Bone Marrow Transplantation (2008) 42, 507–513

www.nature.com/bmt

ORIGINAL ARTICLE

Prospective single-arm study of pegfilgrastim activity and safety in children with poor-risk malignant tumours receiving chemotherapy

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The objective of this study was to assess the efficacy of an injection of 100 µg/kg of pegfilgrastim in haematopoietic recovery and mobilization in children following 32 courses of chemotherapy. End points were duration of neutropaenia, myeloid recovery and PBMC collection. Neutropaenia lasted a mean of 4.7 days (± 2.13 days). Myeloid recovery occurred at a median of 10 days (inter quartile range (IQR) 8–11). Febrile neutropaenia complicated 13 courses (40.6%). Mobilization was observed in 20 out of 26 assessable courses (76.9%). The rise in CD34+ cells occurred at a median of 6 days (IQR 4–7) after PEG and remained >20 per µl for 6 days (IQR 4–8), with a median value of 80 per µl (IQR 48–170.5). The median CD34+ cell peak was 165 per µl (IQR 82.5–331), 9 days (range 6–14) after PEG. PBMC were collected on average at day +5 (+4 to +9) after PEG. In 93.3% of collections, at least 3×10^6 per kg CD34+ cells were collected through a single apheresis. Myeloid recovery occurred in all cases within 15 days, without concomitant thrombocytopaenia. The incidence of primary febrile episodes is in line with data in the literature and with our own historical experience. A long-lasting period of circulating CD34+ cells allowed for more accurate scheduling of apheresis.
Bone Marrow Transplantation (2008) **42,** 507–513; doi:10.1038/bmt.2008.206; published online 21 July 2008
Keywords: pegfilgrastim; neutropaenia; children; PBMC apheresis

Introduction

Chemotherapy-induced neutropaenia is important in increasing the risk of infection in children with malignant diseases. The risk of infection is related to the severity and duration of neutropaenia which, if complicated by fever, often requires the administration of antibiotics and hospital admission.[1] Furthermore, it can also compromise the ability to deliver the full dose of chemotherapy on schedule.[2]

Myeloid growth factors, mostly G-CSF (filgrastim), are used the world over to decrease the period of neutropaenia between courses of chemotherapy as well as to mobilize transplantable haematopoietic progenitor cells in the blood.[3] G-CSF has a short half-life due to its almost complete renal clearance, thus injections must be given daily to achieve full clinical benefits such as PBMC mobilization or haematological recovery. Pegylation (that is, the covalent binding of a 20 kDa PEG molecule to the N-terminal methionine residue of filgrastim) led to a new form of the drug (Pegfilgrastim; Amgen Inc., Thousand Oaks, CS, USA), which has shown a prolonged half-life and sustained serum levels, thanks to the neutrophil-mediated clearance dominant mechanism.[4,5] Pegfilgrastim (PEG) has also shown comparable safety and efficacy to the non-pegylated molecule.[6,7] However, most of these studies were carried out on adults and little information is available on children.

The aim of this study was to evaluate the activity and safety of PEG in enhancing both neutrophil recovery and PBMC mobilization after chemotherapy in children with cancer.

Patients and methods

Eligibility criteria

This prospective, single-arm study was carried out between August 2005 and October 2006, at two Italian paediatric institutions (Gaslini Children's Hospital, Genoa and Regina Margherita Hospital, Turin). The aim was to evaluate the efficacy and tolerability of PEG administration in children with cancer.

Children (<18 years of age) with cancer and a Lansky (or Karnofsky if older than 16 years) score >50, receiving aggressive front-line or salvage myelosuppressive chemotherapy according to various national or international protocols that called for G-CSF stimulation in the postchemotherapy phase, were eligible for this study.

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Received 2 April 2008; revised 27 May 2008; accepted 30 May 2008; published online 21 July 2008

Patients with inadequate renal, hepatic and/or cardiac function were excluded from the study, as were those with leukaemia, as the local institutional review boards (IRBs) did not approve the protocol amendment calling for the use of PEG instead of G-CSF.

