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Effect of cell determinant (CD)34+ cell dose on the cost and consequences of peripheral blood stem cell transplantation for non-Hodgkin's lymphoma patients in front-line therapy

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Abstract

The aim of this study was to assess the effect of cell determinant (CD)34+ cell dose on the cost and consequences of peripheral blood stem cell transplantation for non-Hodgkin's lymphoma (NHL) patients in front-line therapy. Resource utilisation, length of aplasia, overall (OS) and event-free survival (EFS) were assessed for 63 patients. Economic data were calculated taking into account harvest, hospitalisation, blood product requirements and drugs required until discharge. The point of view of the Hospital Institution was chosen. A significantly earlier haematopoietic engraftment was achieved in patients with a count of more than 5×10^6 CD34+/kg. There were no differences for OS and EFS. A high CD34+ cell content resulted in a total cost saving of $4210. This was principally related to a significant reduction in the length of hospitalisation (−$3010) and platelet and red blood cell transfusions (−$815), although the latter was not significant. Several sensitivity analyses showed the robustness of our results. A CD34+ cell dose higher than 5×10^6/kg appeared to be optimal for clinical and economic considerations in NHL patients undergoing transplantation in front-line therapy.

Keywords: Cost; Autologous stem cell transplantation; CD34; Lymphoma; Granulocyte macrophage-colony stimulating factor (GM-CSF)

1. Introduction

Intensive high-dose chemotherapy (HDC) followed by autologous progenitor cell support is a common strategy for many malignant diseases. Autologous peripheral blood stem cell transplant (PBSCT) has been increasingly used instead of autologous bone marrow transplantation, resulting in a more rapid haematopoietic recovery and major cost savings [1].

Because of the continuous development of new treatments, as well as the high cost of the procedure, PBSC transplantation should be optimised. The CD34+ cell content is a major factor predicting engraftment kinetics [2–6]. If the optimal dose is not clearly defined, many reports have shown that a CD34+ cell dose of more than 5×10^6 CD34+/kg is a useful predictor [2,3,5,6]. Previous studies showed that implementing optimal CD34+ content would reduce resource consumption [7–9]. However, these three studies were carried out in many different malignant diseases, including a large number of patients with solid tumours. In this multicentre study, resource utilisation related to CD34+ cell content was assessed in a single disease, non-Hodgkin's

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lymphoma (NHL), which is a frequent indication for PBSCT.

2. Patients and methods

2.1. Patient selection

All patients were enrolled in a phase III multicentre trial, the GOELAMS 072 protocol, that compared conventional chemotherapy cyclophosphamide, doxorubicin, vincristine and prednisone ((CHOP), eight cycles) with HDC and PBSCT in front-line therapy for aggressive NHL patients. Inclusion criteria were: age from 15 to 60 years, high or intermediate grade NHL with high tumour burden or at least one adverse prognostic factor defined by the International Prognostic Index [10]. Written informed consent was obtained from all patients and the protocol design was approved by the Ethical Committee.

Patients assigned to the HDC arm received two consecutive cycles of CEEP within one month (vindesine 3 mg/m^2 day 1, cyclophosphamide 1200 mg/m^2 day 1, epirubicin 100 mg/m^2 day 1, prednisone 80 mg/m^2 days 1–5). When the response was greater than 50%, a third cycle (methotrexate 3000 mg/m^2 day 1, cytarabine 100 mg/m^2 days 1–5) could be given. Those with a response $<50\%$ after two cycles of CEEP received salvage chemotherapy. In cases of bulky tumour (more than 8 cm tumour size), additional focal radiotherapy could be given. Finally, all patients with at least a partial remission (PR) after two or three cycles (PR $>50\%$ or complete remission, CR) received HDC followed by PBSCT.

Between December 1994 and December 1998, 77 patients were enrolled in the PBSCT arm, in 15 different centres of the GOELAMS group. Among these, 63 received HDC and PBSCT according to the study design, and were included in the present economic analysis.

