without a transfusion for the preceding 7 days.

Maintenance therapy of any kind (chemotherapy or radiation therapy) was not permitted after transplantation for these patients, except to treat relapse or if radiation therapy was low-dose, localized, and necessary to treat lesions above the diaphragm (ie, mediastinum, supraclavicular). In the latter case, radiation therapy was administered no earlier than day 100 and completed by day 150.

Statistical Methods

The proportion of patients who had platelet levels ≥150 × 10^9/L, ≥100 × 10^9/L, and ≥50 × 10^9/L; neutrophil counts ≥2.5 × 10^9/L; lymphocyte counts ≥0.5 × 10^9/L; or hemoglobin level ≥13.8 g/dL (male) or ≥12.1 g/dL (female) at 100 days and 6 and 12 months were compared using Mantel-Haenszel chi-square test to assess linear trends across 3 cell dose categories. Continuous outcomes, number of transfusions, and number of units transfused were compared between the cell dose categories using Wilcoxon rank sum test or Kruskal-Wallis test. Multiple comparisons were tested using Bonferroni adjustment. A P value ≤.05 was considered statistically significant, and all analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

HSC Mobilization and Transplantation

A total of 298 patients with NHL were enrolled in Study 3101; of these, 217 were included in this analysis: 52 patients who entered the rescue protocol and 29 patients who did not proceed to transplantation were excluded from this analysis [29,30]. A total of 302 patients with MM were enrolled in Study 3102; of these, 221 patients were included in this analysis: 56 patients who underwent a tandem transplant, 7 patients who entered the rescue procedure, 17 patients who did not proceed to transplantation, and 1 patient who had missing information were excluded from this analysis [28]. Patient disposition, demographics, and baseline characteristics have been described previously [28,29]. In both studies, a significantly higher portion of patients who received plerixafor plus G-CSF for mobilization were able to proceed to transplantation directly, without need for stem cell rescue procedure, than patients who received G-CSF only (90.0% versus 55.4%, respectively; P < .001, in patients with NHL and 95.9% versus 88.3%, respectively; P = .018, in patients with MM) (Table 1). The median numbers of CD34^+ cells transplanted were also significantly higher in patients who received plerixafor plus G-CSF than in those who received G-CSF only for both the NHL (P < .001) and MM (P < .001) groups (Table 1).

Impact of CD34^+ Cell Dose on Neutrophil and Platelet Engraftment

The short-term impact of CD34^+ cell dose, irrespective of the mobilization regimen, on times to neutrophil and platelet engraftment was evaluated in 217 patients with NHL and 221 patients with MM. In NHL patients infused with 2-4 × 10^6 cells/kg (n = 76), 4-6 × 10^6 cells/kg (n = 75), and >6 × 10^6 cells/kg (n = 66), the median time to neutrophil engraftment was 11 days, 10 days, and 10 days, respectively (Table 2). Median time to platelet engraftment was 20 days in patients infused with 2-4 × 10^6 cells/kg (n = 76) or 4-6 × 10^6 cells/kg (n = 75), and 19 days in patients infused with >6 × 10^6 cells/kg (n = 66). The median time to neutrophil engraftment in MM patients was 11 days irrespective of the infused cell dose. The median time to platelet engraftment was 19 days in MM patients infused with 2-4 × 10^6 cells/kg (n = 75), and 18 days in MM patients infused with 4-6 × 10^6 cells/kg (n = 82) or >6 × 10^6 cells/kg (n = 64). The impact of different CD34^+ cell doses on time to neutrophil and platelet engraftment was not statistically significant.