Schedule, monitoring of ANC and CD34+ cells

PEG was administered at a dose of 100 μg/kg through a single, subcutaneous injection given at day +3 from the end of the chemotherapeutic course. In the absence of a paediatric schedule we chose the 100 μg/kg dosage on the basis of several dose-finding studies that showed that 100 μg/kg is comparable to a daily administration of filgrastim 5 μg/kg per day.[8] Furthermore, some data had shown that broad dose dependence was observed and that the maximum effect was seen at 100 μg/kg. This effect disappeared, in terms of granulocyte–macrophage colony-forming cells per ml, by increasing the dosage to 300 μg.[4] Absolute and differential blood counts were evaluated for each eligible patient at the end of the chemotherapeutic course (time 0), on the day of PEG administration (+3) and then at least three times a week until the return to 'normal' values following the chemotherapy-induced WBC nadir and the subsequent WBC peak due to PEG stimulation. As soon as the WBC count began increasing again after neutrophil nadir, the number of CD34+ cells was also evaluated daily until they returned to <20 per μl. The CD34+ cell kinetics was assessed by flow cytometry according to the International Society of Hematotherapy and Graft Engineering guidelines,[9] and it was evaluated daily to assess the efficacy and timing of PEG-induced mobilization.

Leukaphereses to collect PBMCs in children scheduled for SCT were started when CD34+ cells were >20 per μl, and were carried out daily by means of a standard volume procedure using a Cobe Spectra separator (Cobe BCT Inc., Lakewood, CO, USA). They were continued if possible, until at least 3×10^6 per kg CD34+ cells per each scheduled high-dose therapy course had been harvested.

For the purposes of this study, neutropaenia was defined as an ANC $<0.5 \times 10^9$ per litre. Because of the different schedules and types of myelosuppressive chemotherapy regimens given to the study patients, we decided to start the observation of each patient as of the day of PEG administration. Thus, the length of neutropaenia was the total number of days in which the ANC count was $<0.5 \times 10^9$ per litre, whereas myeloid recovery was defined as the interval (in days) between the last day of chemotherapy and the first of 3 consecutive days in which ANC was $>0.5 \times 10^9$ per litre following WBC nadir.

Patients who were analysed for CD34+ cell kinetics were defined as 'good mobilizers' if a CD34+ count higher than 20 per μl was achieved, as opposed to 'poor mobilizers' in whom the CD34+ count remained lower than 20 per μl. Among the good mobilizers, the total number of days with a CD34+ count >20 per μl were also evaluated.

Data were collected for each eligible patient with regard to demographics, underlying disease, date of diagnosis and of relapse if it occurred after the elective end of therapies, and phase of treatment during PEG administration. During follow-up, children were also assessed by routine physical evaluation and in particular to determine the incidence and characteristics of febrile neutropaenia (FN), if any. For the purposes of this study, fever was defined as the presence of an oral or axillary temperature $\geqslant 38.5\,^{\circ}C$ in a single measurement, or $\geqslant 38.0\,^{\circ}C$ on two or more occasions taken at least 1 h apart. Febrile episodes and invasive fungal infections were classified according to internationally accepted criteria.[10,11]

Furthermore, the incidence of manifestations that were potentially related to PEG administration was recorded daily, with particular attention to bone, muscle or joint pain, skin rash and headache.

Clinical end points and statistical analysis

As the aim of this study was to evaluate the efficacy and safety of 100 μg/kg of PEG given in a single dose, we decided to use a composite end point. In more detail, both myeloid recovery and duration of neutropaenia were considered to be equally important for the evaluation of this drug. We considered PEG treatment as being effective on myeloid recovery if it occurred within 15 days from the last day of chemotherapy and if the neutropenic period lasted ⩽1 week in at least 80% of patients. Any delay in the subsequent course of chemotherapy caused by anaemia and/or thrombocytopaenia was also recorded. The 80% minimum success rate was chosen on the basis of our previous experience with the standard use of G-CSF.

