

Factors affecting hematopoietic recovery after autologous peripheral blood progenitor-cell transplantation in aggressive non-Hodgkin's lymphoma: a prospective study of 123 patients

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Purpose: To analyse prognostic factors influencing hematopoietic recovery in patients with aggressive non-Hodgkin's lymphomas prospectively treated with intensive chemotherapy followed by peripheral blood progenitor-cells transplantation.

Patients and methods: Untreated patients with at least two unfavorable factors according to the age-adjusted international prognostic index were included in the LNH 93-3 trial. Patients received three cycles of chemotherapy and PBPC were mobilized using filgrastim. On day 60, a BEAM regimen was initiated followed by PBPC rescue. Among the 123 patients analysed, 60 received G-CSF (5 µg/kg/d) after PBPC transplantation at day 1 and 63 did not.

Results: Patients received a mean number of $12.4 \times 10^6/\text{kg}$ (1.86–111.5) CD34⁺ cells. After transplantation, neutrophil counts exceeded $0.5 \times 10^9/\text{l}$ at a median of 12.4 days (7–41 days) and platelet counts exceeded $50 \times 10^9/\text{l}$ at a median of 15.6 days (9–141 days). Platelets recovery $>50 \times 10^9/\text{l}$ was negatively influenced by BM involvement (20 vs 14 days; $P=0.04$). The number of CD34⁺ cells infused ($> \text{vs} \leq 5 \times 10^6/\text{kg}$) was correlated with faster platelet recovery (18.7 days vs 13.7 days) ($P=0.007$). In 26 patients for whom administration of G-CSF was randomized, time to neutrophil recovery was significantly shorter for patients treated with G-CSF: 10 vs 13 days ($P=0.0005$). The incidence of grade 3/4 infection, was similar in both groups.

Conclusion: In the patient population treated with the same first-line regimen, BM involvement and infusion of fewer CD34⁺ cells delayed platelet recovery. Administration of G-CSF after PBPC significantly reduced neutropenia.

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Introduction

Transplantation of peripheral blood progenitor cells (PBPC) is widely used to limit hematologic toxicity after intensified chemo-radiotherapy in lymphoid malignancies.¹ Although progenitor cells can be harvested from bone marrow (BM) or peripheral

blood, the preference for PBPC over BM is in part due to the non-invasive collection technique and more rapid engraftment.^{2,3} Several studies have examined factors influencing autologous PBPC engraftment kinetics and identified: patient characteristics (sex, age, performance status), treatment (type of mobilization chemotherapy, number of lines of prior chemotherapy, prior radiotherapy), disease type (Hodgkin's or non-Hodgkin's lymphoma (NHL)), administration of hematopoietic growth factor after transplantation and the number of cells injected.^{4–6} The factors most significantly influencing hematopoietic recovery are: age, prior treatment, the

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interval between the last treatment and the PBPC collection and the number of CD34⁺ cells reinfused.⁷ Hematopoietic growth factors have been shown to shorten neutropenia after autologous BM.⁸ However, for patients receiving high-dose therapy with G-CSF-mobilized PBPC, their use after transplantation has remained controversial.^{9,10}

In an attempt to eliminate as much as possible the bias observed in previous studies, we analysed a homogenous patient population treated according to the prospective LNH 93-3 protocol.¹¹ These patients, presenting with untreated aggressive NHL and with at least two unfavorable factors defined by the age-adjusted international prognostic index (IPI),¹² were treated with the same chemotherapy regimen before early PBPC transplantation.

Patients and methods

Eligibility criteria

Between March 1993 and September 1995, 370 patients were included in the NHL 93-3 protocol. To be eligible, patients had to be newly diagnosed with an aggressive NHL according to the Working Formulation and between 15–60 years of age. They had to present at least two of the following adverse prognostic factors, as defined by the age-adjusted IPI: abnormal lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 , or Ann Arbor stage III or IV.¹² Patients with lymphoblastic or small non cleaved cell Burkitt's lymphoma with meningeal or medullary involvement were excluded. Other non-inclusion criteria were positive serology for human immunodeficiency virus, concomitant or previous cancer (except *in situ* cervical carcinoma), congestive heart failure and liver or kidney failure. This study, conducted by the 'Groupe d'Etude des Lymphomes de l'Adulte' (GELA) in France and Belgium, was approved by the institutional Ethics Committee, and all patients gave their written informed consent.

