A prospective study on the efficacy of mobilization of autologous peripheral stem cells in pediatric oncohematology patients

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BACKGROUND: Peripheral blood stem cells (PBSCs) are the preferred source in autologous transplantation. We assessed prospectively the efficacy of mobilization in pediatric patients and risk factors associated with its failure.

STUDY DESIGN AND METHODS: Patients, aged 0 to 17 years, needing a first collection of PBSCs for autologous stem cell transplantation were eligible. The study period was from July 2008 to September 2010. A blood peak of fewer than 20×10^6 CD34+ cells/L was used as the cutoff to define a poor mobilizer.

RESULTS: A total of 145 patients, 57% male (82) and 43% female (63), with a median age of 7 years, affected by solid tumor, 79% (114), and acute leukemia or lymphoma, 21% (31), were enrolled. Granulocyte–colony-stimulating factor used was filgrastim in 69%, lenograstim in 26%, and pegfilgrastim in 5% of patients. A total of 83% (121) of patients mobilized successfully, the median CD34+ count being 120×10^6/L (range, 23×10^6-1840×10^6/L). A single leukapheresis procedure was sufficient to achieve the target CD34+ cell dose in 82% (99/121) of patients. Among 24 poor mobilizer patients, 15 underwent a second mobilizing course and nine required a marrow harvest. Factors associated with poor mobilization were metastatic disease and relapse. Among 99 patients who underwent autologous stem cell transplantation, the median times to neutrophil and platelet engraftment and of hospitalization were longer by 2, 12, and 6 days in poor versus good mobilizer group.

CONCLUSIONS: In pediatric patients undergoing a first mobilization, the incidence of poor mobilization was 17%. Failure of mobilization resulted in an increase in health costs and a longer hospitalization for those who underwent autologous stem cell transplantation.

High-dose chemotherapy with stem cell rescue is still a key strategy in pediatric patients. It is indicated for the treatment of refractory or relapsed Hodgkin's and non-Hodgkin's lymphoma, high-risk solid tumors such as neuroblastoma and brain tumors, and extramedullary late relapse of acute lymphoblastic leukemia.[1-8]

In the past two decades the use of mobilized peripheral blood stem cells (PBSCs) has largely substituted marrow as source of progenitor cells in autologous transplantation because of the easier collection procedure and the faster hematologic recovery.[9,10] The most commonly used strategy of mobilization is the combination of chemotherapy with granulocyte–colony-stimulating factor (G-CSF), although there is a large variation in the type of chemotherapy drugs and the type, dose, and timing of administration of G-CSF.[10,11] Failure to collect a minimum number of PBSCs results in a delay of the intensification-

ABBREVIATIONS: OS = overall survival; PBSC(s) = peripheral blood stem cell(s).

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dose program with stem cell rescue. Moreover, an increase in health costs is expected for a further mobilization course or a marrow harvest.[12,13] In adults, several factors including patient age, prior treatment, type of treatment of underlying disease, and preleukapheresis platelet (PLT) and CD34+ cell counts have been associated with poor mobilization.[14,15] Despite PBSC collection being part of the routine treatment of several pediatric malignancies, no study has hitherto addressed the issue of the efficacy of mobilization regimens in pediatric patients and which factors, if any, may result in the failure of mobilization of peripheral autologous stem cells. The aim of this study was to assess prospectively the incidence of poor mobilizers in pediatric patients and the risk factors associated with failure of mobilization.

PATIENTS AND METHODS

Patients

This is a prospective observational study designed by the working groups for supportive care and hematopoietic stem cell transplantation of the Italian Association of Pediatric Hematology Oncology that was conducted from July 2008 to September 2010 in 10 centers that are members of the Italian Association of Pediatric Hematology Oncology.