Moreover, PEG activity on PBMC mobilization was considered as being effective if at least 75% of the courses yielded good mobilization (that is, CD34+ cell count >20 per μl). Safety end point was the incidence of adverse events attributable to PEG administration.

It was agreed that the effect of PEG would be evaluated after various courses of chemotherapy, and that each patient would be evaluated even after more than one course. Therefore, we took into consideration the total number of courses rather than the number of patients.

Descriptive statistics were reported as percentages for categorical variables. Medians and interquartile range (IQR) were used for continuous and counting data due to the non-normal distribution of the observations and to reduce the effect of outliers.

The IRBs of both institutions participating in this study approved the protocol and the patients' legal guardians gave written, informed consent as per the Helsinki declaration.

Results

During the study period 28 children (13 male, 15 female) were enrolled in the study, 3 of whom received more than 1 course (maximum 3) of PEG for a total of 32 courses. Half of them ($n=14$; 50%) were affected by neuroblastoma (NB), whereas the remaining subjects were affected by bone tumours ($n=8$; 29%; six osteosarcoma, two Ewing's sarcoma), central nervous system tumours ($n=3$; 11%; two medulloblastoma, one germinoma); kidney tumours

($n=2$; 7%; one Wilms' tumour, one clear cell sarcoma) and non-Hodgkin's lymphoma ($n=1$; 3%).

Median (range) interval between diagnosis and PEG administration was 9 months (1–72). The interval between the end of treatment and PEG administration among the patients ($n=15$; 54%) who were treated for tumour recurrence after the elective end of front-line therapy was 34 months (6–72), whereas the interval between last relapse and PEG was 2 months (1–4). Four patients had previously received radiotherapy (craniospinal 2.4 Gy, abdomen 1.5 Gy and lumbar spine 5.1 Gy, and mediastinum 2.8 plus 1.2 Gy involved field, respectively).

Table 1 shows the various types of myelosuppressive chemotherapy courses that were given prior to PEG administration. In particular, the TVD schema (topotecan 1.5 mg/m^2 per day, i.v. for 5 days, followed by a 48-h i.v. infusion of VCR 2 mg/m^2 and doxorubicin 45 mg/m^2) was given to 11 children for a total of 15 courses; nine patients received CY 4 g/m^2 per day, i.v. for 1 day followed by etoposide 100–200 mg/m^2 per day, i.v. for 5 or 3 days, three patients were given CY 4 g/m^2, i.v. for 1 day and two patients received etoposide 2.4 g/m^2 per day, i.v. for 1 day. The ICE schema (ifosfamide 2 g/m^2 per day, i.v. for 3 days + carboplatin 400 mg/m^2 per day, i.v. for 2 days + etoposide 150 mg/m^2 per day, i.v. for 3 days) was given to two patients. Lastly, ifosfamide 2000 mg/m^2 per day, i.v. and etoposide 200 mg/m^2 per day, i.v. for 5 days was the treatment for the remaining patient. All patients were given cotrimoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis, whereas no antifungal or antibacterial prophylaxis was administered for FN.

PEG efficacy

Neutropaenia and myeloid recovery. The efficacy of PEG administration was evaluable after 31 chemotherapeutic courses (96.9%), as one patient did not develop neutropaenia after chemotherapy.

Neutropaenia lasted a mean of 4.7 days ($\pm$2.13 days), and in 87% of cases ($n=27$) the ANC values rose to $>0.5\times10^9$ per litre within 1 week. The ANC nadir value ranged between 0 and 1.5×10^9 per litre (median 0.25×10^9 per litre), and was observed on average at a median of 6 days (IQR 5–7 days) after the end of the chemotherapeutic course. Myeloid recovery occurred within 15 days after all (100%) the evaluable courses at a median interval of 10 days (IQR 8–11) after the last day of chemotherapy. Overall, PEG administration was deemed to be effective in 27 of the 31 evaluable courses (87%; Table 2).

