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ENGRAFTMENT KINETICS AND LONG-TERM STABILITY OF HEMATOPOIESIS FOLLOWING AUTOGRAFTING OF PERIPHERAL BLOOD STEM CELLS

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ABSTRACT

Background. **We analyzed short-term and sustained hematopoietic reconstitution after high-dose therapy with peripheral blood stem cell (PBSC) support in patients with various malignant disorders.**

Methods. **Fifty-six patients, all with malignant hematologic disorders, were autografted between 1989 and 1994 using PBSC (47 pts) or PBSC + bone marrow (BM) cells (9 pts). PBSC were collected after mobilization with chemotherapy±hematopoietic growth factors (GF).**

Results. **All patients engrafted $> 0.5\times10^9$/L polymorphonuclear cells (PMN) and $>50.0\times10^9$/L Plt at a median of 12 (8-32) and 13 (9-365) days, respectively. Thirty-nine patients were evaluable for long-term graft performance, and their hematologic values at 30 and 100 days, at 6 months and at 1, 2, 3, 4 and 5 years were retrospectively analyzed. Steady counts were recorded over the years. None of the patients had late graft failure.**

Conclusions. **PBSC given after high-dose chemotherapy ensure a fast hematologic recovery with stable graft performance up to five years after autograft. Though this is not definitive proof of the presence of uncommitted stem cells in the PBSC population, it gives further support to the idea that PBSC are as safe as bone marrow for long-term engraftment. A delayed or incomplete recovery of platelets may occur with low PBSC counts or when disease relapse occurs rapidly after autograft.**

Key words: PBSC, autograft, engraftment, growth factors

Autologous bone marrow transplantation (ABMT) allows the administration of very high doses of chemotherapy and is now used in the treatment of a variety of tumors. As an alternative to ABMT, the hematopoietic system can be reconstituted with peripheral blood stem cells (PBSC) collected by apheresis during recovery from cytotoxic agents.[1-3]

Since the first PBSC autograft in 1985,[4] this new technique has been increasingly employed. In the last few years clinical evidence has been gathered that PBSC autografting allows more rapid granulocyte recovery[5,6] with reduced post-transplant morbidity and resource utilization.[7] The difficulty in collecting PBSC has been overcome with the use of hematopoietic growth factors (GF) which are able to promote an exodus of PBSC from the bone marrow (BM) into the peripheral blood.[8-10] Since the introduction of GF, PBSC harvesting has been facilitated to the point that the number of PBSC required for a transplant is thought to be obtainable by standard phlebotomy.[11]

Laboratory experiments show that not only committed progenitors, but also long-term repopulating cells enter the circulation after mobilization with chemotherapy and G-CSF.[8,12,13]

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However, the nature of PBSC has not been completely defined.[14,15]

To evaluate the safety of PBSC transplantation (PBSCT) we retrospectively analyzed short-term and sustained hematopoietic reconstitution in a heterogeneous population of patients with various malignant disorders receiving PBSC or PBSC+bone marrow (BM) as autologous rescue after high-dose chemotherapy.

Materials and Methods

Patients

Fifty-six patients (median age 44.5 years, range 9-61, M/F=31/25) with malignant disorders [non Hodgkin's lymphoma (NHL) = 18, Hodgkin's disease (HD) = 9, multiple myeloma (MM) = 20, chronic myeloid leukemia (CML) = 5, acute myeloid leukemia (AML) = 1, amyloidosis = 1, breast cancer = 1, Ewing's sarcoma = 1] were autografted from 1989 to 1994 with PBSC alone (47 pts) or PBSC+BM cells (9 pts) (Table 1). The interval between diagnosis and transplant was similar for patients with MM, NHL and HD (median 14.6, 10.0 and 19.0 months, respectively), while it was longer (49.6 months) for CML patients (Table 2).