Eligible patients were between 0 and 17 years and affected by leukemia, lymphoma, or solid tumor who were candidates for mobilization and PBSC collection for autologous transplant. This was indicated for patients at high risk of treatment failure such as metastatic solid tumors, presence of poor prognostic characteristics in the tumor cells, for example, *N-MYC* oncogene for neuroblastoma, or refractory, relapsed solid tumor, lymphoma, and leukemia. Only patients who were mobilized for the first time with a regimen based on chemotherapy and G-CSF were included. The study was approved by each local institutional review board and all parents or patients (where applicable) gave their informed consent. Follow-up data are as at September 2011.

Mobilization and collection procedures

Being an observational study, mobilizing chemotherapy and G-CSF schedules were left to the choice of the local investigator or were according to the protocol used for the treatment of the underlying disease. Considering a median interval time from the start of chemotherapy to CD34+ cells collection of 10 days,[11] the mobilization course was planned to avoid PBSC collection on a Saturday or Sunday. However, all centers had the facilities to collect and cryopreserve PBSCs at the weekend if needed. After mobilizing chemotherapy, blood count was checked every 2 to 3 days until the nadir of white blood cells (WBCs) was reached and then every 1 to 2 days until PBSC collection by leukapheresis. Daily CD34+ cell monitoring was started as WBC count reached 0.5×10^9 to 1.0×10^9/L and leukapheresis was scheduled when a blood peak of at least 20×10^6 CD34+ cells/L was reached, according to the Italian best practice consensus for peripheral blood cell mobilization and collection.[10] The target of PBSC collection was predefined by the investigator and was according to the patient protocol or investigator choice, but a minimum of 2×10^6 CD34+ cells/kg was always required.

Leukapheresis was performed daily by standard volume procedure using a cell separator (COBE Spectra, CaridianBCT, Inc., Lakewood, CO), although two used a different separator (Com.Tec, Fresenius Kabi AG, Bad Homburg, Germany) and was continued, if possible, until the target of PBSC collection was achieved. Patients failing to achieve a blood peak of 20×10^6 CD34+ cells/L by Day +21 from the start of the mobilizing course or before the withdrawal of G-CSF for WBC count of at least 15×10^9/L were classified as poor mobilizers. The failure of mobilization was managed according to the policy of each center and comprised either a subsequent course of mobilization with G-CSF, with or without chemotherapy, or a marrow harvest.

Clinical endpoints and definitions

The primary endpoint of the study was to assess the percentage of patients who obtained a blood peak of CD34+ cells of at least 20×10^6/L. The secondary endpoints were the proportion of patients who achieved the target of PBSC collection by a single mobilization procedure and the number of leukapheresis procedures needed for a successful procedure. Other secondary endpoints were the duration of severe neutropenia, the incidence and severity of mucositis, the incidence of febrile neutropenia and proven infection, and the time to polymorphonuclear (PMN) and PLT recovery after the mobilization course. Moreover, a descriptive comparison of transplant variables, type and duration of complications, duration of hospitalization, and overall survival (OS) was undertaken in the patients who underwent PBSC transplant according to poor or good mobilization outcome.

Myeloablation followed by autologous PBSC infusion was performed in high-efficiency particulate-filtered air rooms or isolation rooms according to the policy of the center and standard supportive care and preventive measures were adopted to prevent infectious complications during the neutropenic phase, that is, fluconazole for antifungal prophylaxis and acyclovir and cotrimoxazole for prophylaxis of herpes simplex virus and *Pneumocystis* infections, respectively. Fever, defined as the presence of an oral or axillary temperature of at least 38.5°C in a single measurement, or at least 38.0°C on two or more occasions taken at least 1 hour apart, was treated empirically with broad spectrum antibiotics.

Red blood cell and PLT products were filtered to remove WBCs and irradiated (25 Gy). PMN and PLT

recoveries were defined as the first of 3 and 7 consecutive days in which the counts were greater than 0.5×10^9 and 50×10^9/L (unsupported by transfusion), respectively.