FN complicated 13 courses (40.6%). A diagnosis of fever of unknown origin was made for 12 febrile episodes (92.3%), which were empirically treated with broad-spectrum antibiotic therapy. A single case of fungemia due to *Candida albicans* was reported and was treated with specific antifungal therapy. Overall, antibiotics were given for a median of 8 days (range 3–15). Patients became afebrile after a median of 5 days (range 2–8).

PBMC mobilization and leukaphereses

A total of 26 courses in 22 patients were assessable for PEG-induced PBMC mobilization, and among them, 20 courses in 17 children (76.9%) yielded good mobilization (that is, CD34 + cells >20 per μl; Table 3). One of the six courses that yielded poor mobilization (PR, case no. 7) occurred in a patient who had however successfully mobilized PBMCs in the two previous, consecutive chemotherapeutic courses. Of the remaining five poor mobilizer cycles, two were given to two adolescents who had previously been treated with craniospinal or mediastinal irradiation (TD, case no. 9 and DS, case no. 10). The three remaining poor mobilization courses occurred as follows: in a child who had experienced late relapse after autologous PBMC transplant (DCG, case no. 16), in a girl with early relapse following PBMC transplant (MB, case no. 17) and in a child with resistant stage 4 NB and residual marrow infiltration (DPG, case no. 15). No relationship was established between failure of PBMC collection and duration of neutropaenia (median 3 days in the six poor mobilization courses vs 4 days in the entire cohort of cycles). To determine whether any risk factors may have affected the chance of efficient PEG-induced mobilization, we compared several of the patients' characteristics (that is, previous radiotherapy, phase and age at treatment) after poor or good mobilization, and no significant differences were documented, most likely due to the small sample size (data not shown).

Among the 20 courses that were characterized by efficient PEG mobilization, CD34+ cell levels >20 per μl were first observed in the peripheral blood at a median of 6 days (IQR 4–7) after PEG administration and they remained >20 per μl for a median of 6 days (IQR 4–8), with a median value of 80 per μl (IQR 48–170.5). The median peak of CD34+ cells was 165 per μl (IQR 82.5–331) and it occurred after a median interval of 9 days (range 6–14) after PEG administration.

Among the subset of patients who were candidates for autologous SCT, at least one PBMC collection was performed following 15 efficient PEG administrations. The target of $>3\times10^6$ per kg CD34+ cells collected through only one apheresis was achieved by 14 of them (93.3%). One patient alone required additional apheresis the following day to reach the target. It is noteworthy that four patients with an efficient first PBMC collection who were scheduled for repeated high-dose chemotherapy courses underwent a further successful collection the following day. Overall, a total of 19 leukaphereses were performed in 15 children. The first apheresis was performed on average at day +5 (range +4 to +9) after PEG administration, and the median yield of CD 34+ cells per apheresis was 8.4×10^6 per kg (IQR 6.2–22.3).

Safety. Adverse effects were monitored prospectively. PEG was well tolerated and only one patient complained of one episode of mild bone pain that was quite clearly attributable to the PEG-induced increase in the leucocyte count from 17.2 to 36.3×10^9 per litre, and was easily managed with paracetamol. Bone pain (most frequently in the jaw) was reported after seven further courses; in all cases pain started before the WBC count increase and in four cases it was reported following the administration of a VCR-containing regimen and then presumably attributable