2.2. Mobilisation and collection of peripheral blood stem cells (PBSC)

PBSC were collected after the first or the second cycle of CEEP, or both. All patients received granulocyte macrophage-colony stimulating factor (GM-CSF) 5 μg/kg/day administered subcutaneously (s.c.) from the day after the end of chemotherapy until completion of leucapheresis.

Leucapheresis was planned when the neutrophil count was $>1\times10^9$/l and the platelet count was $>80\times10^9$/l. The initial criterion for adequacy of PBSC collections required at least 2×10^8/kg mononuclear cells and 2×10^4/kg colony forming units-granulocyte macrophage (CFU-GM). At the time of the initiation of the protocol, no minimal target CD34+ value was defined and planned in the trial. Nevertheless, this count was performed for all harvests. As the CD34+ cell count is actually a value that can be used to judge the CD34+ harvest content, it was decided to use it for this retrospective economic study.

2.3. Treatment regimen and supportive care

Patients were treated with BEAM 400 (carmustine 300 mg/m^2 day 1, etoposide 400 mg/m^2 days 2–5, cytarabine 400 mg/m^2 days 2–5, melphalan 140 mg/m^2 day 6) followed by PBSCT on day 8.

During the post-transplant period, GM-CSF 5 μg/kg/day was administered according to the protocol. Platelet transfusions were given when the platelet count was less than 20×10^9/l or in cases of bleeding with low platelet count. Packed red blood cells were transfused to maintain the haemoglobin level over 80 g/l. All blood components were leucocyte-reduced and irradiated and red blood cells were phenotyped. Broad-spectrum intravenous (i.v.) antibiotics were given in cases of temperature $\geqslant38^\circ$C and modified according to the local standard practice for neutropenia.

Patients were discharged when the absolute neutrophil count reached $>0.5\times10^9$/l, if they were afebrile and without complications.

2.4. Clinical assessment

Efficacy was measured by the length of aplasia: number of days with neutrophil count $<0.5\times10^9$/l, leucocyte count $<1\times10^9$/l and platelet count $<20\times10^9$/l. For these parameters, day 0 was defined as the first day with these values. Days of neutrophil and leucocyte recovery were respectively defined as the first day with counts greater than 0.5×10^9/l and 1×10^9/l (stable values for at last 2 days). Platelet engraftment was defined as a count of at least 20×10^9/l that was sustained without transfusion for 7 or more days.

2.5. Economic assessment

This retrospective study was a cost and consequences analysis of CD34+ cell dose, performed from the point of view of the Hospital Institution. Based on the data derived from several clinical studies, a threshold of 5×10^6/kg was chosen [2–9].

Data were collected regarding the mobilisation and harvest of PBSC, and the graft period until discharge from hospital. HDC costs (chemotherapy and adjuvant treatments), independent of CD34+ cell count, were excluded.

Major resources used and direct medical costs were identified for each patient, including: (1) hospitalisation; (2) medications (anti-infectious agents, haematopoietic growth factors (HGF); (3) blood products; (4) leucapheresis [11].

The unit price of hospitalisation was obtained from the analytic accounting system of the Besançon University Hospital (1998). These charges included non-medical and medical costs such as medical and non-medical personnel, hospital structure cost (e.g. overheads, financial expenses...), logistic costs (e.g. hotel, laundry, food), small equipment, and medical costs (e.g. medication, medical devices, radiology and biology). Therefore, *per diem* cost was used, except for the variable of direct medical costs, which was obtained from the clinical record for each patient (Table 1).

The cost of apheresis was obtained from the local Blood Bank tariff and included harvest, quality control, processing and cell conservation and thawing the cells to graft. The cost of GM-CSF used for mobilisation was added to obtain the total harvest cost for each patient. The official tariff for blood products applied during 1999 was used. A mean cost *per diem* of anti-infectious agents (antibiotics, antifungal and antiviral) was calculated based on a sample of 21 patients (four centres). Unit prices of drugs (anti-infectious and haematopoietic growth factors) were obtained from wholesale price lists from the Besançon Hospital Pharmacy.

