

Induction of autologous graft-versus-host disease with cyclosporin A after peripheral blood stem cell transplantation: Analysis of factors affecting induction

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Background: Induction of autologous graft-versus-host disease after peripheral blood stem cell transplantation has not been studied well.

Objective: The purpose of this study was to analyze the factors that affect the development of autologous graft-versus-host disease.

Methods: Nineteen patients with non-Hodgkin's lymphoma underwent peripheral blood stem cell transplantation followed by the administration of cyclosporin A for 28 days (group A) or 21 days (group B) and IFN- γ .

Results: Autologous graft-versus-host disease failed to develop in any of the group A patients, who did not receive total body irradiation for conditioning and underwent the transplantation with unmanipulated peripheral blood stem cells, although cytotoxic activity against autologous lymphocytes was detectable in peripheral blood mononuclear cells obtained from all of them after the transplantation. Autologous graft-versus-host disease developed in 2 of 4 patients in group A who received enriched CD34⁺ cells and in 7 of 11 patients who underwent conditioning with total body irradiation. Maculopapular erythema that was compatible with graft-versus-host disease developed on days 19 to 27 after the transplantation in these patients and resolved after 3 to 9 days without treatment.

Conclusions: Either the depletion of regulatory cells from the graft by enrichment of CD34⁺ cells or the abolition of the autoregulation by including total body irradiation in the conditioning regimen may be effective in inducing autologous graft-versus-host disease after peripheral blood stem cell transplantation. Three weeks of cyclosporin A therapy appears to be sufficient to induce autologous graft-versus-host disease in recipients of peripheral blood stem cells. (*J Allergy Clin Immunol* 2000;106:S51-7.)

Key words: Autologous graft-versus-host disease, cyclosporin A, peripheral blood stem cell transplantation

Abbreviations used

BMT:	Bone marrow transplantation
G-CSF:	Granulocyte colony-stimulating factor
GVHD:	Graft-versus-host disease
NHL:	Non-Hodgkin's lymphoma
PBSC:	Peripheral blood stem cell
PBSCT:	Peripheral blood stem cell transplantation
PHA-blasts:	Phytohemagglutinin-stimulated lymphoblasts
TBI:	Total body irradiation

High-dose chemoradiotherapy combined with autologous stem cell transplantation has been used successfully in the treatment of patients with malignant lymphoma. A number of clinical studies have demonstrated that, among the therapeutic options available for relapsing lymphoma, autologous bone marrow transplantation (BMT) is the most effective in achieving long-term survival.¹⁻³ However, clinical trials have failed to demonstrate any advantage of autologous stem cell transplantation over conventional chemotherapy in patients with non-Hodgkin's lymphoma (NHL) who show a slow response to chemotherapy or patients who achieve remission but have poor prognostic factors.^{4,5} These findings suggest that increasing the dose intensity of chemotherapy by the use of autologous stem cell transplantation may not necessarily improve the outcome. For patients who do not achieve sustained remission after conventional chemotherapy, novel approaches such as immunotherapy seem to be needed.

One such approach is the induction of autologous graft-versus-host disease (GVHD) after autologous stem cell transplantation. Autologous GVHD is an autoaggression syndrome that affects mainly the skin and resembles the cutaneous changes of acute GVHD in allogeneic marrow transplant recipients. It is inducible in recipients of autologous bone marrow by the administration of cyclosporin A for a short period.⁶⁻⁹ The risk of relapse of leukemia after allogeneic BMT is lower in patients with GVHD than in those without it.^{10,11} In patients with NHL, allogeneic BMT has a lower relapse rate than autologous BMT,^{12,13} and the higher relapse rate after autologous transplantation is thought to be due to the absence of a graft-versus-lym-

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phoma effect associated with GVHD. However, a lower relapse rate with allogeneic BMT does not necessarily result in an increase of survival because of the higher mortality rate from complications such as severe GVHD and infections.^{12,13} Thus, it would be desirable to induce the immunologic antilymphoma effect of allogeneic transplantation in recipients of autologous stem cells.

