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Optimizing peripheral blood progenitor cell autologous transplantation in multiple myeloma

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ABSTRACT

As in other malignancies, peripheral blood progenitor cells (PBPC) have almost completely replaced bone marrow as the source of stem cells for autologous transplantation in multiple myeloma. PBPC collection could be optimized either by reducing contamination by the malignant clone or by increasing hematopoietic quality of the graft. Currently, the most promising technique for purifying the harvest is CD34 cell selection. Several pilot studies have shown the feasibility of this method in MM. However controlled studies are necessary to assess the clinical impact of $CD34^+$ cell selection. In the IFM 94 study, $CD34^+$ selection was optional. There was no significant difference between 50 patients receiving a $CD34^+$ selected graft and 133 patients receiving non-selected PBPC, as regards duration of neutropenia, duration of thrombocytopenia, response rate, EFS or survival. Hematopoietic recovery after transplantation is related to the number of $CD34^+$ cells infused. The optimal regimen for mobilizing the requested $CD34^+$ yield is not yet known. We have completed a randomized study comparing the combination of SCF plus G-CSF and G-CSF alone after priming with cyclophosphamide $4g/m^2$. The median number of leukaphereses to reach the target yield of 53106 $CD34^+$ cells/kg was 1 in the SCF group (N=55) versus 2 in the G-CSF group (N=47) (p=0.008). The median number of $CD34^+$ cells collected in the first leukapheresis was 11.6×10^6 in the SCF group versus 43106 in the G-CSF group (p=0.003). These results are in line with those observed in other trials testing the combination of SCF and G-CSF to improve PBPC collection.
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In the absence of any significant improvement of conventional chemotherapy (CC) in multiple myeloma (MM), high dose therapy (HDT) with autologous stem cell transplantation (ASCT) has been increasingly used in the past 10 years in this disease. As an example, in 1996, according to the annual survey of blood and marrow transplantation in Europe, MM was the third indication for ASCT after non-Hodgkin's lymphoma and breast cancer.[1] This tendency has been amplified in the past few years by the results of the multicenter randomized study published by the *Intergroupe Français du Myelome* in 1996. Indeed this study showed that for newly diagnosed patients up to the age of 65, autologous bone marrow transplantation gave better results than CC in terms of remission rate, event-free survival and overall survival.[2]

As in other malignancies, peripheral blood progenitor cells (PBPC) have almost completely replaced bone marrow as the source of stem cells in ASCT for MM. Out of 1744 ASCT performed in Europe in 1996, 94.5% used PBPC.[1] The main reasons for this choice are easier accessibility and availability, faster hematopoietic recovery and possibly lower tumor contamination. However, optimizing PBPC collection remains an important issue. In this paper, we will focus on two aspects: contamination by the malignant clone and hematopoietic quality of the graft.

Contamination of the graft

One of the explanations for the rapid shift from bone marrow to PBPC in support of HDT in MM was the hope that the graft would be less contaminated by myeloma plasma cells. However, the frequency of these contaminating cells depends on the sensitivity of the detection method employed.

Initial studies using anti-idiotypic antibodies and Southern blot analysis of immunoglobulin gene rearrangements produced conflicting results. While several investigators showed evidence of circulating malignant precursors,[3-6] others failed to detect immunoglobulin gene rearrangements in peripheral blood lymphocytes, in the absence of circulating plasma cells.[7,8]

More recent data using polymerase chain reaction (PCR) based methods confirmed that cells belonging to the malignant clone were present in a majority of patients with active disease.[9,10] While with Southern blot techniques,[6] no contamination was found in remission, PCR methods were sensitive enough to detect malignant cells in this situation, although in reduced numbers.[9]

Sensitive immunofluorescence studies[11] or PCR

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based techniques have demonstrated that PBPC harvests are frequently contaminated with malignant cells. With the immunoglobulin heavy chain gene fingerprinting method, myeloma cells contamination in found is 44-70% of PBPC samples collected after high-dose chemotherapy.[12-14] With allele-specific oligonucleotide PCR, tumor cells are found in virtually all PBPC harvests.[15,16]

Since PBPC harvests may contain malignant plasma cells, additional purging could be requested. The most promising technique for purifying the harvest is the selection of $CD34^+$ cells. The CD 34 antigen is present on 1-5% of adult bone marrow cells. It identifies a subpopulation of primitive hematopoietic progenitor cells that are capable of restoring hematopoiesis after myeloablative therapy in primates[17] as well as in humans.[18,19]