Statistical analysis

Data of patients were collected prospectively by a specific case report form containing information on demographics (sex, age), disease (type, date of diagnosis, remission status), type of mobilizing chemotherapy, and complications (occurrence and duration of severe neutropenia, mucositis, infections) and PBSC collection (date of CD34+ cell peak, number of leukapheresis procedures to achieve the target PBSC dose); for patients who underwent PBSC transplant during the study period, type of conditioning regimen, number of CD34+ cells infused, early posttransplant complications (neutropenia, mucositis, infection, days of parenteral nutrition, antibiotic therapy), and date of last follow-up. In case of death, date and cause of death were recorded.

Descriptive statistics were reported as percentages for categorical variables and median and ranges for continuous variables. Characteristics of patients who were successful mobilizers were compared with patients who failed using chi-square or Fisher's exact test (as appropriate) in the case of discrete variables or the Mann-Whitney test, in the case of continuous variables. Variables that were significant in the univariate analysis were entered into a multivariate logistic regression model. Variables with a p value of less than 0.05 were considered significant. One-hundred-day OS and transplant-related mortality were assessed in patients who underwent hematopoietic stem cell transplantation by the Kaplan-Meier estimator and cumulative incidence method.

TABLE 1. Main demographic and clinical characteristics of enrolled patients

Characteristics	Number of patients	%
Total	145	
Sex		
Male	82	57
Female	63	43
Age at diagnosis/relapse (years)		
Median (range)	7.5 (0.1-17)	
Underlying disease		
Solid tumors*	114	79
Leukemia or lymphoma†	31	21
Marrow involvement at diagnosis		
Yes	26	18
No	108	74
Not assessed	11	8
Remission status at PBSC collection		
Complete remission	29	20
Very good partial remission	41	28
Partial remission	53	37
Stable disease	9	6
Not evaluable	13	9
Target dose of CD34+ $\times 10^6$/kg		
Median (range)	5.0 (2.0-12.0)	
Number of planned infusions		
1	99	68
2	43	30
3	3	2
Body weight (kg)		
Median (range)	24.4 (5.0-90)	

* Central nervous system, 48; neuroblastoma, 32; osteosarcoma, six; PNET/sarcoma, 21; retinoblastoma, five; Wilms tumor, two.
† Hodgkin's lymphoma, 16; non-Hodgkin's lymphoma, six; acute leukemia, nine.

RESULTS

During the study period 145 eligible patients were enrolled. Table 1 shows the main demographic and clinical characteristics. According to the center policy and/or treatment protocol, the desired target of CD34+ cells/kg reported by local investigators before starting the mobilizing chemotherapy was a median of 5 (range, 2-12).

Mobilization chemotherapy

Stem cell mobilization was obtained by a combination of multidrug chemotherapy and G-CSF. Table 2 shows the type, dose, and combination of drugs. The majority of the patients, 69% (100) received filgrastim as G-CSF whereas 26% (38) received lenograstim and 5% (7) received pegfilgrastim. The median duration of G-CSF administration, except for pegfilgrastim, was 7 days (range, 1-19 days), the dose being 5 to 10 μg/kg/day in 88% of the patients. Two percent of patients (3) received radiotherapy directed at the central nervous system (1), head and neck (1), and head and mediastinum (1) before mobilization with doses of 14.4, 45.9, and 47.7 Gy, respectively.

Toxicity of mobilizing chemotherapy

Severe neutropenia was the main complication reported in 79% of patients (115/145) with a median duration of 5 days (range, 2-46 days), followed by fever of unknown origin in 28% of patients (40/145) that lasted for a median of 3 days (range, 1-7 days). Another complication was mucositis in 15% of patients (22) that was scored as Grade I in six patients, Grade II in 12 patients, Grade III in three patients, and Grade IV in one patient. The median duration of mucositis was 4 days (range, 2-10 days).