Circulating progenitor cell (CPC) mobilization and collection

In order to mobilize PBSC into the circulation we employed high-dose cyclophosphamide (4 to 7 g/m^2) in 34 patients; VCAD (vincristine, 2 mg on day 1, cyclophosphamide, 0.5 g/m^2 on days 1 to 4; adriamycin, 50 mg/m^2 on days 1 and 2; dexamethasone, 40 mg/day iv on days 1 to 4)[16] in 11 patients; VCED (vincristine, 2 mg on day 1; cyclophosphamide, 0.5 g/m^2 on days 1 to 4; epirubicine 120 mg/m^2 on days 1 and 2; dexamethasone, 40 mg/day iv on days 1 to 4) in 4 patients; DHAP (cis-platinum 100 mg/m^2, Ara-C 2×3 g/m^2, dexamethasone 4×40 mg/m^2) in 2 patients; high-dose (4×2 g/m^2) cytosine arabinoside in 1, DAT (daunorubicin, 45 mg/m^2 on day 1, cytosine arabinoside, 240 mg/m$^{2\,0}$ on days 1 to 5; thioguanine 240 mg/m^2 on days 1 to 5) in 1 patient; CY-Dexa (cyclophosphamide, 1.5 g/m^2 on days 1 and 3; dexamethasone, 40 mg on days 1 to 3) in 1, and CE (cyclophosphamide, 4 g/m^2 on day 1, etoposide 200 mg/m^2 on days 2 to 4) in 1 patient. For mobilization 31 patients also received GF, either granulocyte colony-stimulating factor (rhG-CSF, filgrastim) or granulocyte-macrophage colony-stimulating factor (rhGM-CSF, ecogramostim), starting the day after the end of chemotherapy and continuing until the last apheretic procedure or when the WBC count exceeded 40×10^9/L (Table 1). In one case peripheral blood progenitors were recruited by G-CSF alone (16 mcg/day sc for 4 days). Aphereses were started at the time of rapid peripheral count increase (WBC > 1.0×10^9/L and PLT > 50.0×10^9/L) following chemotherapy, with collections performed daily or on alternate days. Procedures were carried out with either continuous flow (Baxter CS 3000, Fresenius AS 104) or discontinuous flow (Haemonetics V-50) devices programmed to collect mononuclear cells; 9-10 litres of blood were processed per run. A median of 3 (range 1-13) aphereses/patient were performed.

Preparative regimens

The preparative regimens employed varied widely. The majority part of patients with lymphoma (HD or NHL) received the CBV combination (cyclophosphamide, 1.5 g/m^2/day on days –6 to –3; BCNU, 150-200 mg/m^2/day on

Table 1. Patient characteristics.

No. of patients		56
Age median (range)		44.5 (9-61)
Sex (M/F)		31/25
Diagnosis:	NHL/HD/MM	18/9/20
	CML/Other	5/4
Transplant type:	PBSC	47
	PBSC+BM	9
Mobilization:	CY 4-7 g/mq ± GF	34
Regimens:	VCAD ± GF	11
	VCED + GF	4
	Other	7

PBSC: peripheral blood stem cells; BM: bone marrow; CY: cyclophosphamide; VCAD: vincristine + adriamycin + cyclophosphamide + dexamethasone; VCED: vincristine + cyclophosphamide + epirubicin + dexamethasone.

Table 2. Details of transplantation.

Disease (N.= 56)	Time diagnosis BMT months median (range)	GF at BMT	Conditioning regimen (N. of patients)	MNC infused x 10^8/kg median (range)	CFU-GM infused x 10^4/kg median (range)	day to: PMN > 0.5 * median (range)	PLT > 50.0 * median (range)	PLT > 100.0 * median (range)
NHL (18)	10.0 (3.9-79.8)	7	CVB (19) BEAM (1)	3.9 (1.5-73)	21.4 (3.8-132.8)	11.0 (8-14)	14 (9-90)	16 (12-59)
HD (9)	19.0 (8.0-73.0)	5	CVB (4) BEAM (1)	5.2 (4.1-8.8)	20.8 (5.2-100)	11.0 (8-17)	14 (10-49)	17 (13-48)
MM (20)	14.6 (3.5-69.3)	10	BU-PAM (2) HD-PAM (5) BEM (15)	3.6 (1.0-6.2)	18.5 (1.7-78.8)	13 (8-17)	12 (9-32)	20 (11-145)
CML (5)	49.6 (24.9-69.1)	–	BU-PAM (5)	1.7 (1.0-2.6)	3.4 (1.6-63.9)	19 (16-32)	48 (10-365)	55 (12-638)
OTHER (4)	16.4 (6.5-47)	2	BU-PAM (1) BU-CY (1) VIP (1) BVM (1)	2.0 (0.2-4.6)	5.0 (1.9-133.5)	9 (8-28)	14 (12-14)	15 (14-18)