Impact of CD34^+ Cell Dose on Long-Term Platelet Recovery

The percentages of patients with platelet threshold levels of 150 × 10^9/L, 100 × 10^9/L, or 50 × 10^9/L were compared across all 3 CD34^+ cell dose categories, regardless of mobilization treatment, at 100 days, 6 months, and 12 months posttransplantation. In
patients with NHL, a significant linear association was observed between CD34⁺ cell dose and percentage of patients with a platelet threshold of 150 × 10⁹/L at the 100-day (P < .001), 6-month (P = .026), and 12-month (P = .020) follow-ups (Table 3). In patients with MM, a significant association was observed at the 100-day follow-up (P = .004), but not at the 6- and 12-month follow-ups (Table 3). In the 3101 study, a significant linear association was observed between CD34⁺ cell dose and the percentage of patients with a platelet threshold of 100 × 10⁹/L at the 100-day (P < .001) and 6-month (P = .023) follow-ups, but not at 12-month follow-up (Table 4). No significant association was observed between cell dose and the proportion of MM patients with platelet counts of 100 × 10⁹/L for any follow-up time (Table 4). For the 50 × 10⁹/L platelet threshold, we did not observe a significant association between cell dose and proportion of MM or NHL patients at any follow-up time period (data not shown).

Impact of CD34⁺ Cell Dose on Long-Term Recovery of Lymphocytes, Neutrophils, and RBC

After controlling for treatment groups, there were no significant differences in mean lymphocyte, neutrophil, or hemoglobin recovery across all CD34⁺ cell doses at 100-day, 6-month, and 12-month follow-ups in either patients with NHL or patients with MM (data not shown).

Impact of CD34⁺ Cell Dose on Transfusion Requirement

The total number of platelet transfusions (defined as transfusion of platelets at a given time regardless of the reported number of units) in the 3101 and 3102 studies was 786 and 402, respectively. Across all 3 CD34⁺ cell dose categories, there was no significant linear association in the percentage of patients with NHL or MM requiring platelet transfusion (Table 5). There was a significant difference in the median number of platelet transfusions between the 2-4 × 10⁶ cells/kg and >6 × 10⁶ cells/kg cell dose categories for NHL patients after adjusting for multiple comparisons (P = .03). There were no significant differences in median number of platelet transfusions in MM patients or median units of platelets transfused in both NHL and MM patients across CD34⁺ cell dose categories.

The total number of RBC transfusions (defined as transfusion of PRBC at a given time regardless of the reported number of units) in the 3101 and 3102 studies...
was 390 and 248, respectively. A significant linear association between higher CD34+ cell dose and a lower percentage of patients requiring RBC transfusion was observed in patients with NHL (P < .006) (Table 5). A similar association approaching a significant level was also observed in patients with MM (P = .052).

No significant differences in median number of RBC transfusions or median units of RBCs transfused were found across CD34+ cell dose categories.

Patient Survival and Posttransplantation Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML)

Patients were followed for at least 1 year after transplantation. In patients with NHL, overall survival (OS) rates at 1-year posttransplantation were 92.1% (70/76), 85.3% (64/75), and 84.8% (56/66) in the 2-4 × 10^6, 4-6 × 10^6, and >6 × 10^6 cells/kg categories, respectively. In patients with MM, the 1-year survival rates were 96.0% (72/75), 96.3% (79/82), and 92.2% (59/64) in the 3 cell dose categories, respectively. There was no significant difference in the 1-year survival rate among the 3 cell dose categories in both NHL and MM studies. Among patients with NHL, 2 patients developed AML posttransplantation: 1 patient had genetic chromosome 6 mutation and developed pancytopenia that transformed into AML and in the other patient development of AML (168 days posttransplant) was assessed to be because of previous exposure to liposomal doxorubicin and etoposide. The 2 patients received a cell dose of 5.04 × 10^6 and 2.74 × 10^6 cells/kg, respectively. Another NHL patient had pre-existing chromosomal 5/7 abnormalities, which was compatible with MDS. None of the patients with MM developed MDS or AML during the 1-year follow-up period.