Proven infections were 6% (9) with a median duration of 5 days (range, 1-12 days), as follows: seven sepsis by *Candida* spp., 1; *Escherichia coli*, 2; *Enterobacter cloacae*, 1; *Pseudomonas* spp., 1; and *Staphylococcus* spp., 2; additionally, there was one urinary tract infection by *E. coli*, one enteritis by *Clostridium difficile*, and one pneumonia of unknown origin. Overall, 19% of patients (28) were hospitalized for toxicities after mobilizing chemotherapy for a median of 6 days (range, 2-16 days).

TABLE 2. Drugs used alone or in combination as mobilizing chemotherapy

Number of drugs used	Type of drugs and doses	Number of patients
1	Etoposide 2400-2600 mg/m^2	27
	Ifosfamide 15 g/m^2	3
	Methotrexate 5 g/m^2	1
	Cyclophosphamide 1.5-3.0 g/m^2	3
		Subtotal 34
2	Cytarabine 18 g/m^2–etoposide 120-500 mg/m^2	3
	Cytarabine 9 g/m^2–mitoxantrone 20 mg/m^2	1
	Cyclophosphamide 4.0 g/m^2–etoposide 600 mg/m^2	16
	Cyclophosphamide 1.0-4.0 g/m^2–vincristine 1.5 mg/m^2	7
	Vincristine 0.5-1.5 mg/m^2–cisplatin 56-80 mg/m^2	25
	Cisplatin 90-120 mg/m^2–etoposide 450 mg/m^2	10
	Ifosfamide 10.0 g/m^2–etoposide 600-625 mg/m^2	2
	Etoposide 450 mg/m^2–cisplatin 120 mg/m^2	1
	Topotecan 4.0 mg/m^2–carboplatin 325.0 mg/m^2	1
	Topotecan 3.5 mg/m^2–cyclophosphamide 1000 mg/m^2	1
	Ifosfamide 12.8 g/m^2–cisplatin 176.0 mg/m^2	1
		Subtotal 68
3	Ifosfamide 10 g/m^2–etoposide 600 mg/m^2–prednisone 300 mg/m^2	11
	Ifosfamide 10 g/m^2–etoposide 300 mg/m^2–prednisone 300 mg/m^2	1
	Ifosfamide 4-10 g/m^2–etoposide 300-500 mg/m^2–carboplatin 500-1200 mg/m^2	6
	Ifosfamide 9 g/m^2–vincristine 1.5 mg/m^2–etoposide 450 mg/m^2	3
	Carboplatin 550-800 mg/m^2–etoposide 360-450 mg/m^2–ifosfamide 5.5-6 g/m^2	2
	Ifosfamide 9 g/m^2–vincristine 1.4 mg/m^2–doxorubicin 90 mg/m^2	1
	Vincristine 1.5 mg/m^2–cyclophosphamide 2100 mg/m^2–etoposide 175 mg/m^2	1
	Topotecan 3.8-7.5 mg/m^2–vincristine 2.0 mg/m^2–adriamicin 45 mg/m^2	3
	Cisplatin 100 mg/m^2–cytarabine 4 g/m^2–dexamethazone 80 mg/m^2	1
		Subtotal 29
4	Ifosfamide 2.4-6 g/m^2–carboplatin 560-600 mg/m^2–etoposide 300-450 mg/m^2–vincristine 1.5 mg/m^2	5
	Vincristine 1.5 mg/m^2–cytarabine 600 mg/m^2–etoposide 200 mg/m^2–methotrexate 5.0 g/m^2	1
	Vindesine 3 mg/m^2–cytarabine 12 g/m^2–etoposide 500 mg/m^2–dexamethazone 100 mg/m^2	3
	Ifosfamide 10.3 g/m^2–carboplatin 1030 mg/m^2–etoposide 680 mg/m^2–rituximab 375 mg/m^2	1
		Subtotal 10
5	Cytarabine 3 g/m^2–IDA 10 mg/m^2–vincristine1.5 mg/m^2–etoposide 450 mg/m^2–dexamethazone 35 mg/m^2	3
		Subtotal 3
6	Dexamethazone 100 g/m^2–6-mercaptopurin 500 mg/m^2–vincristine 1.5 mg/m^2–methotrexate 1 g/m^2–cytarabine 8 g/m^2–L-asparaginase 10,000 U/m^2	1
		Subtotal 1