Autologous GVHD is inducible in 70% to 80% of the recipients of autologous bone marrow by the administration of cyclosporin A in the early posttransplantation period.¹⁴⁻¹⁶ Clinical trials that involve patients with acute myeloid leukemia and NHL have suggested that the induction of autologous GVHD can reduce the relapse rate.¹⁷⁻¹⁹ Peripheral blood stem cell transplantation (PBSCT) is now the main modality of autologous hematopoietic stem cell transplantation because of the rapidity of engraftment and the ease of harvesting compared with BMT.^{20,21} However, the induction of autologous GVHD after PBSCT has not been well studied. We attempted to induce autologous GVHD in 19 patients with NHL by the administration of cyclosporin A and IFN- γ after PBSCT and analyzed the factors that favored its development. We also assessed the cytotoxicity of PBMCs against autologous lymphocytes at different times after PBSCT.

METHODS

Patients

Between February 1996 and March 1999, 19 consecutive patients with NHL underwent PBSCT. Among them, 9 patients experienced remission of high-grade NHL, and the other 10 patients experienced relapse or induction failure at the time of PBSCT. There were 12 men and 7 women: the median age of the entire group was 46 years (range, 35-56 years). Patients 4 and 11 also had hemophagocytic syndrome. Table I summarizes the clinical characteristics of the subjects.

Conditioning regimens for autologous PBSCT

Eight patients (patients 1-6, 8, and 9) underwent conditioning before PBSCT with high-dose chemotherapy that consisted of ramiposine (200 mg/m², intravenously; days -8 and -3), carboplatin (300 mg/m², intravenously; days -7, -6, -5, and -4), etoposide (500 mg/m², intravenously; days -6, -5, and -4), and cyclophosphamide (50 mg/kg, intravenously; days -3 and -2). The remaining 11 patients received a conditioning regimen that consisted of cyclophosphamide (50 mg/kg, intravenously; days -3 and -2) and fractionated total body irradiation (TBI) at 3 Gy daily for 4 days (total, 12 Gy) in combination with cytarabine (4 g/m², intravenously; days -4 and -3) for patients 10, 13, 14, 15, and 17 or etoposide (15 mg/kg, intravenously; days -4 and -3) for patients 12, 16, 18, and 19.

Stem cell harvesting

All patients underwent leukapheresis for the collection of peripheral blood stem cells (PBSCs) after chemotherapy. PBSCs were mobilized by the administration of etoposide (500 mg/kg, intravenously; 3 days) and G-CSF (filgrastim, 50 μ g/m²/d; lenograstim, 2 μ g/kg/d). Leukapheresis was performed with the use of a Cobe Spectra unit (Cobe Laboratories, Heimstetten, Germany) when the white blood cell count exceeded 1.0×10^9 /L. The minimum number of CD34⁺ cells was 1.0×10^6 /kg.

Selection of CD34⁺ cells

Among the histologic subtypes of NHL, follicular lymphoma is likely to infiltrate bone marrow, and a few lymphoma cells are often detected in the marrow, even in the early stage of the disease.²² Patient 11 had hemophagocytosis, and lymphoma cells were detected in the bone marrow. Because contamination of the leukapheresis product by lymphoma cells was suspected in patients 8 to 11, enrichment of CD34⁺ cells was performed. A total of 1×10^{10} mobilized peripheral blood leukocytes were subjected to positive selection of CD34⁺ cells with the use of a magnetic cell separation device (Isolex50; Baxter Immunotherapy, Irvine, Calif). The mean yield and purity of the isolated CD34⁺ cells was 61.7% and 96.0%, respectively. The cells were cryopreserved until used.

Induction of autologous GVHD

Cyclosporin A (2.5 mg/kg/d) was administered intravenously to patients 1 to 6 (group A) from days 1 through 28 after PBSCT and to patients 7 to 19 (group B) from days 1 through 21. Recombinant IFN- γ (50 mg/m²; Shionogi, Osaka, Japan) was administered subcutaneously to all patients on days 7, 14, 21, and 28. G-CSF (5 μ g/kg/d) was administered to the patients from day 1 until the leukocyte count exceeded 5.0×10^9 /L. This treatment protocol was reviewed and approved by the institutional review board, and informed consent was obtained from all patients.