### Table 3. Number and Percentage* of Patients Reaching Posttransplantation Platelet Threshold Level of 150 × 10^9/L

<table>
<thead>
<tr>
<th>NHL (3101 study)</th>
<th>CD34+ Cell Dose</th>
<th>Time Posttransplantation</th>
<th>2-4 × 10^6 Cells/kg (n = 76)</th>
<th>4-6 × 10^6 Cells/kg (n = 75)</th>
<th>≥6 × 10^6 Cells/kg (n = 66)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100 days</td>
<td>28/58 (48.3%)</td>
<td>42/63 (66.7%)</td>
<td>45/55 (81.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>31/55 (56.4%)</td>
<td>36/64 (56.7%)</td>
<td>42/55 (76.4%)</td>
<td>.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>18/32 (56.3%)</td>
<td>21/26 (80.8%)</td>
<td>24/29 (82.8%)</td>
<td>.020</td>
</tr>
<tr>
<td>MM (3102 Study)</td>
<td></td>
<td>100 days</td>
<td>41/60 (68.3%)</td>
<td>57/63 (90.5%)</td>
<td>47/53 (88.7%)</td>
<td>.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>48/61 (78.7%)</td>
<td>61/68 (89.7%)</td>
<td>51/58 (87.9%)</td>
<td>.147</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>25/34 (73.5%)</td>
<td>33/40 (82.5%)</td>
<td>26/32 (81.3%)</td>
<td>.435</td>
</tr>
</tbody>
</table>

*Percentages are based on the number of patients with available data at each follow-up time point.
†P value testing linear trend using Mantel-Haenszel chi-square test.

### Table 4. Number and Percentage* of Patients Reaching Posttransplantation Platelet Threshold Level of 100 × 10^9/L

<table>
<thead>
<tr>
<th>NHL (3101 study)</th>
<th>CD34+ Cell Dose</th>
<th>Time Posttransplantation</th>
<th>2-4 × 10^6 Cells/kg (n = 76)</th>
<th>4-6 × 10^6 Cells/kg (n = 75)</th>
<th>≥6 × 10^6 Cells/kg (n = 66)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100 days</td>
<td>39/58 (67.2%)</td>
<td>57/63 (90.5%)</td>
<td>51/55 (92.7%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>44/55 (80.0%)</td>
<td>47/54 (87.0%)</td>
<td>52/55 (94.6%)</td>
<td>.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>28/32 (87.5%)</td>
<td>23/26 (88.5%)</td>
<td>27/29 (93.1%)</td>
<td>.479</td>
</tr>
<tr>
<td>MM (3102 Study)</td>
<td></td>
<td>100 days</td>
<td>54/60 (90.0%)</td>
<td>63/63 (100.0%)</td>
<td>51/53 (96.2%)</td>
<td>.100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td>54/61 (88.5%)</td>
<td>64/68 (94.1%)</td>
<td>55/58 (94.8%)</td>
<td>.190</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 months</td>
<td>32/34 (94.1%)</td>
<td>33/40 (82.5%)</td>
<td>30/32 (93.8%)</td>
<td>.952</td>
</tr>
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</table>

*Percentages are based on the number of patients with available data at each follow-up time point.
†P value testing linear trend using Mantel-Haenszel chi-square test.
It is generally accepted that the minimum number of CD34⁺ cells required for ASCT is 2 × 10⁶ cells/kg and the optimum number is 5 × 10⁶ cells/kg. Previous studies have demonstrated that a higher number of transplanted CD34⁺ cells is correlated with faster hematopoietic recovery, particularly platelet recovery, longer survival, and reduced cost of care [14-22], justifying the need to collect the optimum number of CD34⁺ cells, regardless of the number of aphereses it takes to obtain these. The analyses presented here are based on 2 large, randomized, phase 3 trials (Studies 3101 and 3102) that compared plerixafor plus G-CSF versus placebo plus G-CSF as the mobilization regimen in patients with NHL or MM [28,29]. We found that following transplantation, the median times to short-term platelet and neutrophil engraftment were similar regardless of CD34⁺ cell dose. The trends reported for the delay in platelet engraftment in patients receiving fewer CD34⁺ cells/kg may be biased by the small number of patients included in prior studies, as well as the much broader range of CD34⁺ counts (<1 to >10 × 10⁶ cells/kg) evaluated in prior studies [14,16].