TABLE 3. Summary of the results of mobilizing chemotherapy

Results	Number of patients	%
Number of patients with blood CD34+ peak >20 × 10^6/L		
Yes	121	83
No	24	17
Value of CD34+ blood count at first mobilization		
Median (range)	120 (23-1840)	
Number of patients who achieved the planned target CD34+ dose		
Yes	102	70
No	42	29
NA	1	1
Yield of CD34+ ×10^6/kg		
Median (range)	12.0 (3.5-78.7)	
Time interval from the start of mobilizing chemotherapy to CD34+ collection (days)		
Median (range)	13 (8-29)	
Number of days of leukapheresis needed for achieving the target CD34+ dose		
Median (range)	1 (1-3)	

Effectiveness of mobilizing chemotherapy

Table 3 shows the results of mobilizing chemotherapy. A total of 83% of patients (121/145) were classified as good mobilizers. In 82% of patients (99) the scheduled target cell dose was collected with a median number of one leukapheresis procedure (range, 1-3); among them, 90% patients (89) achieved this target at first leukapheresis. Among the remaining 22 patients, four patients underwent

TABLE 4. Analysis of factors associated with the outcome of mobilization*

Factors	Good mobilizer	Poor mobilizer	Univariate p value	Multivariate OR	Multivariate p value
Sex	121	24			
Male	69 (84)	13 (16)	0.8		
Female	52 (83)	11 (17)			
Age (years)					
Median (range)	4.6 (1.6-17.6)	7.8 (0.1-19.5)	0.5		
Underlying disease					
Solid tumor†	94 (82)	20 (18)	0.5		
Leukemia or lymphoma‡	27 (87)	4 (13)			
Remission status at PBSC collection§					
CR or VGPR	57 (81)	13 (19)	0.9		
PR or stable disease	51 (82)	11 (18)			
Body weight (kg)					
Median (range)	27 (5-90)	17 (10-90)	0.8		
Bone marrow involvement at diagnosis					
Yes	19 (73)	7 (27)	0.07	3.5 (1.1-11.1)	0.03
No	95 (88)	13 (12)			
Indication to PBSC collection					
High-risk disease at diagnosis	104 (87)	16 (13)	0.04		
Relapse or second tumor	17 (68)	8 (32)		5.7 (1.7-18.8)	0.004
Number of cycles of premobilizing chemotherapy					
Median (range)	3 (0-11)	4 (0-17)	0.1		

* Data are reported as number (%) unless otherwise specified.
† Central nervous system, 48; neuroblastoma, 32; osteosarcoma, six; PNET/sarcoma, 21; retinoblastoma, five; Wilms tumor, two.
‡ Hodgkin's lymphoma, 16; non-Hodgkin's lymphoma, six; acute leukemia, nine.
§ Remission status before mobilizing course not evaluated in 13 patients.
CR = complete remission; PR = partial remission; VGPR = very good partial remission.

a second mobilizing course and one patient underwent autologous marrow harvest to achieve the target CD34+ cell dose, whereas 16 patients proceeded to PBSC transplant despite a suboptimal CD34+ cell dose collection; one last patient became ineligible for autologous transplant and no further procedure of stem cell collection was performed. The second mobilizing procedure was successful in only one patient whereas it failed in three patients. Two of these three patients underwent a marrow harvest whereas one patient underwent a third mobilizing course. Overall, in good mobilizer patients, the need for a second mobilizing course was 3% (4/121), and the need for a rescue procedure of bone marrow harvest was 2% (3/121).