Table 1 Clinical characteristics

UPN	*Initials, gender, age at PEG treatment*	*Diagnosis*	*Type of treatment*	*Protocol*	*Previous RT, site (Gy)*	*BM infiltration*	*No. of PEG courses*	*Side effects*	*Duration of neutropaenia (days)*	*Myeloid recovery (days)*
1	RS, M, 7	NB	Salvage	TVD	No	No	1	Jaw pain	6	8
2	MG, M, 1	MED	Front line	HD ETO	No	No	1	None	4	10
3	DN, F, 1	NB	Front line	HD CICLO	No	No	1	None	2	6
4	DPG, F, 7	NB	Front line	HD CICLO	No	No	1	Joint pain	2	4
5	AA, M, 3	NB	Salvage	TVD	No	No	1	None	3	9
6	HS, M, 4	NB	Salvage	TVD	No	Yes	2	None	6	9
				TVD	No	Yes		None	8	12
7	PR, M, 3	NB	Salvage	TVD	No	Yes	3	Jaw pain	7	10
				TVD						
				TVD						
					No	Yes		Bone pain	3	8
					No	Yes		None	3	9
8	MI, F, 2	NB	Salvage	TVD	No	No	1	None	3	7
9	TD, M, 18	GERM	Salvage	ICE	Yes, C-S, 2.4	No	1	Bone pain	3	10
10	DS, F, 18	NHL	Salvage	HD CICLO	Yes, Mediastinum, 28.8 + boost 4.0	No	1	Bone pain	4	10
11	CE, F, 3	Wilms	Salvage	ICE	No	No	1	None	3	12
12	GE, F, 11	NB	Salvage	TVD	No	No	1	Jaw pain	6	9
13	LT, F, 8	Ewing	Front line	IFO-ETO	No	No	1	None	NA	NA
14	AD, M, 5	NB	Salvage	TVD	No	Yes	2	Bone pain	3	10
			Salvage	TVD	No	Yes		None	3	10
15	DCG, M, 9	NB	Salvage	TVD	No	Yes	1	None	6	9
16	DPG, F, 8	NB	Salvage	TVD	No	Yes	1	None	2	11
17	MB, F, 9	NB	Salvage	TVD	No	Yes	1	None	3	5
18	FM, M, 1	NB	Salvage	TVD	No	No	1	None	2	7
19	PS, F, 8	OS	Front line	CICLO-ETO	No	No	1	None	7	11
20	CC, F, 10	OS	Salvage	CICLO-ETO	No	No	1	None	8	12
21	BG, M, 11	Kidney Sarcoma	Salvage	CICLO-ETO	Yes, Abdomen 1.5 + boost 1.0	No	1	None	5	8
22	SC, F,18	Ewing	Salvage	CICLO-ETO	Yes, Lumbar spine, 5.1	No	1	None	6	10
23	PA, M, 13	OS	Salvage	CICLO-ETO	No	No	1	None	9	12
24	CG, M, 9	MED	Front line	HD ETO	No	No	1	None	3	7
25	DFA, F, 13	OS	Salvage	CICLO-ETO	No	No	1	None	7	11
26	PA, F, 15	OS	Salvage	CICLO-ETO	No	No	1	None	8	12
27	LFG, F,16	Ewing	Front line	CICLO-ETO	No	No	1	None	6	10
28	MA, M, 18	OS	Salvage	CICLO-ETO	No	No	1	None	5	11

Abbreviations: C-S = craniospinal radiotherapy; F = female; GERM = germinal tumour; M = male; MED = medulloblastoma; NA = not applicable; NB = neuroblastoma; NHL = non-Hodgkin's lymphoma; Osteo = osteosarcoma.

to the anti-cancer treatment. The remaining 23 courses were not complicated by any adverse events.

