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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Funding: this study was supported by the European LeukemiaNet and by grants from the Swedish Cancer Fund and the Cancer Society in Stockholm

Manuscript received February 6, 2007.
Manuscript accepted August 6, 2007.

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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 trasplantation, bone marrow trasplantation, reduced intensity conditioning, myeloablative conditioning, multiple myeloma.

Haematologica 2007; 92:1513-1518. DOI: 10.3324/haematol.11353

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[1] is similar in agreement with some,[2-10] but in contrast to other studies in leukemia and other hematologic malignancies indicating better results with PBSC[11,12] or with BM.[13] Engraftment in myeloma was found to be faster with PBSC but this has not translated into less treatment-related mortality (non-relapse mortality=NRM) or into improved survival.[1] The incidence of acute graft-versus-host disease (GVHD) is similar, while chronic GVHD appears to be more frequent with PBSC.[1] These data corroborate observations in other hematologic disorders. However, these studies were performed in patients who have received high-dose myeloablative conditioning (MAC) regimens before transplantation. Since 1997, reduced-intensity conditioning (RIC) transplantation has been used in patients with myeloma, and from 2001 such transplants were more frequently reported to the EBMT registry than standard MAC transplants. Although recent investigations have shown a low treatment-related mortality with RIC[14,15] in multiple myeloma, registry studies within the EBMT have also shown that the relapse rate among patients given RIC is significantly higher than that among patients given MAC.[16] Since the increasing use of PBSC for transplantation paralleled the increased use of RIC, with some years delay, we have undertaken a retrospective registry study comparing the outcome of patients transplanted with PBSC or bone marrow (BM) following RIC or MAC.

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.

Table 1. Patient and transplant characteristics.

Variable available (%)	*Data Number*	*%*	*PBSC Number*	*%*	*BM value*	*p*
Age (years)	100					
0-45		339	29	238	49	<0.0001
>45		840	71	250	51	
Gender	100					
Male		748	63	288	59	0.09
Female		431	37	200	41	
Type of myeloma	91					
IgG		615	57	259	59	0.38
IgA		219	21	90	21	
Light chain		184	17	61	14	
Other		55	5	28	6	
Stage at diagnosis	71					
I		102	12	37	12	0.78
II		178	21	72	22	
III (IIIB, % of III)		584	67 (17)	211	66(19)	
Number of prior treatment regimens	49					
0-1		314	62	186	61	0.82
2-3		196	38	120	39	
Number of prior autotransplants	100					
0		693	59	413	84	<0.0001
1		401	34	62	13	
2 or more		85	7	13	3	
Response status at conditioning	90					
CR		143	13	75	17	0.01
PR		617	58	236	54	
No change		120	11	67	15	
Relapse/progression	100	187	18	60	14	
Year of transplant						
1994-95		14	1	126	26	<0.001
1996-97		97	8	123	25	
1998-99		228	19	120	25	
2000-01		394	33	74	15	
2002-03		446	38	45	9	
Time from diagnosis to transplant (months)	97					
0-12		482	42	282	59	<0.001
>12		667	58	193	41	
Conditioning	85					
RIC		596	60	52	12	<0001
MAC		401	40	369	88	
TBI in conditioning	97					
No		620	54	134	28	<0.0001
Yes		520	46	337	72	
T-cell depletion	88					
None		712	67	236	58	<0.0001
In vivo		9	1	5	1	
Ex vivo		129	12	126	31	
Other		214	20	43	10	
Female donor for male recipient	97					
No		828	72	359	75	0.26
Yes		316	28	119	25	
Total cell dose given×10^6/kg	62					
Low (≤2.0)		20	4	69	57	<0.0001
Intermediate (2.0-4.0)		113	22	33	27	
High (>4.0)		376	74	20	13	
CD34+ dose given x 10^6/kg	59					
Low (≤2.0)		50	12	155	57	<0.0001
Intermediate (2.0-4.0)	29	7	81	30		
High (>4.0)		339	81	34	13	

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 χ^2 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_2 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.

Table 2. Conditioning regimens.

Conditioning regimen	*Reduced intensity conditioning Number of patients*	*Per cent*
Fludarabine + TBI	105	16.2
Fludarabine + Melphalan	137	21.1
Fludarabine + Busulphan	113	17.4
Other	293	45.2
Total	648	100
Conditioning regimen	*Myeloablative conditioning Number of patients*	*Per cent*
Melphalan + TBI	177	23.0
Cyclophosphamide + TBI	216	28.1
Busulphan + cyclophosphamide	51	6.6
Other	326	42.3
Total	770	100

TBI: total body irradiation.

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 (32%). This was irrespective of the pretransplant response status. Thus the CR rate in patients who were

Table 3. Response rate.