Poor mobilizers

Seventeen percent of patients (24/145) were classified as poor mobilizers, the median CD34+ cell count being 7 (range, 1.4-19). They were 13 males and 11 females with a diagnosis of leukemia or lymphoma in four and solid tumors in 20. Eight of 24 patients were mobilized after a relapse. The status of the underlying disease was complete remission in five, partial remission in five, very good partial remission in eight, and stable in six. Three of 24 (13%) achieved the target CD34+ cell dose by repeated leukapheresis procedures (three leukapheresis procedures in two patients, two leukapheresis procedures in one patient) whereas five patients underwent directly a marrow harvest. Among the remaining 16 patients, 15 underwent a second mobilizing course and four of them also required a marrow harvest whereas one patient became ineligible for PBSC collection due to disease progression. Overall, in poor mobilizer patients, the need for a second mobilizing course was 62.5% (15/24) and the need for a rescue procedure of marrow harvest was 21% (5/24).

Risk factors for mobilization

Factors such as sex, age at diagnosis or relapse, body weight, type of underlying disease, remission status before PBSC collection, marrow at diagnosis, PBSC collection at first diagnosis versus PBSC at relapse, and number of courses of chemotherapy before mobilizing chemotherapy were analyzed to assess their impact on mobilization. Only the presence of marrow involvement at diagnosis and a history of relapse were associated with poor mobilization. These factors remained significant in multivariate analysis ($p = 0.03$ and $p = 0.004$, respectively). The results are shown in Table 4.

Transplant data

By September 2011, 69% of patients (99/144) who had stem cells collected underwent transplant. Table 5 summarizes the main transplant data for the groups of poor and good mobilizers. No statistical differences were found between the two groups regarding sex, age, body weight, type of underlying disease, remission status before

TABLE 5. Comparison of main transplant characteristics of good and poor mobilizer patients who underwent hematopoietic stem cell transplantation*

Transplant characteristics	Good mobilizers, 84	Poor mobilizers, 15	Total, 99	p value
Sex				
Male	47 (56)	8 (53)	55 (56)	NS
Female	37 (44)	7 (47)	44 (44)	
Age at diagnosis or relapse (years)				
Median (range)	5.7 (0.1-19.5)	5.1 (1.6-16.8)	5.7 (0.1-19.5)	NS
Body weight (kg)				
Median (range)	20 (5-90)	18 (10-90)	20 (5-90)	NS
Underlying disease				
Solid tumors†	72 (86)	11 (73)	83 (84)	NS
Leukemia or lymphoma‡	12 (14)	4 (27)	16 (16)	
Marrow involvement at diagnosis				
Yes	18 (23)	5 (42)	23 (26)	NS
No	60 (77)	7 (58)	67 (74)	
Remission status at PBSC collection				
Complete remission or very good partial remission	37 (51)	10 (67)	47 (54)	NS
Partial remission or stable disease	35 (49)	5 (33)	40 (46)	
Conditioning regimen				
Busulfan, melfalan, with or without other	28 (34)	9 (60)	37 (38)	NS
Thiotepa	33 (40)	2 (13)	35 (36)	
Other combinations	21 (26)	4 (27)	25 (26)	
Time from mobilizing course to autologous transplant				
Median (range)	98 (35-280)	110 (49-248)	98 (35-280)	NS
CD34+ $\times 10^6$/kg infused†	6.4 (3-46.1)	3 (0.65-4.25)	5.65 (0.65-46.1)	<0.01
Total nucleated cells $\times 10^8$/kg infused‡				
Median (range)		3.55 (2-6.5)	3.55 (2-6.5)	
Neutrophil engraftment (%)§	100	100	100	
Time to neutrophil engraftment (days)				
Median (range)§	11 (8-23)	13 (5-57)	11 (5-57)	0.04
PLT engraftment ($\geq 50 \times 10^9$/L)§	100% (82/82)	93% (14/15)	99% (96/97)	
Time to PLT engraftment (days)				
Median (range)§	17 (5-72)	29 (13-277)	19 (5-277)	0.002
Mucositis§				
Yes	88% (72/82)	100% (15/15)	90% (87/97)	NS
Mucositis, grade				
I-II	78% (64/82)	80% (12)	87% (76)	
III-IV	22% (8)	13% (2)	11% (10)	
Not applicable	0	7% (1/15)	2% (1)	
Duration of mucositis (days)				
Median (range)	10 (3-44)	11 (6-44)	10 (3-44)	NS
Fever of unknown origin				
Yes	18% (15/82)	21% (3/14)	19% (18/96)	
Duration of fever of unknown origin (days)				
Median (range)	1 (1-6)	1 (1-5)	1 (1-6)	NS
Episodes of bacteremia	60% (49/82)	67% (10/15)	61% (59/97)	
Use of G-CSF	58% (49/84)	80% (12/15)	62% (61/99)	NS
Duration of G-CSF (days)				
Median (range)	8 (1-32)	11 (6-17)	8 (1-32)	0.02
Days of hospitalization	18 (2-127)	24 (17-60)	18 (2-127)	<0.01
Alive patients	70	13	83	
Follow-up from transplant (years)				
Median (range)	0.7 (0.16-1.5)	1 (0.15-2.8)	0.8 (0.15-2.8)	
Dead	14	2	16	
100-day transplant-related mortality (CI)	1% (0.2-8)	0%	1% (0.14-7)	
100-day OS (CI)	96% (89-99)	100%	97% (91-99)	
180-day OS (CI)	93% (59-99)	92% (84-97)	92% (85-96)	

