Relapse risk after autologous transplantation in patients with newly diagnosed myeloma is not related with infused tumor cell load and the outcome is not improved by CD34+ cell selection: long term follow-up of an EBMT phase III randomized study

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Background and Objectives

This European Group for Blood and Marrow Transplantation (EBMT) multicentre randomized phase III study was designed to assess the safety and efficacy of CD34+ selection in newly diagnosed myeloma patients undergoing autologous transplantation.

Design and Methods

One hundred and eleven patients responsive to initial chemotherapy were randomized to receive CD34+ selected (arm A) or unselected PBPC (arm B) after conditioning with high-dose melphalan and TBI. ASO-PCR was used to assess purging efficacy and reinfused tumor load. Tumor load could be assessed in 59 patients.

Results

CD34+ selection gave a median tumor cell depletion of 2.2 logs (0.77–5.96). No tumor cells were detected in products infused in 17/26 (A) and 5/33 (B) patients. The five year overall survival (OS), event free survival (EFS) and relapse rate (RR) were 51%, 20% and 80% in arm A and 45%, 18% and 80% in arm B respectively with no significant difference between the two groups. Thirteen patients in arm A and 2 in arm B experienced episodes of serious early infection (p=0.02). There were 3 early transplant related deaths in A but none in B.

Interpretation and Conclusions

Despite significant tumor cell reduction, CD34+ selection does not reduce RR and increases the risk of severe post-transplant infections. There was also no difference in RR between patients in either arm who received grafts with detectable tumor cells and those receiving grafts with no detectable tumor cells, suggesting that reinfused tumor cells may not be the main cause of relapse after autologous transplant in myeloma.

Key words: myeloma, autologous transplantation, CD34+ selection.

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High dose therapy and autologous stem cell transplantation (ASCT) have been shown to improve complete response rate (CR), event free survival (EFS) and overall survival (OS) in patients with myeloma compared with conventional chemotherapy.[1-6] However, complete remission rates remain below 50% and the median duration of remission is only 2-3 years from the time of high-dose therapy.[1,7,8] It is unclear whether reinfused tumor cells contribute significantly to relapse. However, since myeloma cells do not express the CD34 antigen,[9,10,11] positive selection of CD34+ hematopoietic progenitor cells[12,13,14] has been used as a means of myeloma cell "purging" in ASCT.[11,15,16]

In 1995, we initiated a European Group for Blood and Marrow Transplantation (EBMT) centre phase III randomized study to assess the safety and efficacy of CD34+ selection compared to unselected PBPC in patients with myeloma undergoing autologous transplantation. A similar study was initiated at around the same time in the United States, the preliminary results of which suggested that at a median follow-up of 12 months there was no clinical benefit from CD34+ selection.[12] We now report the long-term results of our study at a median follow up of over 5 years, which confirm the observations of the US study.[12,17] In addition, this study shows that there is no apparent correlation between relapse risk and reinfused tumor cell load.

Design and Methods

Study design

The study was open to patients with newly diagnosed myeloma responsive to 3 cycles of VAD (vincristine, doxorubicin and dexamethasone). PBPC were harvested following mobilization with cyclophosphamide and G-CSF (Filgrastim, Amgen Europe). Patients were randomized prior to mobilization to receive CD34+ selected (Arm A) or unselected cells (Arm B) transplants. Patients received high dose melphalan and total body irradiation (TBI) followed by either CD34+ selected or unselected cells. No maintenance therapy was given post-transplant. Patients were followed up at D100, D180, 9 M, 12 M, and every year until death. Quantitative ASO-PCR was used to measure tumor cell contamination in the harvested products and after selection where applicable. The primary aim was to demonstrate that neutrophil engraftment was not adversely affected by CD34+ selection. Assuming a mean time to engraftment of 10 days, a standard error of 3 days, and a clinical equivalence of two days, the minimum sample size per treatment groups A and B was estimated to be 48 evaluable patients. Randomization was centralized and stratified by centres using fixed blocks of 4 patients. The trial was approved by local ethical committees and all patients gave written informed consent.