Monetary values for 1999 French prices were used for all components. The exchange rate used was 1 US $ = 5 French francs. As the economic analysis was carried out over a short period of time for each patient (less than 1 year between diagnosis and PBSCT) and according to the hypothesis that a CD34+ cell count had no effect on overall and event free survival, no discounting was performed.

Extensive sensitivity analyses were conducted to study the effect on the results of modification over a plausible range of values of uncertain clinical and economic parameters [12]. At the outset, two major cost factors were varied simultaneously: length of hospitalisation and number of platelet transfusions. In the second phase, the unit costs of hospitalisation, drugs and apheresis were varied by 50%, because other centres could have different cost standards [13]. Unit costs published by Weaver and colleagues and Shulman and co-workers (USA) were also used, to take into account the differences in healthcare systems [8,9]. Finally, additional analyses were conducted: (1) excluding the very low (less than 2×10^6/kg) and very high (more than 15×10^6/kg) CD34+ cell contents [14–16]; (2) fixing successively a cut-off point of CD34+ cell dose to 4.5 and 5.5×10^6/kg, because of the lack of a centralised procedure of CD34+ cell measurement for this study.

2.6. Statistical analysis

A software program (BMDP 7.0, LA, USA) was used for the statistical analyses. Comparative tests were carried out between the two groups of CD34+ cell content ((5×10^6 CD34+/kg versus $>5\times10^6$/kg). A P value less than 0.05 was considered as significant.

Differences in mean values of patient characteristics and clinical results were tested using the Student t-test or Welch t-test. Data were summarised as mean ±standard deviation (S.D.). Effects of different factors (age $\leqslant$ or >45 years, sex, previous radiotherapy, number of previous cycles of chemotherapy <3 or $\geqslant3$ and status of disease at graft) on aplasia were assessed by a similar method. A second analysis of length of neutropenia and leucopenia was carried out by an analysis of variance, adjusting for post-graft GM-CSF use, which is recognised as a major confounding factor [17]. Categorical data were compared using the Chi^2 test or the Fisher's exact test.

To test the potential influence of the CD34+ cell count on disease outcome, overall survival and event-free survival rates in the two groups were assessed using the Kaplan–Meier method and the log-rank test for comparison.

Table 1
Unit prices or cost *per diem* (US$)

Nature	Unit prices (US $)
Stem cell harvest	
Mobilisation by GM-CSF, peripheral blood CD34+ measurement, one apheresis, quality control and storage	3310
Cost of an additional apheresis	1165
Hospitalisation	
Intensive Haematological Care Unit	900
Platelet transfusion	
Irradiated and leucocyte depleted — apheresis products	610
Red blood cells transfusion	
Irradiated, leucocyte depleted and phenotyped	215
Anti-infectious agents[a]	
Cost *per diem*	85

GM-CSF, granulocyte macrophage-colony stimulating factor.
[a] Based on a sample of 21 patients (four centres).

Table 2
Patient characteristics

Graft	$\leqslant 5\times10^6$ CD34+/kg $n=30$ n (%)	$>5\times10^6$ CD34+/kg $n=33$ n (%)	P value
Gender			
Male	15 (50)	21 (64)	
Female	15 (50)	12 (36)	0.3
Age (years) (mean±S.D.)	44.1±9.4	42.7±12.7	0.6
Type of NHL			
Mixed diffuse	3 (10)	1 (3)	
Diffuse large cells	20 (67)	25 (76)	
Immunoblastic	1 (3)	2 (6)	0.2
Anaplasic Ki1 positive	5 (17)	1 (3)	
T peripheral	0 (0)	3 (9)	
Other	1 (3)	1 (3)	
No. of poor prognosis factors	1.7±0.7	1.5±0.7	0.25
Disease status at graft			
Complete remission	5 (17)	10 (30)	
Complete response unverified	11 (37)	10 (30)	0.45
Partial response	14 (47)	13 (39)	
Delay between diagnosis and PBCT (months)	3.6±0.9	3.6±0.7	0.75
No. of previous cycles of chemotherapy before PBCT	3.1±0.5	2.9±0.2	0.04
Radiotherapy before PBCT	2 (7)	6 (18)	0.15