The clinical relevance of this antigen is clearly demonstrated in the setting of ASCT by the correlation between the number of $CD34^+$ cells infused and time to hematopoietic recovery after HDT.[20,22] Before using $CD34^+$ selected cells in autotransplantation for MM, it was important to demonstrate that this antigen which is present on early-B lymphocyte precursor cells was not present on malignant plasma cells. Vescio *et al.*, using PCR with patient-specific oligonucleotide primers, found no myeloma contamination in highly purified $CD34^+$ cells obtained after passage of bone marrow cells through an immunoadsorption column and fluorescence activated cell sorting.[23] However, Szczepek *et al.* found that in 9 of 11 myeloma patients, peripheral blood mononuclear cells contained $CD34^+$ $CD19^+$ B cells expressing patient-specific IgH VDJ gene rearrangement.[24] This could mean than CD 34 antigen is absent on bone marrow plasma cells but could be present on blood B-cells belonging to the myeloma clone.

In clinical practice, selection of $CD34^+$ cells by immunoabsorption has been evaluated by several investigators in myeloma patients.[25-27] The median purity of the enriched $CD34^+$ cell population was approximately 90% while the median $CD34^+$ yield was only 30-45%. These studies showed the feasibility of autologous transplants with $CD34^+$ selected PBPC in MM. Schiller *et al.* recently reported updated results on 55 patients conditioned by a combination of busulfan and cyclophosphamide.[28] Except in patients receiving less than 2×10^6 $CD34^+$ cells/kg, hematopoietic recovery was prompt. However, response rate, progression-free survival (PFS) and OS are only indicative in the absence of a control arm. Controlled studies were necessary to appreciate the clinical impact of this cumbersome and expensive procedure.

In the IFM 94 protocol, $CD34^+$ selection of the PBPC graft was optional. The August 1998 analysis of this protocol failed to show a significant difference in response rate, EFS or survival, between patients who received a selected (n=50) or a non-selected graft (n=133) (Table 1). However the duration of the neutropenia and thrombocytopenia after transplantation were identical. Although not randomized, this study suggests that, being cheaper and easier to process, non-selected PBPC could be preferred to $CD34^+$ selected PBPC.

Table 1. IFM 94, Results of CD 34 selection (August 1998 Analysis)

	PBSC	*CD 34+PBSC*	*p*
N	133	50	
Days with neutropenia < 500/mm^3	9.8	10.2	NS
Days with platelets < 50,000/mm^3	12.7	12.5	NS
2-year EFS (%)	62	58	NS
2-year OS (%)	83	79	NS

Randomized studies comparing $CD34^+$ selected and unselected PBPC are underway in the US and in Europe. While waiting the final results of these studies there is currently no evidence of the superiority of $CD34^+$ selected PBPC as compared to unmanipulated PBPC.

Positive selection of $CD34^+$ cells results in a 2.5 to 4.5 log-depletion of plasma cells.[25, 26] However sensitive PCR techniques using patient-specific oligonucleotide primers show the persistence of myeloma cells in the $CD34^+$ cell fractions while highly purified $CD34^+$ in Lin– thy^+ stem cells do no apparently contain clonal myeloma cells.[15] Thus, an additional purging step might be necessary to obtain tumor-free grafts. However, in the first study testing this method, the issue of hematopoietic and immunologic recovery was raised.[29]

Optimizing the hematopoietic quality of the graft

Currently PBPC are collected either after priming by chemotherapy (usually high-dose cyclophosphamide) plus G-CSF or GM-CSF, or after G-CSF alone. In a series of 225 patients treated for newly diagnosed or refractory MM, Tricot *et al.* retrospectively analyzed the variables affecting the PBPC mobilization and the speed of engraftment.[21] They found a highly significant correlation between the number of $CD34^+$ cells infused and prompt recovery of both granulocytes and platelets. However, prior exposure to chemotherapy, specially alkylating agents, significantly delayed post-transplant hematopoietic recovery. The threshold dose of $CD34^+$ cells necessary for prompt engraftment was $\geq 2\times10^6$/kg for patients with $\leq$ 24 months of chemotherapy, whereas more than 5×10^6/kg $CD34^+$ cells were required to obtain rapid

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recovery in patients with longer exposure.