Patient characteristics and eligibility

Between May 1995 and November 1999, 127 consecutive patients with newly diagnosed Durie-Salmon18 stage II and III multiple myeloma from 17 EBMT centres were entered. Eligibility criteria were as follows: newly diagnosed stage II or III multiple myeloma; age between 18-65 years; responsive to 3 courses of VAD first line chemotherapy completed within 4 weeks before registration; performance status WHO/ECOG ≤ 2; WBC > 3.0×10^9/L and platelet count > 100×10^9/L; negative pregnancy test if females of child-bearing potential; no other concurrent malignancy; diagnostic bone marrow samples available for PCR analysis. Renal insufficiency was not a cause for exclusion. Sixteen of the 127 randomized patients (8 in Arm A and 8 in Arm B) were subsequently excluded for the following reasons. Nine patients were incorrectly randomized: 2 were unresponsive to the initial VAD therapy, one had a second malignancy at the time of randomization, 3 had ongoing infections at the time of randomization and 3 could not be treated by TBI (either because of prior radiotherapy or TBI refusal). One patient was responsive at randomization but relapsed prior to conditioning, 4 patients withdrew consent and were treated outside the protocol, and no follow-up data were returned for 2 patients.

The present analysis concerns all other 111 randomized patients, who met the entry criteria, received the scheduled graft and continued to be treated within the protocol. Fifty-six received CD34+ selected PBPC (Arm A) and 55 unselected PBPC (Arm B). Disease status and patient characteristics at diagnosis are shown in Table 1. Baseline characteristics were not significantly different between the two arms.

Initial therapy and randomization

All patients received 3 cycles of VAD (vincristine + doxorubicin + dexamethasone) as first line treatment. Courses were given on a 28-day cycle with three pulses of dexamethasone on days 1-4, 9-12, and 17-20 of each course. Patients who responded to VAD with fewer than 30% plasma cells in the marrow smears after the third course were eligible for the study. Randomization was performed at the time of registration prior to PBPC mobilization.

Mobilization and processing of PBPC

All patients received high dose cyclophosphamide 2 g/m^2/day for 2 consecutive days (total dose 4 g/m^2) followed by G-CSF (Filgrastim, AMGEN Europe) 10 μg/kg/day subcutaneously from day 3 until the last day of leucapheresis. A minimum of 2 and a maximum of 4 leucaphereses were performed as soon as possible after ANC rose above 1×10^9/L. The aim was to collect a minimum of 6×10^6 CD34+ cells/kg in Arm A for the cell processing and a minimum of 2×10^6 CD34+ cells/kg for patients in Arm B. For patients in arm A, leucapheresis products collected in the first 2 days were pooled for CD34+ selection. The

Table 1. Patient characteristics at diagnosis.

	CD34+ Selected arm A n=56	*Unselected arm B n=55*	*p value*
ß-2 Microglobulin (mg/L)			0.69
Non-missing values	44	44	
≤2.5	21	25	
> 2.5	23	19	
C-Reactive protein (mg/dL)			0.64
Non-missing values	27	28	
Median	1.4	2.9	
Range	0.2–36	0.2–70	
Albumine (g/L)			0.51
Non-missing values	41	42	
Median	37	39	
Range	19-65	16 - 55	
Number of VAD prior to mobilization			0.62
n=3	53	53	
n=4	3	1	
NA	0	1	
Days from randomization to transplant			0.51
Median	47	50	
Range	29 – 117	27 – 83	

Table 2. PBPC processing.

	Arm A (N=56) CD34+ selected		*Arm B (N=55) unselected*		*p value*
	n	*Mean (Min-Max)*	*n*	*Mean (Min-Max)*	
Leukapheresis	55	1.9 (1 – 3)	54	1.5 (1 – 3)	0.006
	N	Median (Min-Max)	N	Median (Min-Max)	
Apheresis viability	48	99 (79 – 100)	40	99 [89 – 100]	0.19
TNC in start (×10⁶/kg)	47	543 (100 – 1488)	NA	NA	
CD34+ at start (×10⁶/kg)	44	11.4 (4.5 – 69)	NA	NA	
Reinfusion viability	49	87.6 (60 – 100)	43	86.0 (21 – 100)	0.05
TNC reinfused (×10⁶/kg)	52	7.4 (2.2 – 593)	50	302 (2.6 – 99)	<10⁻⁴
CD34+ reinfused (×10⁶/kg)	54	5.8 (1.4 – 50)	50	7.4 (1.9 – 99)	0.06
Purity CD34+	48	87% (18%–100%)	49	3% (0.2%–27%)	<10⁻⁴
Yield CD34+	36	50% (10%–744%)			

Data were evaluated for all 111 eligible patients. CD34+ content and viability were assessed at each step of the processing procedure. CD34+ selected and unselected grafts were both cryopreserved. There was a significant difference in the number of leukapheresis, which was increased in the CD34+ arm. Furthermore, CD34+ cell content was lower (p=0.06) in the CD34+ selected patient cohort.