PBCT, peripheral blood cell transplant; NHL, non-Hodgkin's lymphoma; S.D., standard deviation.

Economic data were compared using a Student t-test or Welch t-test, according to recent guidelines [18]. Data were expressed as means, 95% confidence intervals (CI) and ranges.

3. Results

3.1. Patients

Between 1995 and 1999, 63 patients received HDC and PBSCT as front line therapy. The average age and the sex-ratio were respectively 43.4 years (range: 19–60) and 1.3 (36 men/27 females). Among the 63 patients, 15 (24%) were in CR, 21 (33%) in complete response unverified according to Cheson and colleagues [19] (>80%) and 27 (43%) in PR (>50%) at the time of the graft.

3 patients received salvage chemotherapy, and 8 received radiotherapy before PBSCT. Patient characteristics by CD34+ cell content group are summarised in Table 2.

3.2. Peripheral blood progenitor cells

The average number of apheresis was 2 (range 1–3). Only 1 patient had a second cycle of mobilisation and harvest. The median of CD34+ cell content was 5.2×10^6/kg (range: 0.1–50.1 ($\times10^6$/kg)). For 5 patients, the CD34+ count was less than 2×10^6/kg. Inversely, very high counts (more than 15×10^6/kg) were obtained in 7 cases. PBSC collection data are listed in Table 3.

Table 3
PBSC harvest

Graft	$\leqslant 5\times10^6$ CD34+/kg $n=30$ n (%)	$>5\times10^6$ CD34+/kg $n=33$ n (%)
Timing of harvest		
After first CEEP cycle	6 (20)	11 (33)
After second CEEP cycle	23 (77)	22 (67)
Both	1 (3)	–
No. of leucapheresis	1.9±0.7	2.1±0.6
Progenitor cell content		
CFU-GM (10^4/kg)		
Mean±S.D.	53±72	95±97
Median (range)	34.5 (1–320)	61 (1–374)
CD34+ (10^6/kg)		
Mean±S.D.	3±1.2	12.4±10.2
Median (range)	3.4 (0.1–5)	8.4 (5.2–50.1)

CEEP, vindesine, epirubicin, prednisone, cyclophosphamide, see text for dosage; CFU-GM, colony forming units-granulocyte macrophage; S.D., standard deviation.

3.3. Engraftment kinetics

No graft failure was observed. Among the 4 cases of delayed recovery (more than 21 days), 3 patients received less than 2×10^6 CD34+/kg.

A more rapid engraftment was achieved after re-infusion of more than 5×10^6CD34+/kg; length of grade 4 neutropenia (10.2 versus 11.6, $P=0.07$), leucopenia (9.3 versus 11.8, $P=0.001$) and thrombopenia (6.0 versus 10.4, $P=0.02$) were reduced. No effect of sex, age, status of disease, previous radiotherapy and number of previous cycles of chemotherapy was observed on the length of aplasia. After adjustment for post-graft GM-CSF use, a CD34+ cell count higher than 5×10^6/kg appeared to be a significant factor for early neutrophil ($P=0.01$) and leucocyte ($P=0.02$) recovery. No independent effect of post-graft GM-CSF administration was observed.

3.4. Clinical and economic data

The clinical results are summarised in Table 4. All parameters were in favour of a CD34+ cell dose higher than 5×10^6/kg. A major reduction of 3.3 days of hospitalisation was observed in this group. Blood product requirements, particularly platelet transfusions, were also less. The length of i.v. administration of anti-infectious agents was reduced by 4 days in these patients. Post-graft GM-CSF was not administered in 15 cases, for various reasons.