Patients

Patients were randomized between arm A, four cycles of ACVBP followed by outpatient consolidation lasting four months,¹³ and arm B, short-term intensive induction therapy.¹¹ Among the 205 patients enrolled in arm B, 82 were considered ineligible for the present analysis of hematopoietic reconstitution because they did not undergo PBPC transplantation ($n=68$, because of disease progression or toxicity of chemotherapy), received autologous BM transplants ($n=4$), were not properly enrolled ($n=3$) or received granulocyte/macrophage-colony stimulating factor instead of G-CSF post-transplantation ($n=7$).

Thus, 123 patients, 74 men and 49 women with a median age of 42 years, were evaluated for PBPC

transplantation. The histological subtypes showed a predominance of diffuse large B-cell lymphomas. According to the inclusion criteria, all patients had an IPI > 1 (in 73% of patients, IPI = 3). B-symptoms were present in 73% of the patients and BM involvement in 26%.

Treatment

The LNH93-3 B regimen comprised an induction phase consisting of one cycle of cyclophamide 750 mg/m² on day 1, epirubicin 70 mg/m² on day 1, vincristine 1 mg/m² on day 1, prednisone 40 mg/m² from day 1–5 and intrathecal methotrexate 15 mg on day 1 (CEOP), and two cycles of epirubicin 120 mg/m² on day 1, cyclophosphamide 2000 mg/m² on day 1, vindesine 2 mg/m² on days 1–5, bleomycin 10 mg/m² on days 1–5, prednisone 40 mg/m² from day 1–5 and intrathecal methotrexate 15 mg on days 15 and 38 (ECVBP). G-CSF, 5 μ g/kg/day (filgrastim, Amgen Roche, Neuilly France), was given on day 6 after each ECVBP cycle to reduce toxicity of high-dose chemotherapy and to mobilize PBPC. Intensified chemotherapy (BEAM), consisting of BCNU, etoposide, cytarabine and melphalan began on day 60 and was followed 48 h after the end of chemotherapy by autologous PBPC transplantation.

Harvesting of PBPC

PBPC were collected after the first cycle of ECVBP as soon as the white blood cell count recovered to $> 2 \times 10^9/l$ under G-CSF therapy. When the collection was insufficient, leukaphereses, with continuous-flow blood cell separators, Baxter CS3000 (Baxter Healthcare Ltd, Berkshire, UK) or COBE Spectra (COBE Laboratories Ltd, Gloucester, UK) were repeated after the second cycle of ECVBP. Daily, 3–4-h sessions were performed to process two or three blood mass volumes per session until analysis of the product confirmed collection of $> 2.5 \times 10^6$ CD34⁺ cells/kg. The final product was cryopreserved in the patient's serum with 10% dimethyl sulfoxide in the vapor phase of liquid nitrogen.

Assay of stem-cell content

CD34⁺ cell content of the PBPC collection was determined for 84 patients using three-color flow cytometry on a FACScan (Becton Dickinson, Mountain View, CA, USA). In 1993 the CD34⁺ analysis was not standardized, so each laboratory has used its own antibodies. Granulocyte/macrophage-colony forming units (GM-CFU) were quantified in 107 patients using Methocult SFH 4435 (Terry Fox Laboratories, Vancouver, BC, Canada). Cells were cultured for 14 days in methylcellulose medium at 37°C in a humidified 5% CO₂ atmosphere and counted.

G-CSF post transplantation

Each physician decided whether or not to add G-CSF 5 µg/kg/day post-PBPC transplantation on day 1. The routine use of G-CSF or not after reinjection of G-CSF-mobilized PBPC has not reached consensus and we intended to address this point in a randomized study. Only 26 patients could be included in this randomized study because arm B of the NHL 93-3 protocol was stopped early.¹¹

Supportive care

All patients had an indwelling central venous catheter and were housed in a protected environment for the duration of aplasia. Red blood cell and platelet transfusions were given to maintain respective levels of 8 g/dl and $20 \times 10^9/l$. Blood components were irradiated and filtered to lower the number of contaminating leukocytes. Broad spectrum antibiotics were given for any clinical or microbiological infection or for a persistent undocumented fever ($>38^\circ\text{C}$) after blood had been drawn for culture.