CD34+ selection procedure was performed using the Ceprate-R Stem Cell concentrator device as previously described in the manufacturer's protocol. Briefly, apheresis products were incubated with a biotinylated 12.8 monoclonal antibody. The suspension was then run through the avidin coated beads column of the Ceprate-R stem cell concentrator. Bound positive CD34+ stem cells were then removed from the column by gentle agitation and collected. CD34+ cell collections were then volume concentrated and cryopreserved in 10% DMSO. The median CD34+ and median total nucleated cells before selection were respectively 11.4×10⁶/kg (range 4.5 – 69) and 543×10⁶/kg (range 100–1488). CD34+ selection resulted in a median purity of CD34 cells of 87% and a yield of 50% (Table 2). Two aliquots of at least 1 million cells, one before and one after processing, were frozen to perform the tumor cell contamination assays. PBPC from the subsequent leucaphereses were cryopreserved as a back-up.

For patients in arm B, a minimum of 2×10⁶ CD34+ cells/kg was collected and cryopreserved. An aliquot of at least 1 million cells was also stored for the tumor cell contamination assay.

High-dose therapy and transplantation

At a maximum of 4 to 6 weeks after cyclophosphamide, all patients received high dose melphalan 140 mg/m² and TBI followed by transplantation with either CD34+ autologous PBPC (Arm A) or unselected PBPC (Arm B). TBI was performed according to each institutional irradiation policy, either as a single dose of 8 or 10 Gy usually on day -4 or as a fractionated TBI of 12 Gy (usually 2 Gy × 6 on days -6 to -4). Dose delivery and shielding procedures were performed according to the center policy and were kept the same for all patients treated at the same center. TBI and high dose melphalan schedules were given according to the center policy, so that melphalan could be given before or after the TBI.

In both arms A and B, a minimum of 2×10⁶ CD34+ cells/kg PBPC were infused 48 hours following high-dose melphalan. The median number of CD34+ cells reinfused was 5.8×10⁶ CD34+ cells/kg (range 1.4–50) in arm A and 7.4×10⁶ CD34+/kg (range 1.8–99) in arm B (Table 2). G-CSF (Filgrastim, AMGEN Europe) was given at a dose of 5 µg/kg/day beginning at day 1 until ANC reached 1×10⁹/L for 3 consecutive days. Supportive care was given according to center policy. Patients were hospitalized and nursed in protective isolation. All patients received prophylactic and/or therapeutic antimicrobial therapy according to center policy. All blood products were irradiated after the administration of cyclophosphamide except the graft itself. Platelet transfusions and RBC transfusions were given when clinically indicated to maintain a platelet count >x10⁹/L and hemoglobin concentration >8 g/dL.

After the transplant, patients were followed-up at D100, D180, 9 M, 12 M, and every year until death. Response rate assessment was based on the EBMT criteria:[19] complete remission was defined as no paraprotein measurable

Table 3. Tumor cell purging.

N. of tumor cells	*CD34⁺ selected arm A*		*Unselected arm B*	
	n	*#with detectable tumor cells*	*N*	*#with detectable tumor cells*
PBPC product	27	20	33	28
CD34⁺ selected product	26	9		
	N	Median (range)	N	Median (range)
PBPC product ($\times 10^6$)	17[a]	5.91 (0.041–440)	22[b]	2.1 (0.045–166)
CD34⁺ selected product ($\times 10^6$)	9	0.026 (0.007–0.21)		
Log depletion of tumor cells	23	2.20 (0.77–5.96)		

Graft contamination by tumor cells in the PBPC product (two arms) and in the CD34+ selected product (arm A), and depletion of tumor cells. Median and range are given only in patients with detectable tumor cells. There was no significant difference in the number of tumoral cells in PBPC products is not significantly different between arm A and arm B (p=0.39). In arm A, depletion of tumor cells is estimated assuming that the percent of tumor cells is equal to 0.0002% in patients with undetectable tumor cells. (A) the number of tumor cells cannot be estimated in three patients with an unknown number of nucleated cells (and a known percentage of tumor cells) in arm A. CD34⁺ selected products are significantly less contaminated ($p < 10^{-4}$) than unselected products. (B) the number of tumor cells cannot be estimated in six patients with an unknown number of nucleated cells (and a known percentage of tumor cells) in arm B. N: number of patients with available data.

