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Peripheral blood or bone marrow cells in reduced-intensity or myeloablative conditioning allogeneic HLA identical sibling donor transplantation for multiple myeloma

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ABSTRACT

Background and Objectives
Peripheral blood stem cells (PBSC) following reduced intensity conditioning (RIC) are being increasingly used for allogeneic transplantation in multiple myeloma. The purpose of this study was to compare outcome of patients transplanted with either PBSC or bone marrow (BM) following RIC or myeloablative conditioning (MAC).

Design and Methods
Data from 1,667 patients who had received an allogeneic identical sibling donor transplant for multiple myeloma from 1994 to 2003 were analyzed. Comparisons were made between results of PBSC and BM transplants after conditioning with RIC or MAC.

Results
The engraftment rate was faster with PBSC than with BM (median: 14 and 18 days for neutrophils and 15 and 25 days for platelets respectively) irrespectively of whether RIC or MAC was used. The incidence of acute graft-versus-host disease (GVHD) did not differ significantly between the groups while chronic GVHD was more prevalent in PBSC recipients irrespectively of whether they had RIC or MAC. Non-relapse mortality did not differ between PBSC and BM recipients, but was significantly higher in those treated with MAC than in those given RIC irrespectively of the cell source. The relapse/progression rate did not differ between PBSC and BM recipients, but was significantly higher in those given RIC, irrespectively of the cell source. There was no significant difference in overall or progression-free survival between patients given PBSC or BM transplants.

Interpretation and Conclusions
Although transplantation of PBSC is associated with faster engraftment and more frequent chronic GVHD, overall survival, non-relapse mortality, relapse/progression and progression-free survival are similar to those following BM transplants. However both PBSC and BM transplants are associated with lower non-relapse mortality, lower response rate and higher relapse/progression if RIC is used instead of MAC.

Key words: peripheral blood stem cell transplantation, bone marrow transplantation, reduced intensity conditioning, myeloablative conditioning, multiple myeloma.

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The European Group for Blood and Marrow Transplantation (EBMT) centers have used peripheral blood stem cells (PBSC) for allogeneic transplantation in multiple myeloma since 1994.1 The number of transplants performed with PBSC increased rapidly and since 1998 the majority of transplants have been performed with PBSC. Previous studies indicated that the overall survival of myeloma patients transplanted with PBSC and BM is similar in agreement with some,2-10 but in contrast to other studies in leukemia and other hematologic malignancies indicating better results with PBSC11,12 or with BM.13 Engraftment in myeloma was found to be faster with PBSC than with BM. Previous studies indicated that the overall survival of myeloma patients transplanted with PBSC increased rapidly and since 1998 the majority of transplants have been performed with PBSC.10

Table 1. Patient and transplant characteristics.