Statistical analyses

The effect of the number of CD34⁺ cells was analysed using thresholds of 2.5, 3, 4 or 5×10^6 CD34⁺ cells/kg. Hematological recovery was monitored from the day of PBPC infusion. Two thresholds of neutrophil engraftment were defined as the number of days after the infusion of PBPC until the absolute neutrophil counts were at least (1) $0.5 \times 10^9/l$ and (2) $1 \times 10^9/l$. Platelet recovery was defined as the number of days until the count exceeded $50 \times 10^9/l$ unsupported by platelet transfusions. Duration of hospital stay was determined from the first day of intensive chemotherapy until the patient's discharge from the unit. A χ^2 test was used to compare patient characteristics between the two groups and the frequencies of infectious episodes and mucositis. Continuous variables, including the number of reinjected cells, hematopoietic recovery and hospitalization duration, were analysed with a Kruskal-Wallis test because of the small number of patients.

All of the factors found to have a significant impact on hematological (neutrophils and platelets) recovery were included in a multivariate analysis using the Cox proportional/hazards model.¹⁴ Only 84 patients with complete data on CD34⁺ cell numbers were included in the multivariate analysis.

Results

Patient characteristics

Among the 123 assessable patients, only 60 received G-CSF after PBPC transplantation. Comparison of their characteristics (Table 1) according to whether or not

Table 1 Characteristics of the 123 patients according to G-CSF administration or not after PBPC transplantation

Parameters	No G-CSF (n=63 (%))	G-CSF (n=60 (%))	P
Median age (years)	40	44	0.1
Sex ratio F/M	0.7	0.6	0.7
Histology			
Diffuse B large-cell	35 (56)	37 (62)	
Peripheral T cell	9 (15)	9 (15)	
Immunoblastic	6	2	
Lymphoblastic	2	0	
Burkitt	1	3	
Anaplastic	3	6	
Unclassified	7	3	
B-symptoms	48 (76)	42 (70)	0.4
Tumoral mass ≥ 10 cm	29 (46)	21 (35)	0.1
Stage III/IV	59 (94)	55 (92)	0.7
ECOG ≥ 2	24 (38)	27 (45)	0.4
IPI=2	18 (29)	15 (25)	0.5
IPI>2	45 (71)	45 (75)	
BM involvement	16 (25)	16 (27)	0.9
Abnormal LDH	59 (94)	57 (95)	0.7
β^2 -microglobulin ≥ 3 mg/l ^a	17 (31)	14 (32)	0.1
Serum albumin < 30 g/l	11 (17)	16 (27)	0.2

^aAvailable for 101 patients.

G-CSF was given, showed that the two groups were comparable. At the end of the procedure, 63% of the patients were in complete remission on an *intention to treat* basis.

Cell collection

Leukaphereses were performed after the first ($n=109$) and/or the second ($n=73$) ECVBP cycle with a median of 2 (1–5) leukaphereses. Leukaphereses performed after the first cycle gave a better yield (93×10^4 vs 69×10^4 CFU-GM). The median numbers of GM-CFU and of CD34⁺ cells reinfused were, respectively, $37.8 \times 10^4/kg$ (2–730) and $12.4 \times 10^6/kg$ (1.86–111.6) for the entire population, $37.8 \times 10^4/kg$ and $10.6 \times 10^6/kg$ for the group without G-CSF and $37.2 \times 10^4/kg$ and $13.4 \times 10^6/kg$ for the G-CSF group ($P=NS$).

Factors influencing hematopoietic recovery after PBPC transplantation

All patients attained a neutrophil count $>0.5 \times 10^9/l$ after a mean of 12.4 days (7–41 days) and a platelet count $>50 \times 10^9/l$ ($n=115$ patients) after a mean of 15.6 days (9–175 days).

The effect on hematological recovery of different prognostic parameters present at diagnosis was also evaluated (Table 2). Neutrophil and platelet recovery times as a function of age, LDH level and Ann Arbor stage of the patients were similar. BM involvement negatively influenced platelet recovery and patients with BM involvement needed six more days to achieve a platelet count $>50 \times 10^9/l$ ($P=0.047$) compared to those with normal BM. No effect of BM involvement on neutrophil recovery was observed.