Hospitalisation was the major cost factor: 69% in each group. Despite a harvest cost of +$168), a CD34+ cell content higher than 5×10^6/kg gave an overall procedure cost saving of −$4210. This benefit was principally related to hospitalisation (−$3010) and blood transfusion products (−$815) (Table 5).

3.5. Sensitivity analysis

The results are listed in Table 6. To obtain an almost equal total cost in the two groups, length of hospitalisation had to be 3 days longer and platelet transfusions multiplied by 2 in the second group ($>5\times10^6$/kg). Our results were not affected by excluding extreme values of the CD34+ cell dose (−$3790), or changing the cut-off point value of CD34+ content to 4.5 (−$4300) or to 5.5 (−$4730).

Varying unit costs, the difference of total cost between the two groups was from $2750 to 8360. These results showed the robustness of our analysis and that the re-infusion of more than 5×10^6 CD34+/kg would result in a cost saving of more than $2750.

3.6. Survival

Only 1 patient died early, related to toxicity from the HDC, but after haematopoietic recovery (group $>5\times10^6$ CD34+/kg). At the time of this study, the median follow-up after PBSC transplantation was 16 months. No differences in the probability of overall survival (79% versus 85%, $P=0.86$) and event-free survival (68% versus 69%, $P=0.81$) were observed between the two groups ($\leqslant$ or $>5\times10^6$ CD34+/kg). Similar results were obtained using the date of diagnosis as the start of follow-up.

4. Discussion

Our analysis evaluated the impact of CD34+ cell dose for NHL patients. A homogeneous sample of single pathology patients transplanted in front-line therapy was analysed. The delay between diagnosis and HDC, previous treatments, mobilisation protocol and conditioning regimen were similar in the two groups, which were retrospectively defined according to the CD34+ cell dose. Patient selection also resulted in cancelling out many potential confounding factors.

The CD34+ count was a major independent factor for early haematopoietic recovery. An average reduction of 1.4 and 2.5 days in the length of neutropenia and leucopenia were respectively achieved with re-infusion of more than 5×10^6/kg CD34+ cells. These findings agree with previous studies, including those in solid

Table 4
Clinical parameters

	$\leqslant5\times10^6$ CD34+/kg $n=30$	$>5\times10^6$ CD34+/kg $n=33$	P value
Hospitalisation (days)	25.9±6.3	22.6±4	0.02
Platelet transfusions (units)	3.9±2.9	2.8±1.2	0.04
Red blood cell transfusions (units)	3.6±2.9	3±2.3	NS
Anti-infectious treatment (days)	15.5±6.1	11.5±5.6	0.015
Post-graft GM-CSF use			
Cases (%)	24 (80)	24 (73)	NS
Length (days)	9.8±5.1	8.8±3.9	NS
Documented bacteraemia (%)	8 (27)	5 (15)	NS
Systemic fungal infections (%)	5 (17)	3 (9)	NS

GM-CSF, granulocyte macrophage-colony stimulating factor; NS, non-significant.

Table 5
Cost per patient (US$)