<table>
<thead>
<tr>
<th>Variable available</th>
<th>Data available (%)</th>
<th>PBSC Number</th>
<th>BM Number</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>100</td>
<td>339 29 238 49</td>
<td>840 71 250 51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>100</td>
<td>748 63 288 59</td>
<td>431 37 200 41</td>
<td>0.09</td>
</tr>
<tr>
<td>Type of myeloma</td>
<td>91</td>
<td>615 57 259 59</td>
<td>178 21 90 21</td>
<td>0.38</td>
</tr>
<tr>
<td>Light chain</td>
<td></td>
<td>184 17 61 14</td>
<td>55 5 28 6</td>
<td></td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>71</td>
<td>102 12 37 12</td>
<td>178 21 72 22</td>
<td>0.78</td>
</tr>
<tr>
<td>Number of prior treatment regimens</td>
<td>49</td>
<td>314 62 186 61</td>
<td>196 38 120 39</td>
<td>0.82</td>
</tr>
<tr>
<td>Number of prior autotransplants</td>
<td>100</td>
<td>683 59 413 84</td>
<td>401 34 62 13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Response status at conditioning</td>
<td>90</td>
<td>143 13 75 17</td>
<td>617 58 236 54</td>
<td>0.01</td>
</tr>
<tr>
<td>Conditioning</td>
<td>85</td>
<td>120 11 67 15</td>
<td>187 18 60 14</td>
<td></td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
<td>1994-95 14 1 126 26</td>
<td>1996-97 97 8 123 25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from diagnosis to transplant (months)</td>
<td>97</td>
<td>482 42 282 59</td>
<td>667 58 193 41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Conditioning</td>
<td>85</td>
<td>596 60 52 12</td>
<td>401 40 369 88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TBI in conditioning</td>
<td>97</td>
<td>620 54 134 28</td>
<td>520 46 337 72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F-cell depletion</td>
<td>88</td>
<td>712 67 236 58</td>
<td>672 67 236 58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor sex</td>
<td>97</td>
<td>828 72 359 75</td>
<td>316 28 119 25</td>
<td>0.26</td>
</tr>
<tr>
<td>Total cell dose given x 10^6/kg</td>
<td>62</td>
<td>20 4 69 57</td>
<td>113 22 33 27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low (≤2.0)</td>
<td>59</td>
<td>376 74 20 13</td>
<td>29 7 81 30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intermediate (2.0-4.0)</td>
<td></td>
<td>50 12 155 57</td>
<td>339 81 34 13</td>
<td></td>
</tr>
<tr>
<td>High (&gt;4.0)</td>
<td></td>
<td>20 4 69 57</td>
<td>113 22 33 27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD34+ dose given x 10^6/kg</td>
<td></td>
<td>376 74 20 13</td>
<td>29 7 81 30</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>response status at conditioning</td>
<td></td>
<td>828 72 359 75</td>
<td>316 28 119 25</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Design and Methods

Patients

The population study consisted of patients reported to the EBMT registry, who had received a first allogeneic HLA identical sibling donor transplant between 1994 and 2003 and for whom information was available on basic variables, such as sex and age, as well as source of stem cells. There were 1,667 multiple myeloma patients who fulfilled these criteria: 1,179 had received PBSC and 488 BM. Table 1 shows the characteristics of these patients and their transplants. There were some differences in prognostic factors between the two groups of patients. Patients who received PBSC were significantly older than those who received BM and they had more frequently received autologous transplants before the allogeneic transplant. The year of transplant was more recent for PBSC recipients than for BM recipients. Total body irradiation in the conditioning regimen and T-cell depletion were used less frequently. Other factors, such as stage at diagnosis, female donor to male recipient, number of lines of previous chemotherapy, and

response status at conditioning were similar.

The study was approved by the Ethics Committee of the Karolinska Institutet. Informed consent was obtained locally according to national regulations.
**Conditioning regimens**

The type of conditioning was known for 1,418 cases (648 RIC and 770 MAC). In the absence of a universally agreed definition of RIC the local centers’ definition of RIC and MAC was used. The main types of RIC and MAC used are presented in Table 2.

**T-cell depletion**

T-cell depletion was defined as ex vivo or in vivo. Ex vivo T-cell depletion included all kinds of T-cell depletion of the graft before stem-cell infusion. In vivo depletion included all kinds of monoclonal antibody therapy, antilymphocyte globulin (ALG), antithymocyte globulin (ATG) or serotherapy given in association with the conditioning regimen. Other T-cell depletion was defined as combinations of both in vivo and in vitro T-cell depletion or combinations of any of these with T-cell depleting drugs.

**Statistics**

Comparisons between groups were made using the χ² test for categorical data, and the Mann-Whitney or Kruskall-Wallis test for continuous data. Probabilities of overall and progression-free survival were calculated using the Kaplan-Meier method, and unadjusted comparisons were made using the log-rank test. For outcomes with competing risks, NRM and relapse/progression, and time to engraftment (with death without engraftment as a competing risk) probabilities were estimated using the cumulative incidence non-parametric estimator, and were compared by the Gray test. Multivariate Cox models were used to assess differences for overall survival, progression-free survival, relapse-progression, NRM and engraftment hazards. As the type of conditioning regimen was a potentially strong confounder of the effect of the source of cells, the role of source was assessed in the sub-population of patients for whom the type of conditioning was known (patients with available data n=1418; with missing data n=249), testing differences between PBSC and BM recipients within those given RIC or MAC. It was checked that the group of patients for whom information on this type of conditioning was lacking behaved similarly to the other groups with respect to outcomes, thus indicating the absence of a selection bias. A multivariate analysis of the outcomes was performed in order to assess net differences observed in PBSC and BM recipients. Adjustment factors were selected among: calendar period, age, patient’s sex, patient-donor gender mismatch, time interval between diagnosis and transplantation, stage at diagnosis, β microglobulin level at diagnosis, response status at conditioning, response status at transplantation, number of lines of therapy, number of previous autologous transplants, total body irradiation during conditioning, T-cell depletion, and the dose of CD34-positive cells given. In the case of a high number of patients with missing values for a certain variable, those with missing values were considered as a separate group, and it was checked that this group behaved as a mixed group, such that it was possible to estimate net effects for the main factor of interest without losing information.

