Stem Cell Transplantation

The pros and cons of split-dose granulocyte colony-stimulating factor alone rather than a single high dose for hematopoietic progenitor cell mobilization in small children (< 15 kg) with solid tumors

Hematopoietic progenitor cells were mobilized in 34 children with solid tumors weighing ≤15kg using granulocyte colony-stimulating factor alone at the doses of 10, 20 or 2×12 μg/kg/day. The mobilization with 2×12 μg/kg/day was more efficient than that with 10 μg/kg/day. Although the superiority of the split-dose compared to the single, high daily dose (20 μg/kg/day) was not statistically significant, our results suggest that the 2×12 μg/kg/day regimen is interesting.

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Although treatments with hematopoietic progenitor cell rescue and/or *ex vivo* graft modification require a large number of hematopoietic progenitor cells to be collected, it is particularly desirable to minimize both the number and the duration of aphereses in very low weight children. To accomplish both the above requirements, the mobilization regimens must be optimized. The use of granulocyte colony-stimulating factor (G-CSF) alone to mobilize hematopoietic progenitor cells has been well documented.[1-3] Most of these studies support the administration of G-CSF at a once-daily dose of 10 μg/kg, and only little information is available on split-dose schedules in pediatric patients.[4,5] We present a retrospective comparative study of 3 sequential cohorts of children weighing 15 kg or less with solid tumors who received G-CSF alone at standard, high or split doses for hematopoietic progenitor cell mobilization.

Between January 1995 and July 2005, 34 children weighing 15 kg or less with solid tumors were referred to our center for hematopoietic progenitor cell collection. They all received G-CSF (filgrastim, Amgen) alone for 4 days for mobilization in hematologic steady state and formed three sequential cohorts. Cohorts 1 and 2 received, respectively, a standard dose of 10 μg G-CSF/kg once daily and a high dose of 20 μg G-CSF/kg once daily. Cohort 3 received a split-dose of 12 μg G-CSF/kg twice a day. Aphereses were performed using a Cobe Spectra separator (Gambro BCT, Bourg-la-Reine, France) as described elsewhere.[6] The-end points for this analysis were: (i) blood CD34$^+$ cell count at first collection and peak blood CD34$^+$ count; (ii) the number of CD34$^+$cells harvested from one patient blood volume processed during the first apheresis. Additional evaluations and measures of outcome are reported in Table 1. Statistical analyses consisted of Wilcoxon and χ^2 tests.

All findings are reported in Table 1. There were no differences between the three cohorts with regard to the patients' characteristics or previous treatment. Blood CD34$^+$ cell count at the time of the first apheresis was significantly higher among the patients who received the split-dose G-CSF regimen (median 161×10^6/L, range 10-573) than in those who received a standard, once daily dose (median 27×10^6/L, range 3-126) (p<0.01). The blood CD34$^+$ cell count in the cohort of patient's who received the high, once-daily dose was found to be intermediate (median 121×10^6/L, range 11-195) amd not significantly different from that of either of the two other cohorts (p=0.2). The split dose permitted the collection of a higher number of CD34$^+$ cells from one processed blood volume (6.5×10^6/kg body weight [BW]) compared to the standard, once daily dose (1.11×10^6/kg BW) (p<0.01), and to the high-once-daily dose (2.61×10^6/kg BW) (p=0.1). The overall proportion of patients who required more than one apheresis was notably lower in the split-dose cohort (3/14) than in the standard, once daily dose (10/10, p=0.002) or high, once-daily dose (9/10, p=0.01)

Table 1. Characteristics of the study population, mobilization and yield of hematopoietic progenitor cells after G-CSF mobilization at 10, 20 and 2×12 μg/kg body weight in pediatric patients with solid tumors weighing 15 kg or less.

	10 μg/kg	*20 μg/kg*	*2×12 μg/kg*
N. of patients	10	10	14
Demographic variables of patients			
Age (years, range)	3 (1.5 - 4)	2.6 (1.2 - 4.5)	2.1 (0.7 - 3.6)
Sex (F/M)	3/7	5/5	4/10
Body weight (BW) (kg, range)	12 (10-15)	12.5 (8 - 15)	11 (7.4 - 14)
Body surface area (m^2, range)	0.5 (0.4-0.6)	0.5 (0.4 - 0.6)	0.5 (0.4-0.6)
Diagnosis			
Neuroblastoma	8	5	11
Brain tumor	1	3	0
Rhabdomyosarcoma	1	1	1
Nephroblastoma	0	1	2
Diagnosis apheresis interval (weeks)	24 (11 - 78)	21 (10 - 53)	15 (7 - 34)
		p<0.01	
First apheresis		NS	NS
Blood CD34$^+$ cell count at first apheresis (10^6/L)	27 (3 - 126)	121 (11 - 195)	161 (10 - 573)
Processed blood volume (fold, range)	2.5 (1.7 - 4.6)	3.5 (0.8 - 5)	2.3 (1.6 - 3.2)
		p<0.006	
		NS	NS
Harvested CD34$^+$ cells×10^6/kg BW	3 (0.4 - 11.8)	10.1 (3.2 - 31.7)	14.5 (1.6 - 68.4)
Harvested CD34$^+$ cells×10^6/kg/PBV	1.1 (0.2-3.5)	2.6 (0.7-9)	6.5 (0.7-25.5)
Patients who achieved 2.5×10^6/kg/PBV CD34$^+$cells	2/10	6/10	12/14
		p<0.01	
Total collection (1st+/-2nd+/-3rd apheresis)		NS	NS
Peak of CD34$^+$ cell count (10^6/L)	39 (3-126)	121 (19-195)	161 (10-573)
N. of pts. undergoing more than one apheresis	10/10	9/10	3/14
Processed blood volume (fold, range)	5.8 (4.7-8.4)	4.8 (2.9-7.7)	2.7 (1.6-5.8)
Harvested cells CD34$^+$cells ×10^6/kg	6.6 (1.6-31.1)	11.9 (5.6 - 31.8)	14.5 (4.80-68.4)
Harvested cells CD34$^+$ cells ×10^6/kg/PBV	1.1 (0.3-4.5)	2.7 (0.8-9)	6.5 (0.9-25.5)
Patients who achieved 3×10^6/kg CD34$^+$ cells	9/10	10/10	14/14
Patients who achieved 1.5×10^6/kg/PBV CD34$^+$ cells	3/10	7/10	12/14