*= x10^9/L. GF: growth factor. CVB: cyclophosphamide, carmustine, etoposide; BU-PAM: busulfan, melphalan; HD-PAM: high-dose melphalan; BEM: carmustine, etoposide, melphalan. BU-CY: busulfan, cyclophosphamide; VIP: etoposide, ifosfamide, carboplatin; BEAM: carmustine, etoposide, cytosine arabinoside, melphalan; BVM: busulphan, etoposide, melphalan.

days –6 to –3; etoposide, 250-400 mg/m^2/day, days –6 to –3); the BEAM association (BCNU, 300 mg/m^2 on day –6, etoposide, 100 mg/m^2 on days –5 to –2, cytosine arabinoside, 400 mg/m^2 on days –5 to –2, melphalan, 140 mg/m^2 on day –1) was employed in only two cases.

Patients with MM received one of the following regimens: a) BEM (BCNU, 200 mg/m^2/day on days –8 to –7; etoposide, 250 mg/m^2/day on days –8 to –6; melphalan, 140 mg/m^2 on day –2); b) single high-dose melphalan, 200 mg/m^2 on day –2; c) BU-L. PAM (busulphan, 4 mg/kg/day on days –7 to –4; melphalan, 60 mg/m^2 on day –3). This latter regimen was also employed in patients with CML and, at a lower dosage (busulphan, 3.5 mg/kg/day on days –7 to –4, and melphalan, 40 mg/m^2 on day –3), in the patient with AL amyloidosis. The classic BU-CY regimen (busulphan 4 mg/kg/day on days –9 to –6; cyclophosphamide 50 mg/kg/day on days –5 to –2) was only used in the patient with AML. One patient with breast cancer received the VIP combination (etoposide, 400 mg/m^2 on days –5 to –3; ifosfamide, 4 g/m^2 on days –8 to –6; carboplatin, 450 mg/m^2 on days –5 to –3) (Table 2). Finally, the patient with Ewing's sarcoma was treated with an association of busulphan (4 mg/kg/day on days –9 to –6), etoposide (800 mg/m^2 on days –5 to –3) and melphalan (60 mg/m^2 on day –2).

Post-graft course

All patients were nursed in sterile, positive-pressure or laminar-flow single rooms and received antibacterial, antifungal and antiviral oral prophylaxis. Systemic antibiotics were empirically started for fever > 38°C lasting more than 2 hours, and standard criteria were used to change and/or stop antibiotics. Twenty-four patients also received GFs in the post-graft period (G-CSF, 19 patients; GM-CSF, 5 patients), starting the day following autograft and given by continuous iv infusion for 14 consecutive days or up to recovery of $\geq 1\times10^9$/L PMN, at a dosage of 5-5.5 μg/kg body weight (Table 2). Blood counts and differentials were obtained daily. Patients were supported with irradiated (25 Gy) blood products only. Packed red cells (PRC) were transfused when hemoglobin values were < 8 g/dL. PLT concentrates were given when PLT counts were $< 25\times10^9$/L, or $< 50\times10^9$/L in the case of fever.

CFU-GM assay

Analysis of colony-forming units granulocyte-macrophage (CFU-GM) was performed by the two-layer agar gel technique;[17] 10^5 mononuclear cells were plated on top of the feeder layer. With this method the normal reference range for our laboratory is 6.7-1260, median 436/mL circulating CFU-GM.

$CD34^+$ cell assay

The CD34 assay was performed after immunofluorescent labelling using standard protocols. Briefly, $0.5\text{-}1\times10^5$ mononuclear cells were incubated with 10 μL CD34 anti-HPCA-2 MoAb (Becton Dickinson). For each reading 10^4 cells were collected and analyzed by flow cytometry using a FACScan (Becton Dickinson). To reduce signal overlap, the Ig isotype control was set separately for the lymphocyte and monocyte regions using large contiguous gates on mononuclear cells.[18] With this method the normal reference range in our laboratory is 0-14.6 (median 5.6)$\times10^6$/L $CD34^+$ cells in the steady phase peripheral blood.