* Data are reported as number (%) unless otherwise specified.
† Calculated on 89 patients who received PBSCs and five patients who received both marrow and PBSCs.
‡ Calculated on five patients who received bone marrow and five patients who received both marrow and PBSCs.
§ Data for PMN, PLT engraftment, and mucositis available for 82 of 84 good mobilizer patients.
NS = not significant.

transplant, and conditioning regimen. The poor mobilizer patients received a median number of CD34+ cells/kg significantly lower than good mobilizers (3 versus 6.4, $p < 0.01$). Moreover, eight patients needed marrow stem cells, four to supplement the peripheral stem cell dose and four as the only source of stem cells. Overall, 83 patients are alive at a median follow-up of 0.8 years (range, 0.15-2.8 years), whereas 16 patients died at a median of 187 days (range, 31-373), from autologous transplant. The causes of death were progression of disease or relapse in 11 patients, severe organ toxicity in four patients (venoocclusive disease one, thrombotic thrombocytopenic purpura one, heart failure two), and bacterial meningitis in two patients. The groups of poor and good mobilizers differed significantly regarding the time needed for PMN and PLT engraftment, days of G-CSF administration, and days of hospitalization, these being in median more than 2, 12, 3, and 6 days, respectively. No statistical difference was found in early transplant-related mortality and OS between two groups.

DISCUSSION

The use of mobilized PBSCs has largely substituted the need for a marrow harvest due to the faster hematopoietic recovery that translates into fewer infection-related complications, shorter duration of hospitalization, and eventually lower health costs.[5] Several different mobilization regimens have been used so far but none assures 100% success. The failure to mobilize a minimum of 2×10^6/kg CD34+ cells is reported in approximately 50% of adult patients[16,17] and is usually managed by repeating one or more mobilization courses or by performing a salvage harvest of marrow stem cells. Both these strategies carry the risk of increasing patient morbidity due to neutropenia, mucositis, or infection, while increasing resource utilization and health costs and compromising timely intensification.[13] Although the use of autologous PBSC transplant is well established in the pediatric setting, the data regarding the efficacy of mobilization and the modality of managing the failures have been less often investigated.