Discussion

Our study showed that one administration of 100 μg/kg PEG per cycle was safe and effective. It led to quick haematological recovery and a greater than 75% success rate of PBMC collection. All children but one who received intensive chemotherapy followed by PEG from day +3 after the end of the cycle experienced profound neutropaenia, that however, always resolved within 2 weeks after the end of the cycle. Thus, in the absence of concomitant prolonged thrombocytopaenia, the subsequent cycle of chemotherapy could always be administered in time. The incidence of primary febrile episodes that were observed in 13 out of the 32 courses of PEG (40%) is in line with our historical experience, as recently reported by Castagnola *et al*., who reported the epidemiology of febrile episodes during chemotherapy-induced periods of neutropaenia in 366 children.[1] Only three papers regarding the use of PEG in children have been published to date, and they all only analysed PEG efficacy in haematological recovery.[12–14] These reports state that PEG can be safely administered to children and that the duration of severe neutropaenia and the incidence of FN were comparable to those occurring after filgrastim. One paper reported a delay in treatment caused by persistent neutropaenia in 6% of patients. The same author reported that the main limiting factor related to the timely administration of the subsequent cycle of chemotherapy was thrombocytopaenia, which may have been an unwanted side effect of PEG in one-fourth of cases.[12] Children with poor-risk cancer, responding to first-line therapy or even to rescue therapy are often consolidated with high-dose chemotherapy followed by autologous PBMC transplantation. In this setting, filgrastim is the drug of choice for enhancing PBMC collection after myelosuppressive, mobilizing chemotherapy. Recently, an increasing number of trials studying the efficacy and characteristics of PEG-induced PBMC mobilization have been carried out in adult patients suffering from multiple myeloma, lung cancer and lymphoma.[15–20] All the authors provided support for the comparable efficacy of PEG to filgrastim in PBMC mobilization and CD34+ cell yield. To our knowledge, no data on PEG-induced PBMC mobilization and collection in children are currently available.

In our study, 26 cycles of mobilization were analysed in 22 patients and the success rate was 76.9% (20 mobilizations

Table 2 Neutropaenia and myeloid recovery in 31 assessable cycles

		Neutropaenia ⩽7 days n *(%)*		*Total*
		Yes	*No*	
Myeloid recovery ⩽15 days	Yes	27 (87)	4	31
	No	0	0	0
	Total	27	4	31

Table 3 Results of PBMC mobilization

UPN	*Initials, gender, age at PEG treatment*	*Diagnosis*	*CD34 peak per μl*	*Day of CD34 peak after PEG*	*CD34 >20 per μl (days)*
1	RS, M, 7	NB	90	9	7
2	MG, M, 1	MED	682	10	9
3	DN, F, 1	NB	124	13	8
4	DPG, F, 7	NB	257	14	8
5	AA, M, 3	NB	272	9	6
6	HS, M, 4	NB	75	13	7
			55	14	3
7	PR, M, 3	NB	55	13	5
			145	10	8
			Failure	—	—
8	MI, F, 2	NB	421	9	9
9	TD, M, 18	GERM	Failure	—	—
10	DS, F, 18	NHL	Failure	—	—
11	CE, F, 3	Wilms	207	9	6
12	GE, F, 11	NB	136	8	8
13	AD, M, 5	NB	147	8	6
			33	10	4
14	DCG, M, 9	NB	Failure	—	—
15	DPG, F, 8	NB	Failure	—	—
16	MB, F, 9	NB	Failure	—	—
17	FM, M, 1	NB	390	6	8
18	PS, F, 8	OS	405	7	4
19	CC, F, 10	OS	28	10	2
20	CG, M, 9	MED	809	8	5
21	DFA, F, 13	OS	212	9	4
22	LFG, F, 16	Ewing	182	7	4

Abbreviations: F = female; GERM = germinal tumour; M = male; MED = medulloblastoma; NB = neuroblastoma; NHL = non-Hodgkin's lymphoma.