Source of stem cells	Response rate following RIC Best response to transplantation CR Number of patients (%)	PR Number of patients (%)	No CR-PR/Progression Number of patients (%)	Total number of patients
PBSC	178 (33.5)	152 (28.6)	201 (37.9)	531
BM	8 (16.3)	17 (34.7)	24 (49.0)	49
Total	186 (32.1)	169 (29.1)	225 (38.8)	580

Source of stem cells	Response rate following MAC Best response to transplantation CR Number of patients (%)	PR Number of patients (%)	No CR-PR/Progression Number of patients (%)	Total number of patients
PBSC	139 (41.9)	63 (19.0)	130 (39.2)	332
BM	135 (42.5)	85 (26.7)	98 (30.8)	318
Total	274 (42.2)	148 (22.8)	228 (35.1)	650

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 38% 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

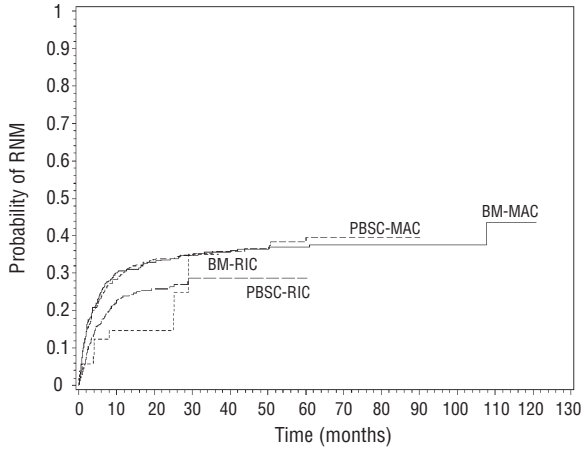

Figure 1. Non-relapse mortality (NRM) in PBSC and BM recipients following RIC and MAC. The overall NRM was lower after RIC than after MAC (p=0.0008). However there was no significant difference in NRM between PBSC and BM recipients within the RIC group (p=0.428) or the MAC group (p=0.970).

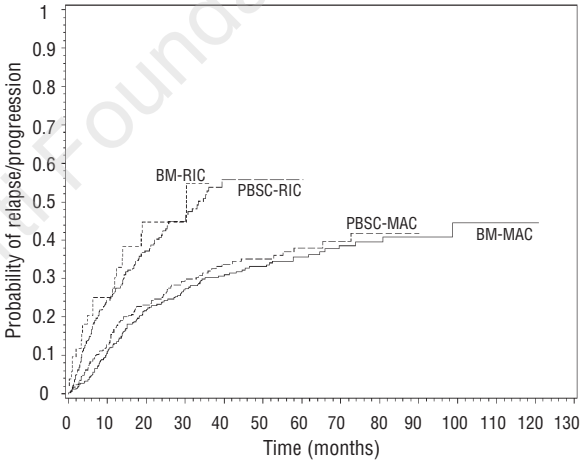

Figure 2. Relapse/progression rate in PBSC and BM recipients after RIC or MAC. The overall relapse/progression rate was significantly higher after RIC than after MAC (p<0.0001). However there was no significant difference in the relapse rate between PBSC and BM recipients within the RIC group recipients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

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, but there was no significant difference between the rates in PBSC and BM recipients within either the RIC or MAC group. These results were confirmed in the multivariate analysis, in which no significant differences were found in progression-free survival or relapse/progression hazard between the PBSC-RIC and BM-RIC groups (p=0.37 and p=0.55 respectively) or between the PBSC-MAC and BM-MAC groups (p=0.07 with HR=1.21 and p=0.08 with HR=1.30, respectively). A weak trend for a poorer progression-free survival and higher relapse rate following PBSC-MAC transplants did not translate into poorer survival with PBSC, as shown later.

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 counterbalanced 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.

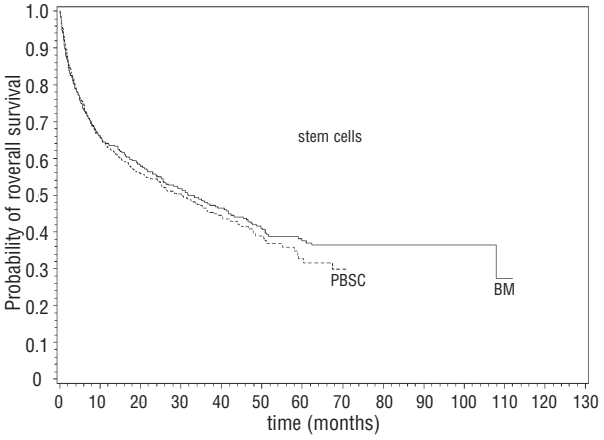

Figure 3. Overall survival of PBSC and BM recipients. There was no significant difference in overall survival between PBSC and BM (p= 0.505) irrespectively of whether they received RIC (p=0.331) or MAC (p=0.951).

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.[1] 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[14-16] 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.[1] 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.[1] This finding corroborates results in other hematologic disorders.[3,6-9,17] 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 (30%) 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.[16] 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 EBMT study comparing autologous and allogeneic RIC transplantation based on genetic randomization may give an answer (*Björkstrand 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, TdW, DN: acquisition of data; revising the article critically and its final approval; the Myeloma Subcommittee of the EBMT.

Conflicts of Interest

The authors reported no potential conflicts of interest.

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