	$\leqslant 5\times10^6$ CD34+/kg $n=30$	$>5\times10^6$ CD34+/kg $n=33$	P value
Mobilisation and harvest			
Mean (95% CI)	4450 (4067–4833)	4618 (4386–4851)	NS
Range	3308–7316	3308–5638	
Hospitalisation			
Mean (95% CI)	23 330 (21 013–25 468)	20 320 (18 997–21 647)	0.02
Range	17 100–47 700	14 400–28 800	
Platelet transfusions			
Mean (95% CI)	2420 (1826–3009)	1730 (1466–2003)	0.04
Range	0–7320	610–3660	
Red blood cells transfusions			
Mean (95% CI)	775 (533–1017)	650 (476–827)	NS
Range	430–3225	0–1720	
Post-graft GM-CSF			
Mean (95% CI)	1400 (997–1804)	1070 (760–1376)	NS
Range	0–4050	0–3000	
Anti-infectious agents			
Mean (95% CI)	1310 (1104–1524)	980 (802–1155)	0.015
Range	425–2975	425–2040	
Total graft period cost			
Mean (95% CI)	29 460 (26 534–32 385)	24 940 (23 184–26 687)	0.006
Range	21 345–55 815	17 245–33 835	
Total procedure cost			
Mean (95% CI)	33 810 (30 898–36 728)	29 600 (27 838–31 368)	0.01
Range	25 818–59 123	21 718–38 308	

95% CI, 95% confidence interval; NS, non-significant; GM-CSF, granulocyte-macrophage colony stimulating factor.

tumours and haematological malignancies [2,5,6,9,20]. In this study, an even larger improvement of platelet recovery (4.4 days) was observed in this group while in the above mentioned studies, shortening of platelet engraftment varied from 3 to 12 days. Our results confirmed the clinical benefit of the re-infusion of more than 5×10^6/kg CD34+ cells in NHL patients. The potential efficiency of very high cell doses ($>15\times10^6$/kg) was recently reported by Ketterer and colleagues [16]. As no minimal target value of CD34+ cells was planned in the initial protocol, 5 patients received less than 2×10^6/kg. Among these, 3 had delayed engraftment, as described in other studies [14,15]. These points justified an economic sensitivity analysis excluding extreme values of CD34+ cell dose. The influence of CD34+ cell dose on long-term survival still remains unknown. Although the follow-up was limited to the time of analysis, no differences in overall survival and event free survival were observed between the two groups, as was also described by Ketterer and colleagues [16].

Re-infusion of more than 5×10^6 CD34+ cell/kg resulted in a large and significant total cost saving (−$4210, −12.5%). This was related to the minimisation of all economic post-graft parameters. Major cost savings were achieved by significantly shortening hospitalisation (−3.3 days, −$3010) and reducing platelet requirements (−1.1 = units, −$690). In previous economic studies, Weaver and Glaspy reported a reduction in length of hospitalisation of 3 (11 versus 14) and 1.7

Table 6
Sensitivity analyses

	$\leqslant 5\times10^6$ CD34+/kg $n=30$	$>5\times10^6$ CD34+/kg $n=33$	Total cost saving (US $)
Overall analysis	33 810	29 600	−4210
Hospitalisation +3 days and platelet transfusions ×2 in group $>5\times10^6$/kg	33 810	34 050	No saving
Excluding extreme values of CD34+ cell dose	33 520	29 730	−3790
Cutpoint of CD34+ dose = 4.5 ($\times10^6$/kg)	34 100	29 800	−4300
Cutpoint of CD34+ dose = 5.5 ($\times10^6$/kg)	33 930	29 200	−4730
Unit cost of harvest, hospitalisation and drugs = −50%	19 290	16 540	−2750
Unit cost of harvest, hospitalisation and drugs = +50%	49 050	43 180	−5870
Unit cost used by Weaver [8]	67 630	59 270	−8360
Unit cost used by Schulman [9]	65 800	57 570	−8230