All analyses were performed in SAS 8.02; the macro CIN created by the Departments of Biostatistics of St. Jude’s Children Research Hospital in Memphis was used to analyze competing risks. All reported p-values are from two-sided tests. Confidence intervals (CI) refer to 95% boundaries.

**Results**

**Engraftment and graft failure**

Engraftment was faster with PBSC than with BM for both neutrophils and platelets. The median time to neutrophil engraftment was 14 and 18 days (p<0.0001) and to platelet engraftment 15 and 25 days (p=0.0002) for PBSC and BM recipients, respectively.

The faster engraftment for both neutrophils and platelets with PBSC as compared to BM was independent of the conditioning regimen. In multivariate analysis, the HR of neutrophil engraftment for PB versus BM was 1.58 (p=0.027) and 1.46 (p=0.0002) in patients given RIC and MAC, respectively; for platelet engraftment it was 2.10 (p=0.007) and 1.78 (p<0.0001), respectively.

The overall graft failure rate with PBSC and BM in the RIC group was 2.9% and 9.8% (p=0.027), respectively, and in the MAC group 6.8% and 4.8% (p=0.273), respectively. Thus with RIC it appeared that PBSC could decrease the risk of graft failure after RIC, whereas it did not seem to be important for the risk of graft failure whether PBSC or BM was used following MAC. Seventy-one patients (4.3%) died without engraftment at a median time of 0.6 months after transplantation. There was no obvious difference between the groups.

**Response to transplantation**

Response to transplantation is shown in Table 3 for PBSC and BM recipients given RIC or MAC. The overall response rates according to Blade’s criteria (complete response [CR] + partial response [PR]) with RIC (61%) and MAC (65%) were similar. However the CR rate was higher with MAC (42%) than with RIC (52%). This was irrespective of the pretransplant response status. Thus the CR rate in patients who were

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**Table 2. Conditioning regimens.**

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Reduced intensity conditioning</th>
<th></th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine + TBI</td>
<td>105</td>
<td></td>
<td>16.2</td>
</tr>
<tr>
<td>Fludarabine + Melphalan</td>
<td>137</td>
<td></td>
<td>21.1</td>
</tr>
<tr>
<td>Fludarabine + Busulphan</td>
<td>113</td>
<td></td>
<td>17.4</td>
</tr>
<tr>
<td>Other</td>
<td>293</td>
<td></td>
<td>45.2</td>
</tr>
<tr>
<td>Total</td>
<td>648</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Myeloablative conditioning</th>
<th></th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan + TBI</td>
<td>177</td>
<td></td>
<td>23.0</td>
</tr>
<tr>
<td>Cyclophosphamide + TBI</td>
<td>216</td>
<td></td>
<td>28.1</td>
</tr>
<tr>
<td>Busulphan + cyclophosphamide</td>
<td>51</td>
<td></td>
<td>6.6</td>
</tr>
<tr>
<td>Other</td>
<td>326</td>
<td></td>
<td>42.3</td>
</tr>
<tr>
<td>Total</td>
<td>770</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

TBI: total body irradiation.
in PR pretransplant was 43% with PB-MAC, and 40% with BM-MAC, but only 28% with PB-RIC and 17% with BM-RIC. Among the patients with progressive/relapsed disease pretransplant, the CR rates were 56% in the PB-MAC group and 21% in the PB-RIC group while the numbers of patients were too low for a comparison of the BM-RIC and BM-MAC groups.