Data are presented as median values and ranges. p-values were calculated using Wilcoxon test. BV denotes calculate blood volume of the patients. PBV: processed blood volume.

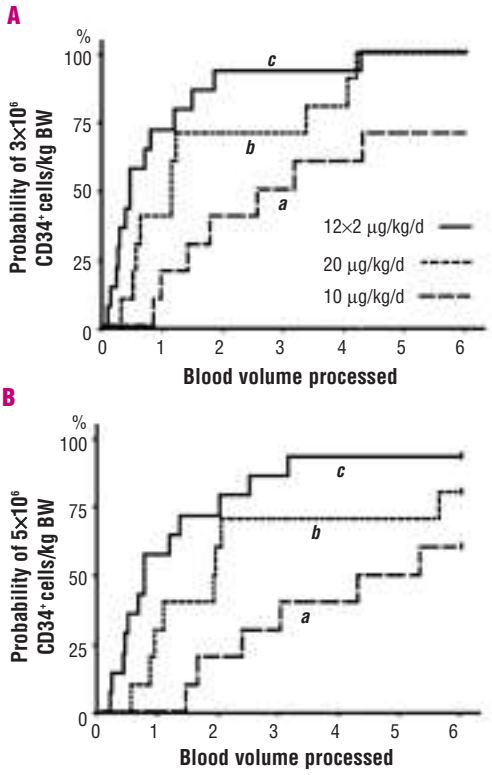

Figure 1. Probability of obtaining a target graft depending on the number of blood volumes processed: *a* (n=10), 10 µg/kg/BW once daily (– –); *b* (n=10), 20 µg/kg/BW once daily (- - - -); c (n=14), 12 µg/kg/BW twice daily (—). A. Probability of obtaining a target dose of 3×10^6 CD34⁺cells/kg BW: a *vs* b (p=0.05); B. Probability of obtaining a target dose of 5×10^6 CD34⁺ cells/kg BW: a *vs* b (p=0.05); b *vs* c, (p=0.1).

(Table 1) cohorts. The only three patients who did not achieve the threshold value of 31×10^6 CD34⁺ cells/kg BW within six processed blood volumes belonged to the first cohort. They had not been more heavily pretreated and had not been expected to be *bad mobilizers*. Mobilization regimens were well tolerated with adverse events limited to low-grade fever, general discomfort and nausea. Mild thrombocytopenia ($\times10^9$/L) occurred in three patients, and hyperleukocytosis >70×10^9/L in one patient, but in no case led to discontinuation of G-CSF. Neither the frequency nor the severity of adverse events was increased in the third cohort (p=0.6).

We found a clear enhancement of CD34⁺ cell collection efficiency by using a high dose of G-CSF split into two daily doses (2×12 µg/kg/day) compared to the standard dose (10 µg/kg/day administered once daily). This confirms the benefits suggested in older children by Sevilla and Perez-Duenas.[4,5] In this study we were not able to show statistical differences in terms of overall CD34 collection, CD34/kg/processed blood volume, CD34 collection in the first apheresis and CD34 blood count between the cohorts receiving 20 µg/kg/once daily and the 12 µg/kg twice daily. The limited population is a possible explanation. Although the number of CD34⁺ cells harvested was not significantly different between patients receiving 20 µg/kg/once daily or 2×12 µg/kg/twice daily, more patients in the single-dose group underwent more than one apheresis (90% vs. 20%). Likewise, large volume leukaphereses (>3 processed blood volumes) were more frequently performed in those patients receiving a single dose of G-CSF per day (60% vs. 7%). Finally, the minimum target cell number collected with < 3 processed blood volumes was obtained in 93% of patients receiving two doses of G-CSF per day vs. 80% of those receiving the high dose once daily. These findings seem to counterbalance the disadvantages of the higher number of G-CSF injections administered in patients receiving two daily doses. Administering G-CSF in a single dose and avoiding one subcutaneous injection would be beneficial, but avoiding a second apheresis would be a greater advantage in infants.

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