Preparation of phytohemagglutinin-stimulated lymphocytes

Heparinized peripheral blood was collected from the patients before conditioning chemotherapy, and PBMCs were separated with density-gradient centrifugation, suspended in RPMI 1640 medium (Gibco, Grand Island, NY), and cryopreserved at -80°C after being divided for aliquoting. For the testing of autocytotoxic activity, thawed PBMCs were cultured for 5 to 7 days in the presence of 1 μ g/mL of phytohemagglutinin (PHA, Wellcome, Dartford, UK). After being washed with RPMI 1640, the phytohemagglutinin-stimulated lymphoblasts (PHA-blasts) were used for the chromium release assay.

Cytotoxicity assay

PHA-blasts were suspended for 1 hour in 10 μ L of ⁵¹Cr (400-1200 Ci/g chromium; Dupont NEN Products, Boston, Mass). After being washed with PBS, 10^4 cells were cultured with 8×10^5 autologous PBMCs from each patient after PBSCT. After 4 hours of incubation, ⁵¹Cr release into the medium was measured with a gamma-counter. The percent-specific lysis (mean $\pm$ SE) was determined from triplicate cultures as follows: $100 \times (\text{experimental release counts per minute} - \text{spontaneous release counts per minute}) / (\text{maximum release counts per minute} - \text{spontaneous release counts per minute})$.

Statistical analysis

Complete remission was defined as the disappearance of all measurable or evaluable disease for at least 12 weeks after transplantation. Partial remission was defined as a 50% or more reduction in the product of the bidimensional lesion measurements at all sites of measurable disease. Data were analyzed as of August 1, 1999. Disease-free survival curves were calculated in relation to the PBSCT data, according to the method of Kaplan and Meier.²³

RESULTS

Hematologic recovery and treatment-related toxicity

Table II summarizes the hematologic recovery and treatment-related toxicity after PBSCT. The duration of

TABLE I. Clinical characteristics

Group	Patient no.	Age (y)/sex	Histologic condition	Clinical stage	Disease state	No. of prior regimens	Conditioning regimen before PBSCT	Duration of cyclosporin A administration (d)
A	1	44/M	Diffuse large	IVA	CR	1	MCNU-CBCD-VP-CY	28
	2	44/M	Diffuse large	IVA	CR	1	MCNU-CBCD-VP-CY	28
	3	47/M	Angioimmunoblastic	IIIB	PR	1	MCNU-CBCD-VP-CY	28
	4	36/M	Diffuse large + hemophagocytosis	IVB	PD	1	MCNU-CBCD-VP-CY	28
	5	52/F	Diffuse large	IVB	PR	1	MCNU-CBDCA-VP-CY	28
	6	48/F	Anaplastic large	IVA	PR	2	MCNU-CBDCA-VP-CY	28
B	7	37/M	Angioimmunoblastic	IB	CR	1	TBI+CY	21
	8	47/F	Follicular medium	IIIA	PD	1	CD34 (MCNU-CBDCA-VP-CY)	21
	9	48/M	Follicular medium	IIIA	PR	1	CD34 (MCNU-CBDCA-VP-CY)	21
	10	46/M	Follicular mixed	IVA	PR	2	CD34 (TBI+CY+AraC)	21
	11	56/M	Diffuse large + hemophagocytosis	IVB	CR	1	CD34 (TBI+CY)	21
	12	35/M	Follicular mixed	IVA	CR	1	TBI+CY+ETP	21
	13	44/M	Follicular mixed	IVA	PR	3	TBI+CY+AraC	21
	14	41/F	Diffuse large	IVA	PR	2	TBI+CY+AraC	21
	15	51/M	Diffuse mixed	IVA	CR	2	TBI+CY+AraC	21
	16	48/F	Diffuse large	IVA	CR	2	TBI+CY+ETP	21
	17	48/M	Angioimmunoblastic	IIIA	CR	2	TBI+CY+AraC	21
	18	56/F	Diffuse mixed	IVA	CR	1	TBI+CY+ETP	21
	19	50/M	Angioimmunoblastic	IIIA	PR	3	TBI+CY+ETP	21

M, Male; F, female; CR, complete remission; MCNU, ranimustine; CBDCA, carboplatin; VP, etoposide; CY, cyclophosphamide; PR, partial remission; PD, progressive disease; CD34, positive selection of CD34⁺ cells; ETP, etoposide; AraC, cytarabine.