In this study the poor mobilizers were 17%, which is less than the incidence usually reported for adults but comparable to that found in a recent Phase II study where the efficacy of pegfilgrastim was assessed against a historical control group stimulated with filgrastim.[11] This can be explained by the fact that the study population lacked risk factors considered predictive of poor mobilization such as older age, previous mobilization failure, and previous receipt of high-dose chemotherapy, and also the exposure to radiation was limited to only 2% of patients. Moreover, almost 80% of this population was affected by a solid tumor in which, as distinct from leukemia and lymphoma, the involvement of marrow is less frequent.[14] In concordance with this, the factors associated with inadequate mobilization of PBSCs in our analysis were the presence of metastases at diagnosis and disease in relapse, which may both reflect a marrow hypocellularity due to disease involvement or limited regenerative capacity due to previous intensive chemotherapy.

Many combinations of chemotherapy drugs have been adopted because, in line with an observational study, PBSC collection was almost always performed after a cycle of first-line treatment protocols. In this study, the dosages of G-CSFs were consistent with recent recommendations,[10] although most patients received filgrastim. On the basis of available data, the efficacy of PBSC mobilization is not influenced by the type of G-CSF, that is, filgrastim versus lenograstim, while pegfilgrastim is advantageous for its easier single-shot administration but not for a superior efficacy.[18]

We confirm that the occurrence of poor mobilization was associated with an increased use of health resources as demonstrated by the need for a second mobilization course or marrow harvest in more than 80% of poor mobilizer patients compared to only 5% of good mobilizer patients. Moreover, the poor mobilizers needed a higher number of leukapheresis procedures to collect the target number of CD34+ cells and were more frequently transplanted with a suboptimal dose of CD34+ cells that resulted into a longer duration of posttransplant G-CSF administration, slower PMN and PLT engraftment, and additional length of hospitalization.

The recent demonstration that plerixafor has a synergistic effect in stem cell mobilization when combined with G-CSF raises the question of whether its high cost is justified to prevent poor mobilization or improve management without increasing patient morbidity or duration of hospitalization.[16,17,19] In this study, the treatment of complications of the mobilizing course such as febrile neutropenia, sepsis, and mucositis resulted in 19% of patients being hospitalized. Although plerixafor has the potential for improving the efficacy of all mobilization regimens, its universal use is not justified in a population with a limited incidence of poor mobilizers. Rather, plerixafor is ideal for a patient who is predicted to be a poor mobilizer on the basis of a low CD34+ peak after G-CSF stimulation or considered at high risk of failure for the presence of unfavorable characteristics or the failure of a previous mobilization.[20,21] This early intervention can become the mainstay to manage pediatric poor mobilizers instead of repeating the mobilization course or performing a marrow harvest. Currently, the use of plerixafor is off-label for pediatric patients and the published data are limited to case reports or small case series of five to eight patients.[22-28] Overall, plerixafor has been used on a compassionate basis in 36 patients affected by solid tumor or non-Hodgkin's lymphoma, as add-on or salvage therapy together with G-CSF. Eighty-one percent (29/36) of

patients achieved the collection of a minimum CD34+ dose of 2×10^6/kg and all transplanted patients engrafted successfully.

In this study, no difference was found between good and poor mobilizers in terms of early transplant-related mortality and OS. Despite a reported possible impact of low stem cell dose on OS, our data are in line with the observation that a higher CD34+ cell dose has a role in speeding the posttransplant hematopoietic recovery and reducing the length of hospitalization, whereas it does not affect OS provided that a minimum of 2×10^6 CD34+ cells is infused.[29,30]

In conclusion, we showed that poor mobilization can occur in pediatric patients with an incidence of 17%. The management of poor mobilizers is associated with an increased utilization of health resources and a longer time of myeloid recovery and hospitalization. These data can help design the strategy of future mobilization protocols in pediatric patients with the aim of minimizing cost and optimizing the use of health resources.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to **TRANSFUSION**.

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