In a retrospective study of thrombopoiesis in 359 patients undergoing autologous transplantation, the achievement of a platelet count of ≥150 × 10⁹/L by 100 days posttransplant (or initial engraftment) was independently associated with a significantly higher number of transplanted CD34⁺ cells/kg and improved posttransplant survival [31]. Similar to these previous findings, we observed a significant linear association between CD34⁺ cell dose and percentage of patients with a platelet threshold of 150 × 10⁹/L at 100 days for both NHL and MM and at 6 and 12 months for NHL patients. These patients also experienced a need for fewer platelet transfusions (at a cell dose of >6 × 10⁶ cells/kg) and a lower percentage of patients with NHL receiving RBC transfusions. These results are in agreement with the findings of previous studies that show a positive impact of higher transplanted cell doses on faster platelet recovery [16-18] and decreased transfusion requirements [16,21,22].

**DISCUSSION**

<table>
<thead>
<tr>
<th>Table 5. Impact of CD34⁺ Cell Dose on Platelet and RBC Transfusion</th>
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<tbody>
<tr>
<td><strong>CD34⁺ Cell Dose, Cells/kg</strong></td>
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<tr>
<td>NHL (3101 Study)</td>
</tr>
<tr>
<td>2-4 × 10⁶ (n = 76)</td>
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<tr>
<td>Platelet transfusion</td>
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<tr>
<td>Number of patients who received transfusion (%)</td>
</tr>
<tr>
<td>Number of transfusions per patient</td>
</tr>
<tr>
<td>Median (range)</td>
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<tr>
<td>Number of units transfused per patient</td>
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<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>RBC transfusion</td>
</tr>
<tr>
<td>Number of patients who received transfusion (%)</td>
</tr>
<tr>
<td>Number of transfusions per patient</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Number of units transfused per patient</td>
</tr>
<tr>
<td>MM (3102 study)</td>
</tr>
<tr>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>Number of patients who received transfusion (%)</td>
</tr>
<tr>
<td>Number of patients who received transfusion (%)</td>
</tr>
<tr>
<td>Number of transfusions per patient</td>
</tr>
<tr>
<td>MM indicates multiple myeloma; NHL, non-Hodgkin lymphoma; NS, not significant; RBC, red blood cell; SD, standard deviation.</td>
</tr>
<tr>
<td>P value testing linear trend using Mantel-Haenszel chi-square test (for dichotomous outcomes) or Wilcoxon rank sum test (for continuous outcomes).</td>
</tr>
<tr>
<td>†Significant difference only between the 2-4 × 10⁶ cells/kg and &gt;6 × 10⁶ cells/kg cell dose categories.</td>
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</tbody>
</table>
We did not find a significant impact of CD34+ cell number on the recovery of other blood cells (lymphocytes, neutrophils, and RBCs). These results are somewhat inconsistent with previously published data, which showed a positive correlation between CD34+ cell number and recovery of lymphocytes, neutrophils, and RBCs [14-16,21,22]. The reasons for the discrepancies are unknown and may be related to the differences in mobilization regimens, patient population, study design, and sample size. Prior correlative studies utilized growth factor (G-CSF or granulocyte-macrophage colony stimulating factor [GM-CSF]) alone, chemotherapy alone, or a combination of growth factor with chemotherapy in their mobilization regimens [14-16,21,22]. With a cutoff of approximately $5 \times 10^6$ CD34+ cells/kg, median time to recovery of neutrophils [16,21,22], and leukocytes [21] was significantly improved in patients receiving $\geq 5 \times 10^6$ CD34+ cells/kg. Duggan and colleagues [14] showed that following G-CSF and chemotherapy mobilization, CD34+ cell dose (1-5, 5-10, 10-16, and $>16 \times 10^6$ CD34+ cells/kg) was significantly and inversely correlated with the percentage of patients with low neutrophil and platelet (but not RBC) recovery.