Table 4. Primary and secondary end-points.

	CD34⁺ selected arm A (n=56)		*Unselected arm B (n=55)*		
	n	*Median (range)*	*n*	*Median (range)*	*p Value*
Days to neutrophil engraftment	51	10 (8–14)	52	10 (8–21)	0.53
Days to platelets platelet engraftment	53	11 (5–26)	53	9 (5–42)	0.005
Platelet transfusion (events/patient)	53	3 (0–11)	49	2 (1–25)	0.006
RBC transfusions (units/patient)	53	2 (0–15)	49	2 (0–76)	0.33
Days of initial hospitalization	52	25 (10–87)	48	23 (15–52)	0.42
Number of Patients rehospitalized	52	18	48	6	0.01
Days of rehospitalization	18	8.5 (1–59)	6	9 (5–29)	0.79
Number of patients with at least one SAE	49	13	49	3	0.01
Days of G-CSF post-BMT	51	10 (2–19)	45	10 (1–27)	0.76

Primary endpoint assessment showed no difference in neutrophil engraftment. Platelet engraftment showed a significant difference (p=0.005) between the two arms with a delayed engraftment in Arm A. There was an increased number of platelet transfusion events in Arm A. There was no difference in initial hospitalization but a significant difference in rehospitalization (p=0.01) in disfavor of the CD34⁺ arm. There was a significantly higher number (p= 0.01) of severe infections in the CD34⁺ selected cohort leading to an increased number of SAE. SAE: severe adverse events; n: number of patients with available data.

in blood and urine on electrophoresis and immunofixation on at least 2 occasions 6 weeks apart, and fewer than 5% plasma cells on bone marrow (BM) aspirate.

Tumor cell contamination assay

For the PCR tumor cell contamination assay, the Ig heavy chain sequence of the myeloma clone was used as a tumor marker. This Ig sequence was identified from the diagnostic bone marrow sample using previously described methods.[20,21]

Quantitative PCR assay

Nucleic acid extraction, sequencing of the myeloma Ig gene, the design of ASO primers and the quantitative PCR assay were performed as previously described.[21] The lower limit of detection of the assay was 0.0002% tumor cells in the sample. The number of clonal cells was expressed as a percentage of total MNC in the sample.

Statistical analysis

Comparisons of quantitative variables between the two treatment arms were performed using Wilcoxon's rank order test. Fisher's exact tests were used to compare the repartition of patients among classes. Survival curves were compared by Log-rank test. All the statistical tests were two-sided. *p*-values less than 0.05 are significant. Significance of the tests was not adjusted to account for multiple testing.[22,23,24]

Results

Tumor cell contamination and purging efficacy

Sequencing of the clonal IgH rearrangement was successful in 71 out of the 111 patients. Reasons for failure to sequence the rearrangement included light chain only myeloma (8 patients), inadequate sampling,[17] and technical failure due to insufficient RNA quality or polyclonality.[15] Allele-specific oligonucleotides were designed and tested. In 59 patients the ASOs performed well with regard to specificity and sensitivity, allowing assessment of tumor cell contamination in these 59 patients (26 in arm A and 33 in arm B). Tumor cell contamination was assessed both before and after processing in 23 patients in arm A (Table 3), for 4 only before and 3 only after CD34⁺ selection. Before selection, there were no detectable tumor cells (i.e. <0.0002%) for 7 patients, and the total number of tumor cells ranged from 0.04–440$\times 10^6$ (median 5.9$\times 10^6$) in the 20 remaining patients. After CD34⁺ selection, tumor cells were below the detection limit of the assay in 17 patients and ranged from 7$\times 10^3$–211$\times 10^3$ with a median of 26x10^3 in the remaining 9 patients. Tumor load reduction was estimated in 23 patients who had their tumor cell load evaluated before and after CD34⁺ selection. The CD34⁺ selection procedure resulted in a log tumor load reduction ranging from 0.77 to 5.96 (median=2.20). Thirty-three PBPC harvests were tested in arm B. There were no detectable tumor cells in 5 of the

Table 5. Early serious infections after CD34+ selected (arm A) and unselected (arm B) autologous transplantation.