Results

Cell infusion and hematopoietic reconstitution

As graft the patients received a median of 3.9 (range 0.28-8.8)$\times10^8$/kg mononuclear cells (MNC) and 18.1 (range 1.6-133.5)$\times10^4$/kg CFU-GM (Table 2). Autologous (BM) cells were also infused in 9 patients, with a median count of 3 (range 0.5-15)$\times10^4$/kg CFU-GM. The decision to include BM cells was based on a poor CFU-GM yield ($<10\times10^4$/kg CFU-GM) in the PBSC samples. No significant differences in CFU-GM yield were observed after any of the mobilizing regimens utilized. The median dose of $CD34^+$ cells infused, as evaluated in only 21 patients, was 7.0 (range 1.3-86)$\times10^6$/kg.

No severe life-threatening reactions occurred during or after cell infusion, while mild disturbances such as chills, fever, and abdominal pain were occasionally seen.

All patients engrafted >0.5 and $>1.0\times10^9$/L PMN at a median of 12 (range 8-32) and 14 (range 8-55) days, respectively. The median time to reach an unsupported level of >50.0 and $>100.0\times10^9$/L PLT was 13 (range 9-365) and 17 (range 11-826) days, respectively (Figure 1). Seven patients never achieved a PLT count $>100.0\times10^9$/L. CFU-GM dose influenced PLT recovery. In fact, patients receiving more than 18×10^9/L recovered $>100.0\times10^9$/L PLT significantly faster than the other patients (Figure 2, Peto-Wilcoxon analysis, p= 0.008). $CD34^+$ cell dose correlated with recovery of $>50.0\times10^9$/L PLT (linear regression analysis, $r=-0.76$; $p=0.02$) only in 7 patients who constituted a select population with homogeneous characteristics.

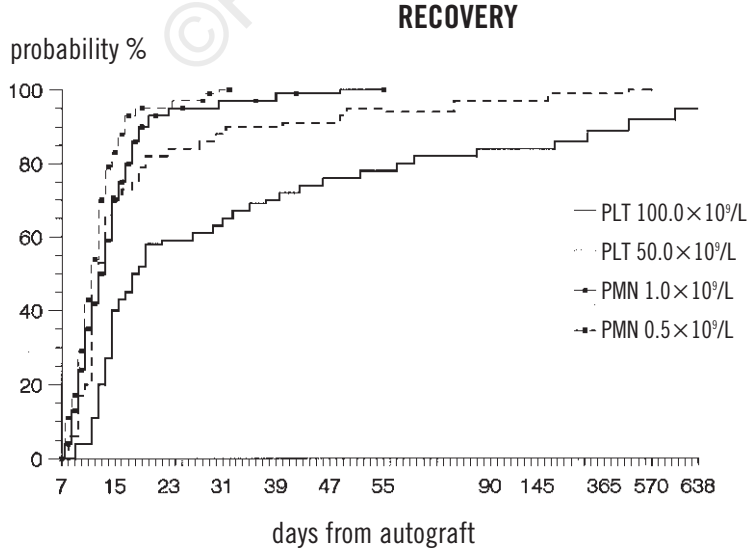

Figure 1. Probability of short-term reconstitution after transplantation of circulating progenitor cells±bone marrow in 56 patients with various malignancies. The median time to achieve an absolute PMN count > 0.5 x 10^9/L and PLT > 50 x 10^9/L was 12 (8–32) and 32 (9-365) days, respectively.