The optimal regimen for mobilizing the requested CD34+ yield is not yet known. High-dose cyclophosphamide (up to 7 g/m^2) is currently extensively used for PBPC mobilization. As demonstrated by Gianni *et al.,* as early as 1989,[30] and confirmed by others,[31,32] the addition of hematopoietic growth factors (GM-CSF or G-CSF) increases the PBPC yield. There is apparently no difference in CD34+ yield between GM-CSF and G-CSF.[33] Marit *et al.* recently confirmed that the administration of GM-CSF or G-CSF after high-dose cyclophosphamide was the most important pronostic factor for an adequate collection.[34]

The optimal dose of cyclophosphamide for priming PBPC in MM has yet to be determined. There is an apparent dose-effect relationship. In comparative studies, higher doses of cyclophosphamide (7 g/m^2) are more efficient and increase the number of PBPC harvested, as compared to lower dosages (4 g/m^2 or less).[35,36] Moreover higher doses could reduce both the graft contamination by malignant plasma cells[36] and the tumor cell mass.[37] However, the administration of cyclophosphamide at a dosage of 7 g/m^2 is also associated with increased toxicity. Significant morbidity as well as several toxic deaths have been recorded with this dosage,[30,34-36] mostly in pretreated patients. Although the number of CD34+ cells collected appears to be higher after priming with high-dose cyclophosphamide followed by GM-CSF or G-CSF as compared to G-CSF alone, collection with G-CSF alone in steady state should also be considered, at least in newly diagnosed patients. The CD34+ cell yield achieved with G-CSF alone is greater than 2.5×10^6/kg and allows a safe and rapid hematopoietic reconstitution in most cases.[27] The main advantages of collecting PBPC after priming with G-CSF alone are to reduce the risks and the costs of the procedure and to avoid hospitalization.[38]

Combinations of hematopoietic growth factors could further enhance PBPC collection. The combination of SCF and G-CSF appears to be promising. SCF is a glycoprotein growth factor that acts on hematopoietic blood cell progenitors. While SCF alone exerts little colony-stimulating activity on normal human bone marrow cells *in vitro*, the combination of recombinant SCF and other recombinant hematopoietic cytokines results in a synergistic increase in the numbers of colonies. Addition of SCF to recombinant G-CSF (filgrastim) synergistically increases PBPC mobilization, compared to filgrastim alone.[39-42] Several clinical trials have reported the ability of the combination of SCF with filgrastim to mobilize PBPC in patients with lymphoma, breast and ovarian cancers.[40,42,43] Combination of SCF with filgrastim has been observed to improve CD34+ cell mobilization in heavily pretreated lymphoma or myeloma patients, known to be at risk of poor mobilization.[41,44]

We report here the results of a large randomized controlled trial evaluating the addition of SCF to filgrastim for PBPC mobilization in the chemotherapy-based mobilization setting. The study was conducted in patients with MM, most of them newly diagnosed. The primary objective was to determine whether addition of SCF could reduce the number of leukaphereses required to achieve a target yield of 5×10^6 CD34+ cells/kg.

Patients up to the age of 65 were eligible if they had either newly diagnosed MM or chemosensitive relapsed MM. Patients were randomized to one of two PBPC mobilization regimens, consisting of cyclophosphamide 4 g/m^2 followed 24 hours later by either filgrastim alone (5 µg/kg/day sc) or a combination of SCF 20 µg/kg/day sc) plus filgrastim (5 µg/kg/day sc). Leukaphereses (blood volume of approximately 10 L) were initiated when the white blood cell count was $\geq 4\times10^9$/L and continued until a total of $\geq 5\times10^6$ CD34+ cells/kg were collected.

One hundred and two patients were enrolled; 55 received SCF and filgrastim, 47 filgrastim alone. The two groups were well balanced for demographics, disease stage, ECOG score, number of prior therapy cycles and prior radiotherapy (Table 2).

The median number of leukaphereses to reach the target yield of 5×10^6 CD34+ cells/kg was one in the SCF group versus two in the filgrastim group ($p=0.008$). The proportion of patients reaching the target yield of 5×10^6 CD34+ cells/kg after a single leuka-

Table 2. Comparison of SCF plus G-CSF alone for PBPC collection in MM. Patient demographics and baseline disease characteristics.

	SCF + Filgrastim	*Filgrastim*	*Total*
n	55	47	102
Sex n (%)			
male	36 (65)	24 (51)	60 (59)
female	19 (35)	23 (49)	42 (41)
Age (years)			
median	60	59	59
range	38-66	37-65	37-66
Stage (DS) at diagnosis n. (%)			
I	1 (2)	3 (6)	4 (4)
II	10 (18)	10 (21)	20 (20)
III A	42 (76)	33 (70)	75 (74)
III B	2 (4)	1 (2)	3 (3)
ECOG score n (%)			
0	19 (35)	21 (45)	40 (39)
1	32 (58)	23 (49)	55 (54)
2	4 (7)	3 (6)	7 (7)
Prior cycles of CT			
median	3	3	3
range	1-38	3-19	1-38
Number of patients receiving prior RT n (%)	12 (22)	13 (28)	25 (25)

CT: chemotherapy; RT: radiotherapy.