Arm	Patient	Onset D/BMT	type	Culture	Serious	Outcome
A	101	52	Viral	*Herpes*	Yes	Favorable
A	104	17	Protozoal	*Lamblia*	Yes	Favorable
A	111	53	Viral	RSV	Yes	Favorable
A	503	18	Viral	Parainfluenza type 1	Yes	Lethal D25
A	505	19	Clinical	N/D	Yes	Favorable
A	1201	34	Viral	CMV	Yes	Favorable
A	1201	90	Viral	CMV	Yes	Lethal D98
A	1405	53	Viral	*Herpes Zoster*	Yes	Favorable
A	1501	0	Bacterial	*Micrococcus* myocarditis	Yes	Lethal D50
A	1501	9	Bacterial	*Xanthomonas*	Yes	Favorable
A	1506	42	Viral	*Herpes Zoster*	Yes	Favorable
A	1603	19	Viral	Unknown	Yes	Favorable
A	1801	11	Bacterial	*Pneumococcus*	Yes	Favorable
A	5016	24	Fungal	*Aspergillus*	Yes	Favorable
A	5016	24	Viral	CMV	Yes	Favorable
A	5016	60	Viral	EBV	Yes	Favorable
B	502	74	Viral	N/A	Yes	Favorable
B	1302	95	Bacterial	*Pneumocystis carinii*	Yes	Favorable
B	1302	95	Bacterial	*Staphylococcus aureus*	Yes	Favorable
B	1302	95	Bacterial	*Campetalitinum xerosis*	Yes	Favorable
B	1302	95	Fungal	*Candida albicans*	Yes	Favorable
B	1504	88	Bacterial	*Klebsiella pneumoniae*	Yes	Favorable

Description of the 22 early serious infections. Twelve patients experienced 16 episodes of severe infection in arm A vs. 3 patients experiencing 6 episodes in arm B.

PBPC products tested, and in the 28 remaining patients the total number of tumor cells ranged from 45 103 to 166x10^6 (median 21×10^6/L). Of the 59 patients (26 arm A and 33 arm B) whose reinfused tumor load was measured, 22 (17 arm A and 5 arm B) received PBPC with undetectable tumor cells.

Engraftment data and transfusion requirement

The median time to neutrophil engraftment (ANC >0.5×10^9/L) was 10 days in both arms (Table 4). The median duration of G-CSF treatment was also 10 days in both arms. The median time to platelet engraftment (platelets >20×10^9/L for two consecutive days without platelet transfusion) was 11 days (range 5–26) in Arm A and 9 days (range 5–42) in Arm B (p=0.005). One patient in arm A died before platelet engraftment. The mean number of platelet transfusions per patient was 3.6 (range 0–11) in arm A and 3.0 (range 1–28) in Arm B (p=0.006). Red cell transfusion requirement was similar in both groups).

Clinical outcome

The initial median duration of hospitalization was 25 days in Arm A (range 10–87) and 23 days in Arm B (range 15–52). Eighteen patients in Arm A and 6 patients in Arm B required rehospitalization (p=0.01). During the early post-transplant period (before day 100), 12 out of 49 evaluable patients in arm A had episodes of serious infection versus only 3 out of 49 evaluable patients in arm B (Table 5). Half of the serious infections were viral. Infections were fatal in three patients in arm A. These were due to parainfluenza (day 25), CMV (day 98) and myocarditis (day 50), resulting in an early transplant related mortality (i.e. deaths not due to progressive disease/relapse occurring before day 100) of 3% in arm A. There was one death due to progression in the first 100 days. This was a patient in arm B who died on day 79 from a neuromeningial relapse. There was no difference in the best response achieved in the 1st year post transplant: 27% of the patients were classified in CR accord-