In fact, they were all affected by NHL, all in complete

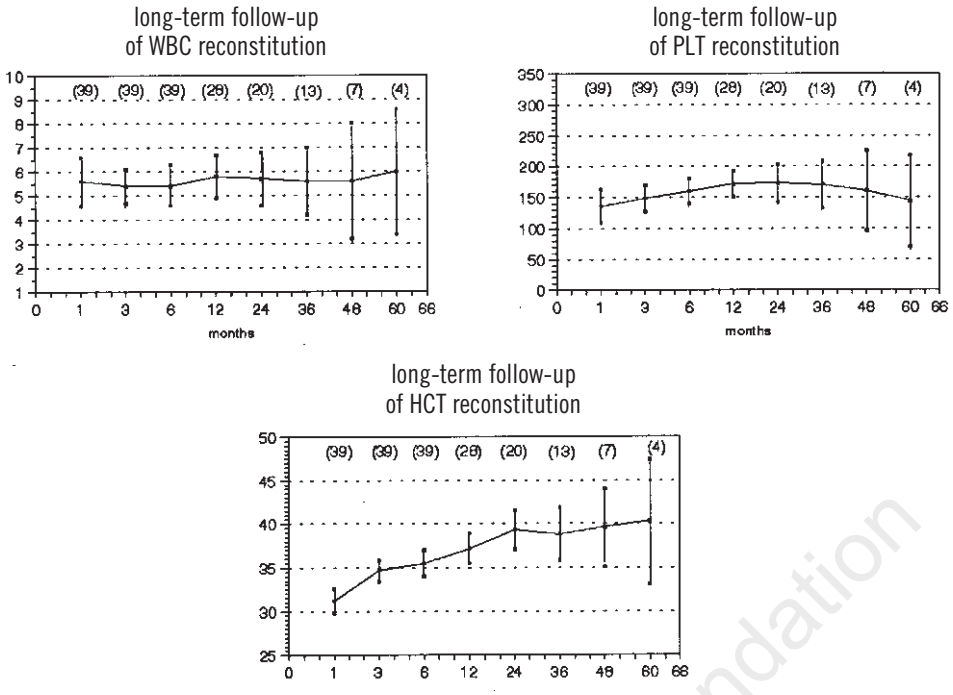

Figure 2. Retrospective analysis of long-term hemopoietic reconstitution in 39 patients autografted with circulating progenitor cells. Mean values of WBC, PLT, and Hct count with 95% confidence interval were recorded at 30 and 100 days, at 6 months and at one (28 pts), two (20 pts), three (13 pts) four (7 pts) and five (4 pts) years. No patient had late graft failure.

remission after first-line treatment, and bone marrow involvement was not present in any of

Table 3. Characteristics of patients showing late platelet reconstitution.

Pts	Diagnosis	GF at BMT	IFN post BMT	BMT type	MNC infused x 10^8/Kg	CFU-GM infused x 10^4/Kg	days to:	
							PLT > 50.0 *	PLT > 100.0 (f.u.)
1	HD	No	Yes	PBSC	5.2	23.6	49	N.R. (1960)
2	MM	Yes	Yes	PBSC	3.4	36.4	13	N.R. (1095)
3	NHL	No	No	PBSC	3.6	4.5	50	N.R. (150)
4	AML	No	No	PBSC + BM	0.3	2.4	N.R. (120)	N.R. (120)
5	NHL	Yes	No	PBSC	3.3	3.8	17	N.R. (30)
6	NHL	Yes	No	PBSC +BM	3.6	7.9	20	N.R. (150).
7	NHL	Yes	No	PBSC	5.4	105.3	90	N.R. (150)
8	MM	No	Yes	PBSC + BM	2.3	1.7	32	145
9	MM	No	Yes	PBSC + BM	3.2	18.0	12	365
10	CML	No	Yes	PBSC+ BM	1.1	1.6	164	638
11	CML	No	Yes	PBSC	2.7	4.8	365	570

* = x10^9/L. IFN= Interferon; PBSC= Peripheral blood progenitor cells; BM= Bone Marrow; MNC = Peripheral blood mononuclear cells infused; CFU-GM= peripheral blood granulocyte-macrophage colony-forming units infused. N.R. = not reached. f.u.= follow-up.

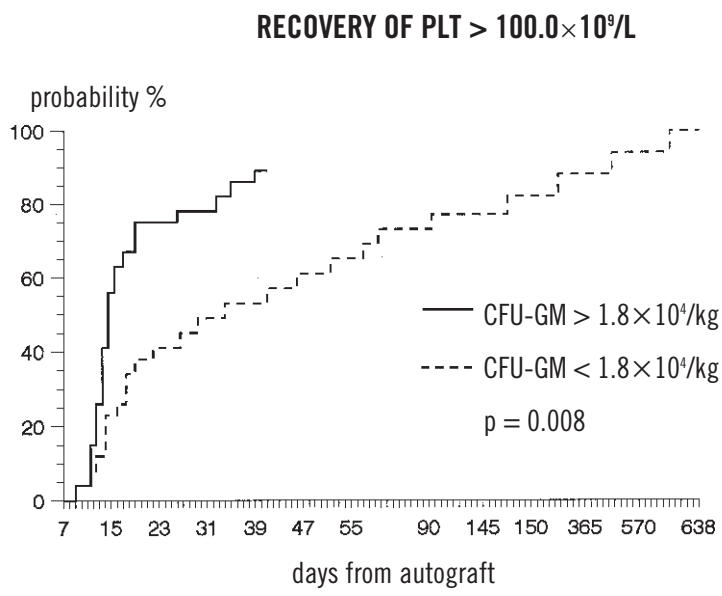

Figure 3. Probabilty of recovery to >100.0 x10⁹/L PLT for patients receiving more than 18 x 10⁴/kg CFU-GM compared to that of the other patients.

them.