TABLE II. Hematologic and biochemistry parameters after PBSCT

Group	Patient no.	Day to granulocytes > 500/ μ L	Day of platelets > 50,000/ μ L	Day of last platelet transfusion	Day of reticulocytes > 1%	Maximum bilirubin level (mg/dL)	Maximum creatinine level (mg/dL)
A	1	9	11	9	13	0.6	1
	2	10	11	10	11	0.8	0.9
	3	12	15	13	14	0.9	0.9
	4	9	11	9	11	0.5	1.3
	5	9	14	13	14	1.3	1.3
	6	11	11	9	11	0.8	0.7
B	7	11	13	8	11	0.7	0.6
	8	9	9	8	12	0.8	0.9
	9	11	18	10	13	0.9	0.9
	10	13	32	15	13	0.6	0.7
	11	11	28	10	13	0.8	0.8
	12	11	13	11	11	0.6	0.8
	13	12	21	12	12	0.5	1.2
	14	9	11	11	13	0.7	0.5
	15	11	11	10	11	0.6	0.8
	16	11	13	11	13	1.7	0.6
	17	11	13	9	11	0.8	0.7
	18	9	13	11	11	0.8	0.6
	19	11	15	12	13	1.1	0.9

neutropenia (a neutrophil count of $<0.5 \times 10^9/L$) was 9 to 13 days, and the median time between transplantation and the last platelet transfusion was 15 days. The patients showed rapid recovery of hematopoiesis, which was comparable to that of patients who had undergone PBSCT but who did not receive cyclosporin A and IFN- γ .^{20,21} There was no increased toxicity related to the administration of IFN- γ , except for transient fever on the day of injection.

Autologous GVHD

Table III summarizes the occurrence of autologous GVHD after PBSCT. Autologous GVHD did not develop in the initial 6 patients, who had conditioning regimens without TBI and received unmanipulated PBSCs. In contrast, autologous GVHD developed in 2 of the 4 patients who had undergone transplantation with enriched CD34⁺ cells and in 7 of the 11 patients who underwent TBI in



FIG 1. Maculopapular erythema that appeared on the back of patient 9 on day 28 after PBSCT.

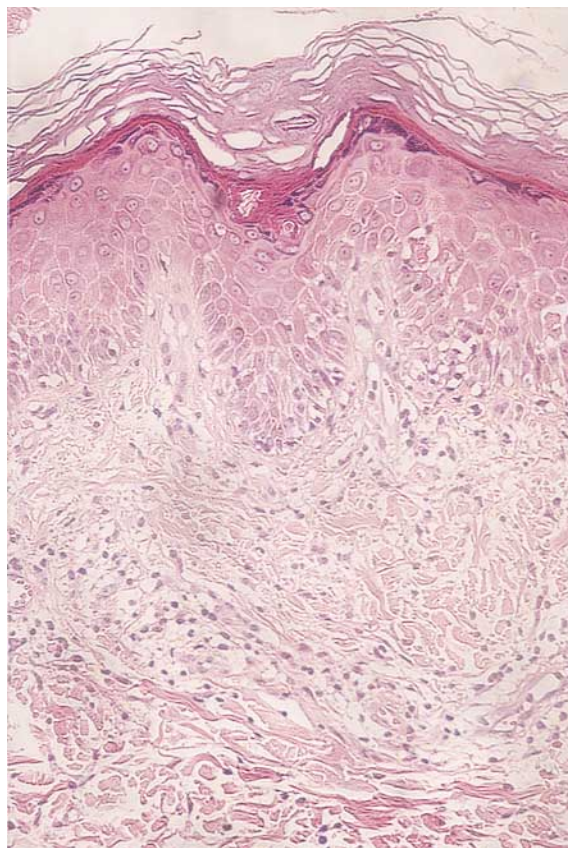


FIG 2. Histologic features of the skin biopsy specimen, which was obtained on day 28 after PBSCT from patient 9. There is diffuse intraepidermal infiltration of lymphocytes with vacuolation of basal cells and balloon degeneration of squamous cells. (Hematoxylin-eosin stain; original magnification, $\times 250$.)