The effect of the number of CD34⁺ cells infused, on hematopoietic recovery after PBPC transplantation was examined in the 84 patients with relevant data for all parameters using different thresholds. The engraftment of $>0.5 \times 10^9/l$ neutrophils was not influenced by the level of CD34⁺ cells infused. However, for patients transplanted with $>5 \times 10^6/kg$ CD34⁺ cells, a significantly shorter median time to recover a platelet count $>50 \times 10^9/l$ was noted (Table 3).

The effect of G-CSF administration post PBPC transplantation was evaluated in 26 patients included in a prospective randomized study. Neutrophil recovery was faster in patients receiving G-CSF post transplantation (Table 4). For the G-CSF group, the mean times to obtain a neutrophil count $>0.5 \times 10^9/l$

Table 2 Hematopoietic recovery according to initial status of various disease parameters

Parameter	Median number of days to recover		P	P
	Neutrophils $>0.5 \times 10^9/l$ (n=120)	Platelets $>50 \times 10^9/l$ (n=115)		
Normal BM (n=88)	12.6	14		
Involved BM (n=31)	12	20.1	0.6	0.047
Stage I/II (n=9)	12.6	17.9		
Stage III/IV (n=111)	12.5	15.4	0.9	0.5
Age <40 years (n=42)	12.5	16.5		
Age \geq 40 years (n=78)	12.4	15.1	0.5	0.6
Normal LDH (n=7)	13.4	12.2		
Abnormal LDH (n=113)	12.4	15.8	0.2	0.6
IPI=2 (n=32)	13	14.8		
IPI>2 (n=88)	12.3	15.9	0.2	0.7

Table 3 Hematopoietic recovery according to the number of CD34⁺ cells count reinfused (n=84)

Hematopoietic threshold	Median number of days (range) to recover		P
	CD34 ⁺ cells $\leq 5 \times 10^6/kg$ (n=15)	CD34 ⁺ cells $> 5 \times 10^6/kg$ (n=69)	
Neutrophils $>0.5 \times 10^9/l$	13.1 (9-20)	12.1 (7-24)	0.2
Neutrophils $>1 \times 10^9/l$	14.5 (10-23)	12.8 (8-25)	0.09
Platelets $>50 \times 10^9/l$	18.7 (10-47)	13.7 (5-64)	0.007

Table 4 Hematopoietic recovery and toxicity according to randomized G-CSF administration post PBPC transplantation

Parameter	Median number of days (range) to recover		P
	No G-CSF (n=13)	G-CSF (n=13)	
Neutrophils $>0.5 \times 10^9/l$	13.1 (10-18)	10.1 (8-16)	0.0005
Neutrophils $>1.0 \times 10^9/l$	15.1 (12-19)	10.5 (9-16)	0.0002
Platelets $>50 \times 10^9/l$	16.8 (9-47)	13.8 ^a (9-22)	0.6
Hospital stay	26.5 (20-44)	23.2 (17-44)	0.04

^aAvailable for only 11 patients.

and $>1 \times 10^9/l$ were significantly shorter by three days ($P=0.0005$) and 4.6 days ($P=0.0002$), respectively. Compared to the group without G-CSF, the G-CSF group showed a mean of three days fewer to reach a platelet count $>50 \times 10^9/l$ ($P=0.6$). The shorter time to neutrophil recovery was associated with a shorter hospital stay (Table 4).

Transplant morbidity

The numbers of patients experiencing infectious episodes and mucositis were not influenced by G-CSF treatment. Severe infections (WHO grade 3/4) occurred in six patients (9.5%) in the group without G-CSF and in eight patients (8%) in the G-CSF group. Mucositis (WHO grade 3/4) was observed in eight patients (12.6%) in the group without G-CSF and in nine patients (15%) in the G-CSF group. Among the seven early deaths observed, five patients were in complete remission (toxic death rate of 4%).

Multivariate analysis

A multivariate analysis was performed to evaluate the factors influencing hematologic recovery after PBPC transplantation in this setting. For a recovery of neutrophils $>0.5 \times 10^9/l$ above or under the median time the only significant factor was the use of G-CSF after ASCT ($P=0.002$). For a recovery of platelet count $>50 \times 10^9/l$ above or below the median time, the only significant factor was the CD34⁺ cells level $>5 \times 10^6/kg$, no further influence of BM was found. In contrast, the use of G-CSF after ASCT negatively influenced platelet recovery ($P=0.04$).