There was no significant difference in CR rate between PBSC or BM recipients given MAC (42% and 43% respectively), while the overall response rate was somewhat lower with PBSC than with BM (p=0.023). In the RIC group there appeared to be an advantage from using PBSC (CR rate 34% with PBSC and 16% with BM). The overall response rate (CR+PR) of PBSC recipients given RIC was 62% versus 51% among BM recipients (p=0.047). Thus the response was worse with RIC than with MAC, but could be improved somewhat by using PBSC instead of BM.

Non-relapse mortality
There was no significant difference in NRM between PBSC and BM recipients irrespectively of whether reduced intensity or myeloablative conditioning was used (Figure 1). However, NRM was lower with RIC than with MAC, for both PBSC and BM recipients. NRM at day 100 was 11% and 17% with PBSC and 6% and 18% with BM with RIC and MAC, respectively. The lack of significant differences was confirmed in multivariate analysis (p=0.4 and p=1.0 for RIC and MAC, respectively). Thus, the more rapid engraftment rate with PBSC did not translate into lower NRM after either RIC or MAC.

Relapse rate and progression-free survival
The overall relapse/progression rate (Figure 2) appeared to be higher among PBSC recipients than among patients transplanted with BM, but this turned out to be due to the higher number of RIC transplants in the PBSC group as compared to the MAC group. The relapse rate was significantly higher following RIC than after MAC (p=0.0008). However there was no significant difference in NRM between PBSC and BM recipients within the RIC group (p=0.0428) or the MAC group (p=0.970).

Figure 1. Non-relapse mortality (NRM) in PBSC and BM recipients following RIC and MAC. The overall NRM was lower after RIC than after MAC (p=0.0008). However there was no significant difference in NRM between PBSC and BM recipients within the RIC group (p=0.428) or the MAC group (p=0.970).

Figure 2. Relapse/progression rate in PBSC and BM recipients after RIC or MAC. The overall relapse/progression rate was significantly higher after RIC than after MAC (p=0.0001). However there was no significant difference in the relapse rate between PBSC and BM recipients within the RIC group recipients (p=0.547) or the MAC group (p=0.077).
Overall survival

There was no significant difference in overall survival between PBSC and BM recipients (Figure 3). The median overall survival was 30 months and 32 months for PBSC and BM recipients, respectively, and the 5- and 7-year survival rates were 33% and 30%, and 38% and 36% for PBSC and BM recipients, respectively. Differences in overall survival between PBSC and BM recipients were confirmed to be non-significant in the multivariate analysis ($p=0.33$ in the RIC group and $p=0.95$ in the MAC group). The overall survival of both PBSC and BM recipients was independent of the use of RIC or MAC. Thus, the lower NRM with RIC was counter-balanced by the higher relapse rate within both the PBSC and BM groups, resulting in a similar overall survival.

Graft-versus-host disease

There was no apparent difference in acute GVHD between PBSC and BM recipients. Grade II-IV GVHD was seen in 34.7% of patients receiving PBSC and in 39.5% of those receiving BM ($p=0.08$). However, overall chronic GVHD was more frequent with PBSC (54.0%) than with BM (41.4%) ($p=0.001$), while there was no significant difference in extensive chronic GVHD between the two groups (25.0% and 23.1% in the PBSC and BM groups, respectively; $p=0.58$). When PBSC and BM recipients were analyzed separately according to whether they were given RIC or MAC, the findings were similar. Although there was a weak tendency for better survival in patients with chronic GVHD, assuming that the chronic GVHD occurred within 1 year after transplantation and adjusting for the fact that patients had survived for at least 1 year, the difference was not statistically significant ($p=0.129$). Among the population of patients for whom the type of conditioning was known, sufficient information on chronic GVHD was available for only 461. Therefore, further subgroup analysis could not be done.

Discussion

The EBMT centers have used PBSC in allogeneic transplantation for multiple myeloma since 1994. A previous EBMT study showed that results of allogeneic transplantation improved dramatically from 1994, i.e. in parallel with the increasing use of PBSC. The improvement was due to a reduction in NRM, but this did not appear to be the result of the use of PBSC. No improvement in relapse rate was seen with either PBSC or BM, but the observation period may not have been long enough to reveal a difference.