days (18.5 versus 20.2), respectively [7,8]. More recently, a difference of 3.3 days (13 versus 16.3) has been described [9]. In these studies, a decrease in platelet transfusions varied from 1.2 to 2.5 units. In addition, it was found that a CD34+ cell content of at least 5×10^6/kg could significantly reduce the length of i.v. anti-infectious administration (−4 days, −$330), as described by Schulman and coworkers (−3.1 days) [9]. Scheid and colleagues demonstrated that this dose of CD34+ cells resulted in significantly fewer days with fever (1 versus 3.5 days), resulting in a reduction in antibiotic use (7 versus 10 days) [21]. Contrary to Schulman and coworkers and Weaver and colleagues, the influence of CD34+ cell dose on red blood cell transfusions and length of post-graft HGF administration was not significant, but there was a trend towards the more than 5×10^6/kg ($455) [8,9]. To offset our economic findings, the length of hospitalisation had to be 3 days longer and simultaneously platelet transfusions multiplied by 2 for each patient with a CD34+ cell dose higher than 5×10^6/kg. These improbable values showed the robustness of our results. Our economic results were not sensitive to the exclusion of extreme values (<2 and $>15\times10^6$/kg) of CD34+ cell content (−$3790). Although it would be difficult to demonstrate, the restriction of blood products and antibiotic requirements could avoid toxic, immunological and infectious adverse effects and thus, reduce major costs.

The large variation in unit costs per centre and country appears to be a common limitation in economic studies [13]. As a French multicentre study was carried out, unit costs of harvest, hospitalisation and drugs were varied by −50% and +50%. Cost savings were also respectively −$2750 and −$5870. Unit costs published by Weaver and colleagues and Schulman and coworkers were also applied, to take into account the differences in the healthcare systems [8,9]. Total cost savings of approximately $8300 for our clinical costs were obtained. In the above mentioned studies, similar cost savings ($8220 and $9120) were achieved with a CD34+ cell dose of at least 5×10^6/kg [8,9]. The absence of a centralised CD34+ measurement was a severe limitation to our study. In the sensitivity analysis, the level of the CD34+ count was varied, successively to 4.5 and 5.5 ($\times10^6$/kg), but the results remained unchanged (−$4300 and −$4730). Another limit could be related to the fact that all patients were enrolled in a clinical trial. Clinical practice could also be modified [18]. As the aim of the clinical trial was independent of our economic study, the results can be considered to be representative of standard practice in France. This hypothesis was supported by a previous study of feasibility, in which 28 consecutive and non-selected NHL patients were included in our centre [22]. A cost saving of $2700 was achieved after re-infusion of more than 5×10^6/kg CD34+ cells.

These clinical and economic results would suggest that the mobilisation and harvest strategies be optimised. Chemotherapy followed by cytokine administration is an optimal mobilisation protocol [23]. Granulocyte-colony stimulating factor (G-CSF) and GM-CSF appear to have a similar ability to mobilise PBSC [24]. Timing of the harvest should be related to the peripheral blood CD34+ measurement. A level of less than 10/μl appears to be predictive of poor collection [25]. Inversely, a peripheral count higher than 50/μl predicts, in some cases, an effective harvest with only one apheresis [26]. As a large reduction in graft-period cost (−$4400) was found, the benefit of one or two additional aphereses (+$1150 or +$2300) for easy-to-mobilise patients could be considered in order to obtain more than 5×10^6/kg CD34+ cells. However, the management for hard-to-mobilise patients remains a severe problem. The factors affecting mobilisation, such as the number of previous cycles of chemotherapy, prior exposure to stem cell toxic drugs and radiotherapy, have been well identified [3,27,28]. Whenever possible, mobilisation and harvest could be planned early after the initial diagnosis for transplant candidates [27,28]. Different mobilisation strategies for these patients have been described by Stiff, as dose escalation or combinations of cytokines [23]. New HGF, such as stem cell factor and thrombopoietin, could lead to a potential interest [29,30]. Recently, a study has shown that post-transplant neutropenia could be markedly reduced (even abrogated for some patients) by re-infusion of *ex-vivo* expanded CD34+ cells [31].

In conclusion, our results demonstrated that a CD34+ cell count higher than 5×10^6/kg was an optimal dose for clinical and economic considerations in NHL patients transplanted in front-line therapy. These results are in agreement with other previous studies including different stages of diseases and/or solid tumours. On the basis of these clinical and economic data, the development of new strategies to improve PBSC yields should be combined with economic studies.

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