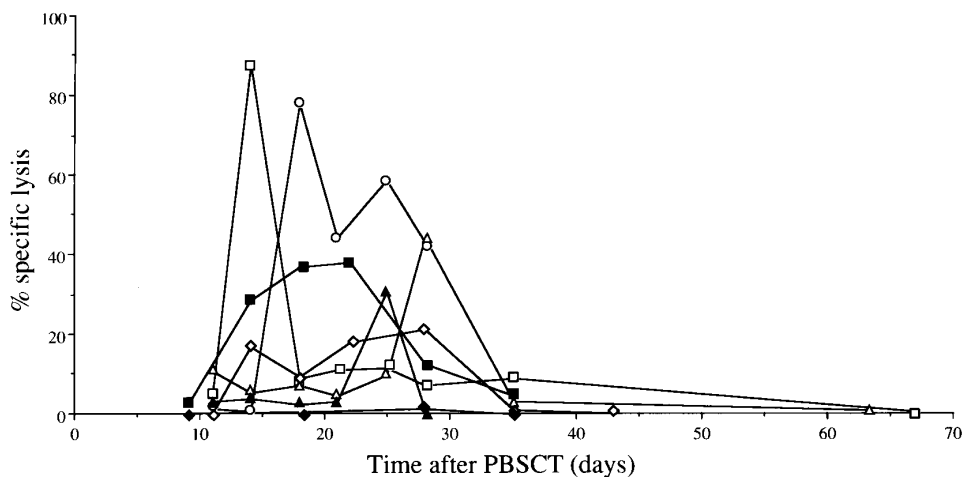


FIG 3. Changes in the cytotoxicity of PBMCs for autologous PHA-blasts after PBSCT in group A. Cytotoxicity for autologous PHA-blasts obtained at different times after PBSCT was determined with the use of the standard ^{51}Cr release assay with an effector/target ratio of 80:1. $\square$, Patient 1; $\triangle$, patient 2; $\circ$, patient 3; $\diamond$, patient 4; $\blacksquare$, patient 5; $\blacktriangle$, patient 6; $\blacklozenge$, a patient who did not receive cyclosporin A and IFN- γ .

their conditioning regimen. Maculopapular erythema developed between days 19 and 27 after PBSCT in these patients and then disappeared after 3 to 9 days without treatment. Skin biopsy results confirmed a diagnosis of

GVHD in all patients. For example, patient 9 experienced the development of erythematous maculopapular eruptions on the neck and lower extremities on day 25 after CD34 $^{+}$ cell transplantation. After 3 days, the erythema

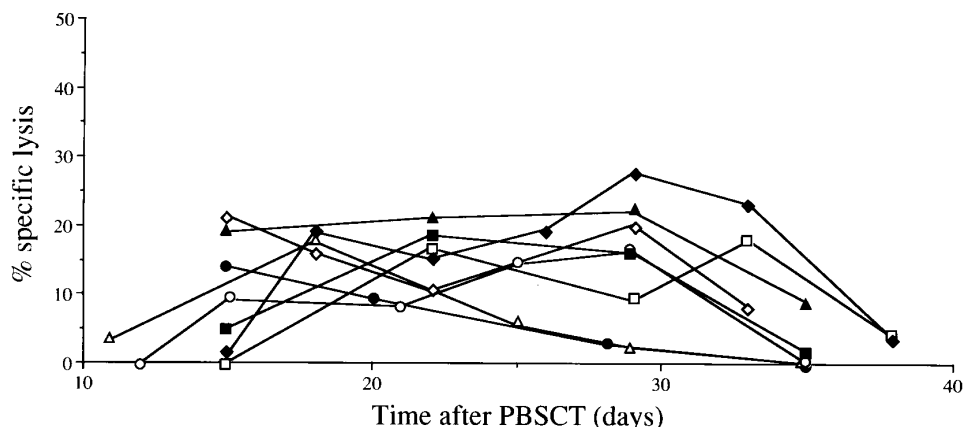


FIG 4. Changes in the cytotoxicity of PBMCs for autologous PHA-blasts after PBSCT in group B. Cytotoxicity for autologous PHA-blasts obtained at different times after PBSCT was determined with the use of the standard ^{51}Cr release assay with an effector/target ratio of 80:1. □, Patient 7; △, patient 8; ○, patient 9; ◇, patient 10; ■, patient 11; ▲, patient 12; ●, patient 13; ◆, patient 14.

