

Whether Methotrexate Administration in Graft-Versus-Host Disease Prophylaxis Significantly Delays the Engraftment in Allogeneic Peripheral Blood Progenitor Cell Transplantation

To the Editor:

The use of peripheral blood progenitor cells (PBPCs) for allogeneic transplantation (allo-PBPCT) is raising considerable interest.¹ One of the main potential advantages of allo-PBPCT is a rapid neutrophil and platelet engraftment.² In a recent issue of *Blood* three reports³⁻⁵ describe the clinical results of using PBPCs for allografting. Whereas two of them^{3,4} find that allo-PBPCT is associated to a very rapid engraftment, the third group⁵ shows a neutrophil and platelet recovery similar to that seen after allogeneic bone marrow transplantation (allo-BMT). This last group attributes this delay to the administration of methotrexate after grafting of PBPCs. We performed a study with four patients receiving transplants of allogeneic PBPCs in which cyclosporine and methotrexate were used for graft-

versus-host disease (GVHD) prophylaxis. However, three of the four patients showed a rapid neutrophil and platelet engraftment.

Eight patients underwent allo-PBPCT in our institution from January 1994 to April 1995. Four of them received unmanipulated leukapheresis from HLA-identical sibling donors for primary allotransplantation and are the basis of our report. The characteristics of these patients are shown in Table 1. All were acute leukemia patients in the second phase of the disease. The median age was 37 years (range, 21 to 45 years). Donors received granulocyte colony-stimulating factor (G-CSF) at 10 $\mu\text{g}/\text{kg}/\text{day}$ via subcutaneous injection for 5 days. On day 5 (cases no. 1 and 2) and days 5 and 6 (cases no. 3 and 4), donors underwent 10 L (3 hours) of leukapheresis with the Fenwall CS-3000 plus separator (Baxter, Deerfield, IL). The number of nucleated cells and CD34⁺ and CD3⁺ cells per recipient weight in the leukapheresis product is shown in Table 1. These patients

Table 1. Donor and Patient Characteristics

Case No.	Donor's Sex/Age (yr)	Apheresis			Patients					
		Nucleated Cells	CD34 ⁺	CD3 ⁺	Sex/Age	Diagnosis	Status	Neutrophils >0.5 × 10 ⁹ /L	Platelets >20 × 10 ⁹ /L	Acute GVHD
1	M/37	6.6	3.5	271	F/45	ALL	2nd phase	+21	+51	IV
2	M/18	4.5	4.1	153	M/21	ALL	2nd CR	+17	+11	0
3	M/31	7	6.4	255	F/38	AML	2nd CR	+14	+11	0
4	M/45	10	7.1	295	M/36	AML	2nd CR	+14	+6	I

Values are expressed as 10⁶/kg recipient's weight for total nucleated cells and 10⁵/kg recipient's weight for CD34⁺ and CD3⁺ cells. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CR, complete remission.

received the preparative regimen with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy; four fractions), followed by the infusion of noncryopreserved apheresis product as the sole source of progenitor cells. No growth factors were administered after transplantation. In all four cases GVHD prophylaxis consisted of cyclosporine (3 mg/kg) and a short course of methotrexate (day +1, 15 mg/m²; days +3 and +6, 10 mg/m²). Engraftment in the four patients was substantiated by the apparition of neutrophils reaching a level greater than $0.5 \times 10^9/L$ at a median of 15.5 days and of platelets reaching a level greater than $20 \times 10^9/L$ at a median of 11 days (Table 1). In our historical control group of acute leukemia patients in which an allo-BMT was performed in second complete remission (n = 40) using similar conditioning and GVHD prophylaxis regimens, the median time to reach $\geq 0.5 \times 10^9/L$ neutrophils and $\geq 20 \times 10^9/L$ platelets was (median \pm standard deviation) of 20.6 ± 0.8 and 29.1 ± 2.5 days, respectively. Thus, even from the limited number of cases reported here it seems that the speed of the engraftment of allo-PBPCT group compares favorably with that of the allo-BMT group. Acute GVHD was of clinical grade IV (case no. 1), 0 (cases no. 2 and 3), and I (case no. 4), requiring treatment with methylprednisolone (case no. 4) and methylprednisolone and ATG (case no. 1). Skin, gut, and liver were involved in case no. 1 and the patient did not respond to GVHD treatment and eventually died. Case no. 3 is presenting an extensive chronic skin GVHD at 150 days posttransplant and is currently being treated with prednisone with a good response. The minimal follow-up of these patients is 60 days.

The application of PBPCs for allografting as an alternative to marrow cells has been recently discussed and questions have been raised.¹ The following should be addressed before its clinical use becomes generalized: kinetic and stability of engraftment, incidence and severity of both acute and chronic GVHD, antileukemic effect, and speed of the immunologic reconstitution. The three clinical reports recently published in *Blood*³⁻⁵ indicate that the incidence of acute GVHD is not greater than what could be expected with allo-BMT and that the incidence of chronic GVHD must be still determined. In all 25 of the patients described the PBPCs engrafted. It is noteworthy that there is a discrepancy in relation to the speed of the engraftment; whereas for two groups^{3,4} allo-PBPCT provides a very rapid hematologic reconstitution, the third⁵ shows a neutrophil and platelet recovery similar to that seen after allo-BMT. Although this group and another group⁶ consider that the use of methotrexate as GVHD prophylaxis may be an important factor limiting the ability of allo-PBPCT to enhance engraftment, in our experience the engraftment was very rapid in three of four patients. Besides, the patient with delay in the engraftment was heavily pretreated and there was persistent disease at the time of transplantation. It is recognized that the median time to granulocyte engraftment in these four

cases is slightly longer than often seen in autologous PBPCT or in the group of allo-PBPCT in which cyclosporine and prednisone is used for GVHD prophylaxis,⁴ most likely because of the administration of methotrexate. Yet, median times to granulocyte and platelet engraftment are shorter than the median observed for both lines with allo-BMT in our center. The claim that methotrexate does not seem to significantly delay the engraftment in allo-PBPCT cases is in accordance with the experience from other groups.^{2,3} Our contention is that, because the combination of cyclosporine and methotrexate is the standard for GVHD prophylaxis, its use should not be circumvented until there is absolute certainty that allo-PBPCT is not associated with increased risk of GVHD.

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