Discussion

Indications for high-dose therapies and hematopoietic stem cell rescue continue to expand with the results of published studies on lymphomas.¹⁵ Our results are similar in terms of hematological recovery to those of other studies on G-CSF-primed PBPC transplantation, with the median times to a neutrophil count $>0.5 \times 10^9/l$ and a platelet count $>50 \times 10^9/l$ being 12.4 and 15.6 days, respectively.^{6,7} Our patients had not been heavily pretreated and the median number of CD34⁺ cells collected was high, but we did not observe a shorter period of cytopenia compared to a previous study concerning relapsing patients.³

Among the initial characteristics studied to identify factors that would predict an early hematopoietic recovery, only BM involvement was found to have a negative effect by lengthening the time to platelet recovery. This finding is in disagreement with results that do not show a relationship between BM involvement and neutrophil or platelet recovery.⁷ Instead, their patients had a variety of diseases with different kinds of BM involvement (eg, low-grade NHL or myeloma). Other variables studied and included in the IPI did not affect hematopoietic reconstitution. The

lack of an effect of age on hematological recovery has also been shown by previous studies on 692 patients with various cancers⁴ and on 101 patients with malignant lymphoma.¹⁶ However, the results of the three studies cited above differ from those of another study demonstrating that a younger age (<40 years) is predictive of a better hematological recovery.¹⁷

The relationship between the number of CD34⁺ cells infused and the speed of platelet recovery was confirmed and infusion of $\leq 5 \times 10^6$ CD34⁺ cells/kg delayed platelet recovery. No such effect was found on neutrophil recovery. While CD34⁺ cell counts do influence neutrophil and platelet recoveries,¹⁸ the results of three studies¹⁹⁻²¹ on patients suffering from various malignancies indicated a threshold of 2.5×10^6 CD34⁺ cells/kg to be predictive of complete and rapid engraftment. Furthermore, a study in malignant lymphoma patients ($n=101$) autografted with PBPC recommended a threshold of 3.5×10^6 CD34⁺ cells/kg for rapid platelet engraftment.¹⁶ In agreement with our findings, it has been reported that patients receiving $< 5 \times 10^6$ CD34⁺ cells/kg experience slower platelet recovery^{4,5} and require a threshold of 8×10^6 CD34⁺ cells/kg to achieve a good hematologic recovery.¹⁷ In another study the reinfusion of $> 15 \times 10^6$ CD34⁺ cells/kg was able to shorten the time to hematopoietic reconstitution.⁷

We evaluated the benefit of administering G-CSF after PBPC. Indeed, such adjunction of G-CSF significantly shortened the period of neutropenia (neutrophil count $< 0.5 \times 10^9/l$) by three days. Some randomized studies indicated a reduction of the neutrophil recovery time by three or four days for the group treated with G-CSF post PBPC transplantation.^{22,23} Other prospective and randomized studies did not show a significant advantage,^{24,25} or showed only a

marginal one with a significant delay in platelet recovery.¹⁰

G-CSF was able to shorten the duration of neutropenia but not eliminate it. Indeed, after myeloablative conditioning regimens, neutropenia lasted at least nine days. For these reasons, some teams studied the delayed administration of G-CSF, five or seven days after PBPC transplantation,²⁶⁻²⁸ and observed the same kinetics of neutrophil recovery; others evaluated the G-CSF dose given and did not find an advantage for a higher dose.²⁹ Although the results of most studies have agreed on a beneficial effect of G-CSF on early neutrophil recovery, in agreement with our findings, no diminution of infectious episodes was observed.

The shortened duration of neutropenia led to earlier discharge of our patients; two other studies also reported reductions of hospital stay (three days).^{24,25} Thus, this management might translate into cost reduction for shorter hospital stays. Two economic analyses considered G-CSF cost, duration of hospitalization, use of antibiotics and transfusion requirements, and concluded with a cost saving for patients treated with G-CSF post-transplantation.^{25,26}

In conclusion, our results show that the infusion of a low number of CD34⁺ cells ($< 5 \times 10^6/kg$) or BM involvement delayed platelet recovery. The administration of G-CSF post-PBPC transplantation in NHL patients accelerated neutrophil recovery and shortened hospital stay without improving the number of infectious episodes.

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