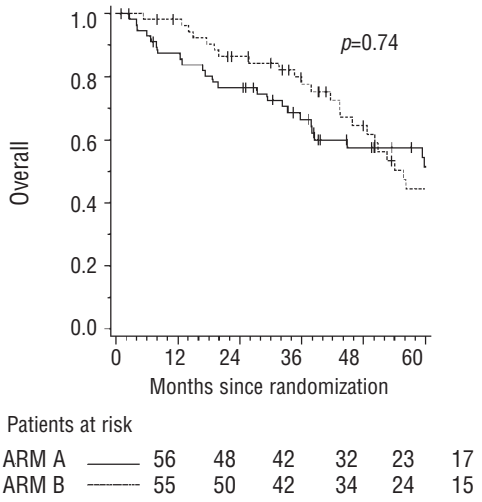

Figure 1. Overall survival (OS). Overall survival at 5 years was 51% in Arm A and 45% in Arm B. The log rank test comparing the two curves was not significant (p=0.74).

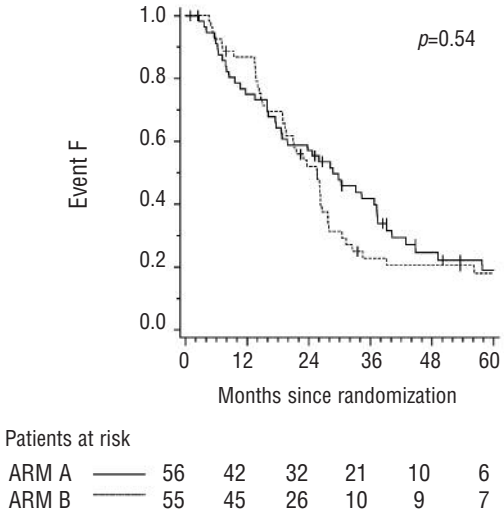

Figure 2. Event-free survival. Event-free survival at 5 years was 20% in Arm A and 18% in Arm B. The log rank test comparing the two curves was not significant (p=0.54).

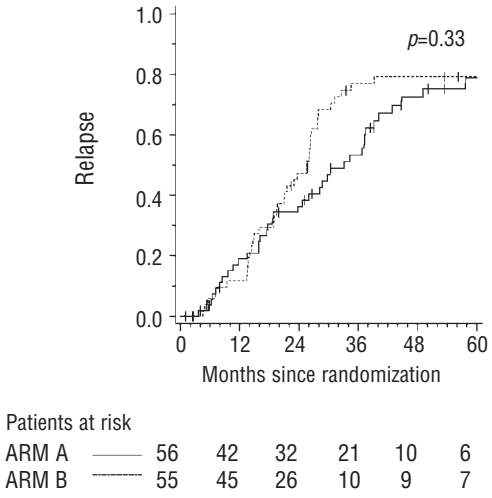

Figure 3. Relapse risk. Relapse risk at 5 years was 80% for Arm A and Arm B. The log rank test comparing the two curves was not significant (p=0.33).

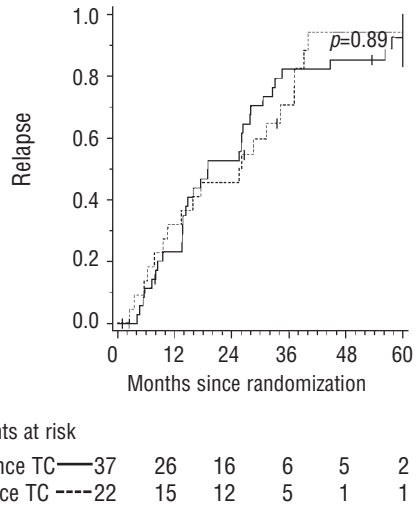

Figure 4. There is no difference in relapse risk according to tumor cell content at 5 years for Arm A and Arm B. The log rank test comparing the two curves was not significant (p=0.89).

ing to EBMT/IBMT/ABMTR criteria[30] at least once during the 1st year in arm A versus 20% in arm B (p=0.50). During follow-up, 78 patients relapsed or progressed 54 of whom have died. Eight patients died without evidence of relapse/progression, 6 in arm A and 2 in arm B. In arm A, 3 patients died of infection before day 100, as already noted, one patient transplanted with renal impairment died of multi-organ failure at day 117, one of hepatitis C at day 178, and one of leukoencephalitis at day 556. Two patients in arm B died without relapse, one from septic shock at day 129 and the other from an astrocytoma after 4.5 years. At the time of analysis, the median follow-up time (FU) was 65 months. There was no significant difference between arm A and arm B in overall survival (p=0.74), event free survival (p=0.54) or relapse risk (p=0.33) (Figures 1-3). Furthermore, there was no difference in relapse risk between patients with detectable tumor cell contamination and those receiving cells without detectable contamination (p=0.89) (Figure 4).