in 17 patients). All the patients in this cohort bore one or more factors associated with the risk of mobilization failure, such as repeated cycles of myelosuppressive chemotherapy, previous or minimally persistent marrow infiltration, age above 10 years and craniospinal irradiation, which may explain the apparently low mobilization success rate. Furthermore, it must be pointed out that failure to harvest PBMCs was also observed under subsequent filgrastim stimulus in four of the six 'poor mobilizing' courses. This failure rate is in keeping with what was reported by Kroschinsky *et al*.,[17] who observed that patients bearing a similar series of risk factors did not respond to a 6 mg, single-dose administration of PEG. The author assumed that there was an equivalence between 6 mg of PEG and 5 μg/kg of filgrastim, therefore he presumed that a higher dose of PEG (that is, 12 mg, equivalent to approximately 10 μg/kg of filgrastim) was needed to treat the so-called 'poor mobilizers'. In our study, PEG administration was followed by PBMC harvest for a total of 19 procedures, and in 18 cases a cell dose higher than 3×10^6 per kg was yielded with only one apheresis. One interesting characteristic of PEG-induced PBMC mobilization is the long-lasting period during which circulating levels of CD34+ cells are higher than 20 per μl, that is, from 3 to 9 days (median 6.5 days). The PEG-induced PBMC mobilization kinetics, that substantially differs from what is usually observed in filgrastim-stimulated patients, can be explained by the increased serum residence time of PEG that is associated with nonfluctuating blood levels. As already reported by Isidori *et al*.,[16] the apparently greater mobilizing efficacy of PEG plays a relevant role, from an organizational point of view, by providing a wider range of days in which one or repeated apheresis can accurately be planned. Thus, we can confirm, even in a single-arm study and in a small number of patients, that PBMC mobilization in children receiving PEG is at least as feasible and effective as has been reported both in adults[16–20] and in a comparable cohort of paediatric patients who received filgrastim.[21] Even though performing a financial analysis was not an end point of the study, the higher cost of PEG has to be taken into account and studied together with all the other factors that are involved in the global care of the patient. The price of one single vial of PEG is comparable to that of approximately 11 daily vials of filgrastim (1489.49 vs 127.95 Euros per vial), thus, the current formulation of the pegylated form, which contains 6 mg of the drug, would be only financially advantageous in case of numerous filgrastim administrations. Moreover, most paediatric patients weigh less than 60 kg, and as the standard dosage is 100 μg/kg, a large part of the vial would be wasted. Furthermore, the number of filgrastim administrations is strictly related to the starting day of mobilization, which in most protocols is either day +3 or +5 after the end of chemotherapy, with a total of five/seven administrations needed for PBMC collection. At our centre, when filgrastim is given for mobilization, the policy is to delay administration until neutrophil nadir. This approach, which implies no more than 5 days of growth factor therapy at most, has proven to be cost effective.[22,23] In this case, the cost of PEG is clearly higher and its use is apparently not justifiable from a solely financial point of view.

Other factors have to be analysed when the costs and characteristics of PEG and filgrastim are compared. First, pain and discomfort associated with daily subcutaneous filgrastim administration can lead to a decrease in the child's compliance, whereas i.v. filgrastim administration requires daily management of the indwelling central venous catheter that is associated with an increased risk of infection, consequent hospitalization and the need for antibiotics.[24] Second, daily therapy means repeated visits to the outpatient clinic and an increased burden for health care professionals. Furthermore, if PEG were actually associated, as reported by some authors,[25] to a lower incidence of FN and to an easier and more successful PBMC yield, its higher cost could be warranted. Third, the long-lasting CD34+ cell mobilization may significantly reduce the risk of PBMC yield failures that often occur when the CD34 peak level is reached on weekends or during holidays.

In conclusion, the pegylated molecule of filgrastim has a great deal of appealing aspects, even for paediatric patients, especially in terms of improved compliance and better quality of life. Additional and relevant benefits such as a reduction in the incidence of FN and in the relative use of resources, better CD34+ mobilization and a wider window of PBMC collection time have to be verified in prospective trials involving large cohorts of patients. Likewise, in-depth studies need to be carried out in several areas, such as the role and dosage in 'poor mobilizers', the long-term side effects and the concerns related to the adult-oriented formulation and costs.

Acknowledgements

We thank Mrs Valerie Perricone for reviewing the text. This study has been supported in part by the Italian Ministry of Health, Programma di Ricerca Finalizzata 2005, ex Art. 12 D.Lgs 502/92, 'Assistenza Domiciliare in Bambini ed Adulti affetti da Patologie Emato-Oncologiche'.

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