RIC transplantation did not start until 1998. Thus it seemed important to compare outcomes of PBSC and BM transplants in patients given RIC and MAC separately, since an effect of hematopoietic cell source may be different in the two conditioning regimens considering that more chronic GVHD was seen with PBSC in the previous investigation. During the period 2002-2003, 91% of the allogeneic transplants in myeloma recipients reported to the EBMT registry were performed with PBSC as compared to 66% during the period 1998-99. During the same time the use of RIC transplants increased from 37% to 75%. Thus, with a few years delay there has been a parallel increase in PBSC and RIC transplants in myeloma patients reported to EBMT centers.

In this study we found that despite the slower engraftment of RIC transplants compared to MAC transplants, the more rapid engraftment rate with PBSC as compared to BM was similar in both RIC and MAC recipients. The overall NRM mortality was similar in PBSC and BM recipients but was heavily influenced by the use of RIC or MAC. Thus, as shown previously, the NRM in myeloma was lower with RIC than with MAC but we have now shown that it is similar for PBSC and BM recipients within each conditioning group.

The overall higher relapse rate with PBSC as compared to BM was almost entirely due to the concomitant use of RIC with increasing use of PBSC. Within the RIC groups there was no significant difference between PBSC and BM recipients. However, within the MAC group the multivariate analyses indicated a weak trend to PBSC being associated with a slightly higher relapse rate and poorer progression-free survival; however, this did not translate into a poorer overall survival.

Overall survival was similar in PBSC and BM recipients, corroborating our previous results observed in patients given MAC. This lack of difference in overall survival was also present when patients were separated into RIC and MAC groups, since the lower NRM with RIC was offset by the higher relapse rate, irrespectively of whether PBSC or BM was used for the transplant.

As shown, there was no significant difference in acute GVHD disease depending on whether PBSC or BM were used, while the incidence of chronic GVHD was higher with PBSC. This finding corroborates results in other hematologic disorders. In the present study this difference seemed to be more pronounced in patients given RIC, perhaps due to a somewhat higher T-cell depletion.
rate in BM-RIC (58%) than in PBSC-RIC (50%) transplants. There may also have been an impact of the somewhat higher median age and later transplants in the PBSC group (both with RIC and with MAC) than in the BM group. Despite the relatively long follow-up, the higher rate of chronic GVHD following PBSC-RIC did not seem to translate into a lower relapse rate than that following BM-RIC. However, the number of BM-RIC transplants was small (n=52), as compared to the PBSC transplants (n=596), so it could be difficult to detect a significant difference.

Allogeneic transplantation in myeloma patients is still hampered by high transplant-related mortality, irrespective of the use of PBSC or BM. Although the use of RIC is associated with a lower NRM than that with MAC transplants, unfortunately this does not translate into better overall survival, irrespectively of whether PBSC or BM is used, due to the higher relapse rate following RIC.

Thus new strategies need to be explored for myeloma patients; for example, new targeted and immunomodulatory drugs (IMID) in the conditioning in RIC-like regimens, to improve cell killing, may be one approach. The relapse rate following MAC allogeneic transplantation in myeloma is lower than that after autologous transplantation. Very few myeloma patients treated with MAC allogeneic transplants relapse or progress between 5 and 7 years after transplantation. Whether this is also true for RIC transplants remains to be seen. The recently closed prospective EBMGT study comparing autologous and allogeneic RIC transplantation based on genetic randomization may give an answer (Bjerkstrand et al., unpublished data). Prospective studies using unrelated donors and RIC conditioning are also warranted and being planned (Niederwieser et al.)

Authors’ contributions
GG: conception and design of the study; drafting the article and its final approval; SI: analysis and interpretation of data; revising the article critically and its final approval; GB, BB, PC, CC, UH, GM, NK, AS, SOS, LVF, LV, TW, DN: acquisition of data; revising the article critically and its final approval; the Myeloma Subcommittee of the EBMGT.

Conflicts of Interest
The authors reported no potential conflicts of interest.

References