extended to the trunk and upper extremities (Fig 1). Skin biopsy results revealed diffuse intraepidermal lymphocytic infiltration with vacuolation of basal cells and ballooning of squamous cells, findings that were compatible with a diagnosis of GVHD (Fig 2). The erythema faded spontaneously after day 28 and disappeared by day 35.

Autocytotoxic activity of lymphocytes after PBSCT

Fig 3 shows the changes of autocytotoxic activity in group A patients, whose conditioning regimens did not include TBI and who underwent transplantation with unmanipulated PBSCs. Lymphocytes that showed autocytotoxicity appeared as early as day 11 and remained detectable until day 36, despite the fact that autologous GVHD developed in none of these patients. Such autocytotoxic lymphocytes were not detectable in another patient after PBSCT who did not receive cyclosporin A and IFN- γ . Group B patients were treated with cyclosporin A for 21 days after PBSCT, instead of 28 days as in group A. Fig 4 illustrates the changes in the autocytotoxic activity in the 8 group B patients (patients 7-14). Autocytotoxic activity of PBMCs was detected between day 11 and day 38 after transplantation in all group B patients. Although this activity was somewhat weaker than in group A patients, it tended to persist for a longer period of time.

Response and survival

Eight of the 11 patients are in continuous complete remission after a median of 19 months (range, 6-36 months). Six of the 8 patients with partial remission before transplantation achieved complete remission after PBSCT. The disease-free survival curves are presented in Fig 5. At a median follow-up time of 22 months, the disease-free survival rate of all patients was 63%, but none of the 8 patients who experienced the development of autologous GVHD had experienced relapse (Table III).

DISCUSSION

Autologous GVHD is reported to be inducible in 70% to 80% of autologous bone marrow recipients by the administration of cyclosporin A in the early posttransplantation period.¹⁴⁻¹⁶ Although autocytotoxic activity of PBMCs was detected in our 6 patients who were treated with cyclosporin A plus IFN- γ , none of them experienced the development of autologous GVHD. Recent reports on the treatment of NHL with PBSCT followed by cyclosporin A administration have also revealed a relatively low incidence of autologous GVHD.²⁴ The leukapheresis product used as a source of stem cells contains a large number of monocytes that may inhibit autoreactive T cells more effectively than after bone marrow grafting.²⁵ The leukapheresis product collected after G-CSF administration may also contain an increased number of regulatory T cells, such as CD4-CD8⁻ T cells.²⁶ It is thus possible that the use of PBSC grafts depleted of monocytes and T cells may favor the induction of autologous GVHD. In keeping with this hypothesis, 2 of our 4 patients who underwent transplantation with enriched CD34⁺ cells that were obtained from the peripheral blood leukapheresis product experienced the development of autologous GVHD.

Autocytotoxic activity of PBMCs was detected in all patients who were treated with cyclosporin A plus IFN- γ , regardless of the development of autologous GVHD; and T cells that showed autocytotoxicity appeared in the circulation as late as 21 days after PBSCT. We therefore speculated that administration of cyclosporin A for 3 weeks might be sufficient to induce autocytotoxic T cells and that cyclosporin A treatment during week 4 after PBSCT might suppress the development of autologous GVHD. On the basis of this hypothesis, patients 7 to 19 only received cyclosporin A for 21 days after PBSCT; this shorter regimen induced GVHD in 8 of 13 patients. These results indicate that the administration of cyclosporin A for 3 weeks is enough to induce autolo-