We did observe a significant impact of cell dose on the number of platelet transfusions as well as on the proportion of patients requiring RBC transfusions. In patients with NHL (Study 3101), there was a significantly lower median number of platelet transfusions as well as a lower percentage of patients who received RBC transfusions with increasing cell doses. Prior studies of patients infused with $\geq 5 \times 10^6$ CD34+ cells/kg showed fewer platelet [21,22] or RBC [22] transfusions compared with patients infused with $<5 \times 10^6$ CD34+ cells/kg, and consequently significantly reduced resource utilization [22]. Sola et al. [16] showed an inverse correlation between the number of mobilized CD34+ cells (by cyclophosphamide and G-CSF) and the number of platelet transfusions.

We did not observe any significant differences in 1-year posttransplantation survival across cell dose categories. In addition, a separate survival analysis based on mobilization regimen demonstrates that 1-year OS estimates for patients in the plerixafor plus G-CSF versus placebo plus G-CSF groups were similar in both Study 3101 and 3102 [32]. Given the low death rate at 1 year, longer follow-up periods may be warranted to detect a significant difference. Given the fact that 1-year survival rates are usually high in these patients, it remains possible that any cell dose above the $2 \times 10^6$ cells/kg threshold will achieve similar survival outcomes. To date, as expected, posttransplantation myeloid malignancies have been rare in our study, with only 1 case of pre-existing MDS and 2 cases of AML, all in patients with NHL, although this will bear watching because the median time to develop these posttransplantation complications is much longer and there has been relatively short follow-up to date. A long-term monitoring study of these populations is ongoing. Indeed, this large data set may ultimately help clarify the importance of CD34 dose on the development of these complications.

Collective evidence in a 2000 review by Siena and colleagues [15] provides support for the clinical relevance of CD34+ cell dose in transplantation. The recommended CD34+ cell dose for ASCT was $\geq 5 \times 10^6$ cells/kg (minimum $2 \times 10^6$ cells/kg; optimal $\geq 8 \times 10^6$ cells/kg to achieve 100% engraftment) and has been considered a key factor in hematopoietic recovery and satisfactory engraftment. This guidance has proven reliable in providing consistent results in studies where G-CSF was the standard treatment for mobilizing CD34+ cells. Studies 3101 and 3102 have established the role of plerixafor as part of stem cell mobilization regimen that improves the success rate of stem cell collection. Our analyses are based on cell dose categories, regardless of mobilization regimen (plerixafor plus G-CSF versus placebo plus G-CSF). Taken together, these data suggest that the recent incorporation of plerixafor as part of the mobilization regimen contributes to improving the chance of transplanting a higher number of CD34+ cells (which in turn, correlates with better platelet recovery) without negatively impacting graft durability or patient survival.

**ACKNOWLEDGMENTS**

The development of this manuscript was supported by Genzyme Corporation. The authors thank Wei Jiang, PhD, and Julie Kern, PhD, for editorial support. Studies 3101 and 3102 were sponsored by Genzyme Corporation. All authors have full access to the data and have reviewed and approved the manuscript. The corresponding author has the final responsibility to submit the manuscript. Assistance in manuscript writing was provided by SciStrategy Communications, which received financial support from Genzyme Corporation. Part of the results in this article was presented at the 50th (2008) and 51st (2009) annual meetings of the American Society of Hematology.

**Financial disclosure:** Patrick Stiff received research funding and serves on an advisory board for Genzyme Corporation. Ivana Micallef received research funding from Genzyme Corporation. Auayporn Nademanee serves on the advisory boards for Allos Therapeutics, Inc., and Spectrum Pharmaceuticals, Inc. Richard Maziarz received research funding from and serves on the advisory board for Genzyme Corporation. Brian Bolwell serves on the advisory board for Genzyme Corporation. Sachin Marulkar is an employee of Genzyme Corporation. Gary Bridger was an employee of Anormed Inc, now Genzyme.
Corporation; he is now a consultant with Genzyme Corporation. Frank Hsu is an employee of Genzyme Corporation. John DiPersio received honoraria from Genzyme Corporation.

REFERENCES