We did not find any correlation between CFU-GM and MNC dose nor between CFU-GM and CD34⁺ cell number.

As far as evaluation of long-term graft performance is concerned, we included the hematological values of the patients in the analysis as long as they did not require any other chemotherapy treatment for progression or relapse of their disease. Thirty-nine patients were evaluable and we recorded their hematologic counts (WBC, PLT, HCT) at 30 and 100 days, at 6 months and at 1 year (28 pts), 2 years (20 pts), 3 years (13 pts), 4 years (7 pts) and 5 years (4 pts) after autograft (Figure 2). Hemopoietic reconstitution remained stable over the entire observation period and none of the patients experienced late graft failure. Moreover, 1 year after transplantation 71% of patients showed normal hematologic counts as defined by HCT ≥30%, WBC ≥4.0×10⁹/L and PLT ≥100.0×10⁹/L.

Discussion

Our study confirms once again that mobilized PBSC ensure rapid granulocyte and platelet recovery.[19,20] In our series the heterogeneity of diseases contrasts with the substantial uniformity of hemopoietic reconstitution, making analysis of the factors influencing the speed of recovery less uniform. While the majority of patients showed fast and complete platelet engraftment, 11 of them recovered their platelets late (Table 3). In particular, 7 patients failed to engraft > 100.0×10⁹/L PLT and this was associated with rapid disease progression in 3, and with heavy pretransplant treatment in another. Maintenance treatment with α-interferon is a possible explanation for the poor platelet recovery in 6 out of the 11 patients. However, a low progenitor cell count remains the most convincing argument since 5 of the 9 patients also receiving BM cells as a consequence of poor PBSC collection had delayed or incomplete platelet engraftment.

Using univariate analysis (Peto-Wilcoxon) we found that autografting of at least 18×10⁴/kg CFU-GM was followed by a significantly faster reconstitution of > 100.0×10⁹/L PLT (Figure 3, p = 0.008). That the number of CFU-GM infused influences hematopoetic reconstitution has also been reported by others, but because the CFU-GM assay is not reproducible the threshold is only applicable at individual centers.[21] We were not able to correlate CFU-GM with CD34⁺ and MNC cells. This finding is probably due to the fact that clonogenic cultures show a wide range of results in our laboratory. Finally, our data suggest that the use of GF during the post graft period might have an

influence on recovery to $>0.5\times10^9$/L PMN (unpublished results).

The second aim of this paper was to evaluate long-term hematopoietic reconstitution after PBSC transplantation (PBSCT). The question of whether autologous blood-derived stem cells can permanently reconstitute hematopoiesis after high-dose chemotherapy is a complex one. In fact there is little doubt that some stem cells can survive pretransplant conditioning,[5] thus contributing to steady long-term hematopoiesis. In the autologous setting, however, the point is merely theoretical and has no practical consequences. As a matter of fact, of the 17 patients supported with PBSC alone and then followed for minimum of 2 years, none showed either a transitory or a permanent drop in peripheral cell counts.

On the other hand, laboratory data on peripheral cell counts indicate that long-term culture-initiating cells (LTC-IC) can be mobilized into the blood in numbers similar to or higher than those of the bone marrow.[8,22]

Experiments[23] in mice using sex-mismatched transplants and a molecular probe have demonstrated that PBSC are able to provide not only immediate but also sustained blood repopulation. Extrapolation from mice to humans must be regarded with caution[8] but several studies have been published concerning allogenic PBSCT in humans,[24-28] and all of them document complete trilineage engraftment of donor origin.

In conclusion, this study demonstrates that the infusion of high-dose cytotoxic chemotherapy plus PBSC not only produces an accelerated immediate hematologic recovery, but is also followed by stable long-term hematopoiesis. Our data also encourage applying PBSC technology to the allogenic setting, where definitive proof of its long-term repopulating capacity is only a matter of time.

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