Discussion

A variety of approaches have been developed in an attempt to improve the outcome of high-dose therapy in multiple myeloma patients, including tandem high-dose therapy,[25,26] reduced intensity allogeneic transplantation[27,28] purging strategies based either on negative or positive selection,[29-39] and new approaches to conditioning. Although the present study used a combination of melphalan and TBI for conditioning, it has since been established that high dose melphalan alone is less toxic and at least as effective as regimens including total body irradiation.[40,41] High dose melphalan alone (200 mg/m^2) is now the established conditioning regimen for autologous transplant in myeloma.

Vescio *et al.*[17] showed in their randomized study of 131 analyzed patients that CD34 positive selection using the Ceprate System significantly reduced contaminating tumor cells from the autograft without impairing engraftment. However, despite a median tumor cell depletion of 3.3 log in the selected graft, no difference in event free or overall survival was observed after a median follow-up period of 12 months. A later analysis by the same group[32] on a cohort of 190 patients who received a CD34$^+$ graft confirmed no improvement in EFS or OS at a median follow-up of 37 months. A similar approach using the Isolex 300 I system for selection of CD34$^+$ cells also failed to demonstrate any clinical benefit of CD34$^+$ selection and there was an increased incidence of serious infections in the recipients of CD34$^+$ selected cells.[13]

Although these previous studies have not suggested that CD34$^+$ selection confers a benefit in terms of overall or event free survival, follow-up in these reports was only 12-37 months, and the clinical benefit of a new transplant procedure may only become apparent after a longer follow-up. The IFM group (Inter Groupe Francophone du Myélome) recently showed a clinical benefit from tandem autologous PBPC transplantation in myeloma, but the improvement in EFS and OS with double transplant was not seen until six years from the start of the study.[6] In the present study, we followed patients for a median of 65 months prior to the final analysis but even after this length of follow-up, we observed no significant difference in terms of EFS and OS. Not only there was no observed benefit from CD34 positive selection in this study, but there was also a higher incidence of viral infections in the CD34$^+$ selected arm. This may reflect an impaired T cell

response against microorganisms.[42,43] It is consistent with previous reports of a higher rate of infectious complications in CD34+ selected autologous transplant patients.[13] The reasons for the failure of tumor cell reduction to translate into clinical benefit could be either that the purging efficacy is not great enough to reduce relapse risk, i.e. that small numbers of myeloma cells persisting below the limit of detection of RT-PCR are able to cause relapse, and /or alternatively that reinfused myeloma cells are not a significant cause of relapse. While relapse risk after transplant for myeloma is significantly higher after autografts than after allografts,[27,45] this could be explained at least partly by the absence of graft-versus myeloma effect, and does not necessarily imply relapse from reinfused cells. A new finding in the present study was that relapse risk was independent of whether or not there were detectable tumor cells in the reinfused product. This would suggest that reinfused myeloma cells do not contribute significantly to relapse, and that improved disease eradication within the patient may be a more important goal than tumor purging of the grafts. This is borne out by the high risk of relapse seen after allogeneic BMT for myeloma, which approaches 50%.[46]

Authors' Contributions

JHB: conception and design, provision of study material and patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; YB: conception and design, provision of study material and patients, collection and assembly of data, data analysis and interpretation, final approval of manuscript; SK: conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; MB: conception and design, collection and assembly of data, data analysis and interpretation, final approval of manuscript; HG: conception and design, provision of study material and patients, final approval of manuscript; GD: conception and design, provision of study material and patients, final approval of manuscript; GS: conception and design, provision of study material and patients, final approval of manuscript; WF: conception and design, provision of study material and patients, final approval of manuscript; JA: conception and design, provision of study material and patients, final approval of manuscript; DS: conception and design, provision of study material and patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; BB: provision of study material and patients, final approval of manuscript; DN: conception and design, provision of study material and patients, final approval of manuscript; GG: conception and design, provision of study material and patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; JLP: conception and design, provision of study material and patients, final approval of manuscript; HG: conception and design, provision of study material and patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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