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Table 3. Comparison of SCF plus G-CSF and G-CSF alone for PBPC collection in MM. Cumulative number and proportion of patients reaching a CD34⁺ cell yield of 5×10⁶/kg according to day of leukapheresis.

	Day 1 n (%)	*Day 2 n (%)*	*Day 3 n (%)*	*Day 4 n (%)*
SCF + filgrastim (n=55)	36 (65.4)	45 (81.8)	45 (81.8)	47 (85.4)
Filgrastim (n=47)	19 (40.4)	28 (59.6)	33 (70.2)	36 (76.6)
Odds Ratio	2.79	3.05	1.91	1.80
95% C.I.	1.25-6.25	1.24-7.51	0.76-4.83	0.65-4.92

Table 4. Comparison of SCF plus G-CSF versus G-CSF alone for PBPC collection in MM. CD34⁺ cell yields (×10⁶/kg) in patients with or without prior treatment with melphalan.

	Without melphalan		*With melphalan*	
	SCF + Filgrastim (n=36)	*Filgrastim (n=34)*	*SCF + Filgrastim (n=19)*	*Filgrastim (n=13)*
CD34+ cells (×10⁶/kg)				
Mean	24.6	14.1	8.8	5.0
(all leukaphereses)				
Median	21.3	9.3	7.1	5.3
Range	0.1-90.4	1.1-65.9	0.0-47.1	0.3-9.7

pheresis was 65% (36/55) in the SCF group versus 40% (19/47) in the filgrastim alone group (p=0.011, Table 3). Although not an endpoint of the study, we also analyzed the proportion of patients reaching a yield of 2×10⁶ CD34⁺/kg in a single leukapheresis. This cell yield was reached in a single leukapheresis in 80% (44/55) versus 62% (29/47) of patients in the SCF + filgrastim and filgrastim alone groups, respectively (p=0.041).

The median number of CD34⁺ cells collected in the first leukapheresis was significantly higher in the SCF group (11.3×10⁶ CD34⁺ cells/kg) than in the filgrastim group (4.0×10⁶ CD34⁺ cells/kg) (p=0.003). The increase in the number of CD34⁺ cells/kg collected after exposure to the combined cytokines was also observed in the subgroups of patients with and without prior treatment with melphalan (Table 4).

In this randomized study conducted in a large number of myeloma patients, addition of SCF to a stem cell mobilization regimen consisting of cyclophosphamide and filgrastim resulted in a three-fold enhancement of the number of PBPC collected in the first leukapheresis and a related decrease in the number of leukaphereses required to collect 5×10⁶ CD34⁺ cells/kg. These results are in line with those observed in other trials of the combination of SCF and filgrastim to improve PBPC collection.

The use of SCF and filgrastim significantly reduced the number of leukaphereses procedures needed. This is important as leukaphereses can be associated with adverse experiences.

In the future, use of a combination of SCF and filgrastim could reduce the duration of the first leukapheresis required to collect a target number of CD34⁺ in a substantial proportion of patients. Indeed, in this study, cell yields reached a median of 11.3×10⁶ CD34⁺ cells/kg in the first leukapheresis in patients exposed to this combination, potentially allowing a 50% reduction in apheresis blood volume in most patients.

Combining SCF to filgrastim could also be of benefit for patients who have had prior exposure to melphalan, who are known to be at risk of failure to mobilize sufficient progenitor cells. In this subset of patients at risk of insufficient mobilization, treatment with SCF plus filgrastim was also associated with higher cell yields although the difference with the filgrastim group was not statistically significant.

It would now be of interest to compare the combination of SCF and filgrastim, without cyclophosphamide, to the cyclophosphamide and filgrastim regimen used as a control in the present study. If equivalent or superior CD34⁺ cell collections could be achieved with cytokines alone, the morbidity associated with cyclophosphamide use would be avoided.

The present study also suggests that, since high numbers of CD34⁺ cells can be collected in a vast majority of patients, several cycles of high dose chemotherapy with autologous stem cell support could be explored. Indeed, tandem autologous transplantation has been reported as an encouraging therapeutic option, at least for some young patients with myeloma.[45]

The combination of SCF with filgrastim could also facilitate clinical studies on *ex vivo* manipulations of progenitor cell products such as tumor cell purging or expansion and maturation of progenitor cells in culture and, in the future, gene therapy.

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