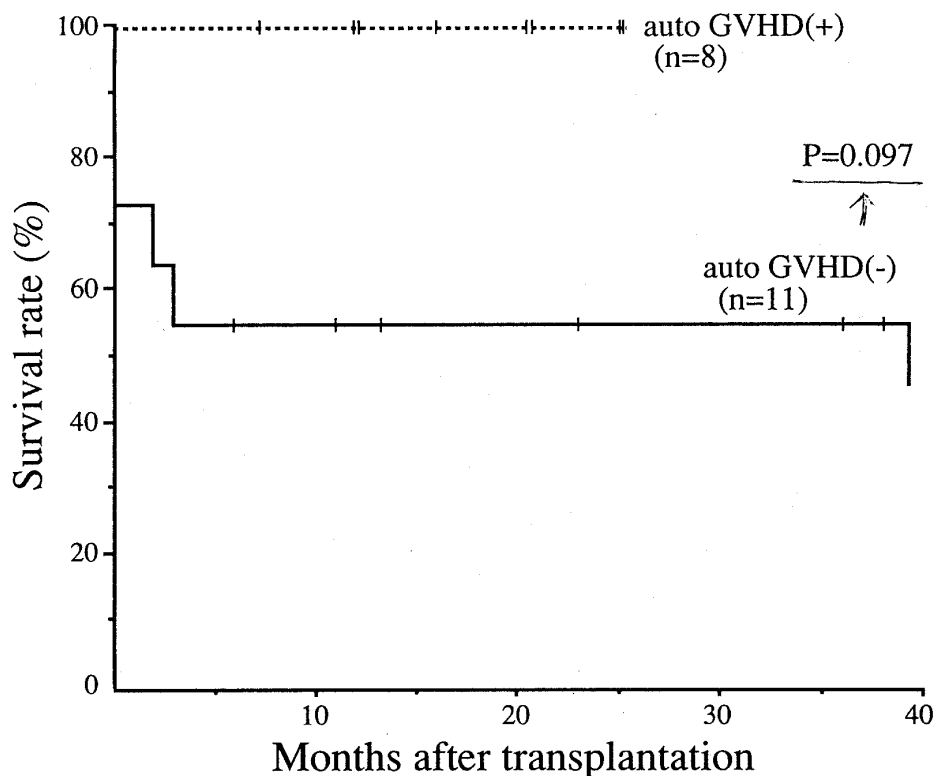


FIG 5. Kaplan-Meier analysis of disease-free survival in the 19 patients with NHL who were treated with PBSCT. Significance was determined by the Wilcoxon rank test.

TABLE III. Outcomes of treatment

Group	Patient no.	Development of GVHD		Response to PBSCT	Current Status
		Day of onset	Duration		
A	1	(—)*	(—)	CR	Alive (42 m), with disease
	2	(—)	(—)	CR	Alive (36 m), NED
	3	(—)	(—)	CR	Alive (38 m), NED
	4	(—)	(—)	PD	Died of disease (27 d)
	5	(—)	(—)	CR	Alive (23 m), NED
	6	(—)	(—)	PR	Alive (22 m), with disease
B	7	19	5	CR	Alive (26 m), NED
	8	(—)	(—)	NR	Alive (30 m), with disease
	9	24	6	CR	Alive (26 m), NED
	10	(—)	(—)	CR	Alive (20 m), with disease
	11	27	5	CR	Alive (21 m), NED
	12	(—)	(—)	CR	Alive (20 m), NED
	13	25	7	CR	Alive (16 m), NED
	14	26	9	PR	Alive (15 m), with disease
	15	23	3	CR	Alive (14 m), NED
	16	25	6	CR	Alive (12 m), NED
	17	(—)	(—)	CR	Alive (12 m), with disease
	18	29	6	CR	Alive (7 m), NED
	19	(—)	(—)	CR	Alive (6 m), NED

CR, Complete remission; NED, no evidence of disease; PD, progressive disease; PR, partial remission; NR, no response;

*Indicates that GVHD did not develop.

gous GVHD in PBSC recipients. Transplantation of autologous CD34⁺ cells is associated with a higher incidence of viral infection, probably because of the low number of T cells and natural killer cells in the periph-

al blood soon after transplantation compared with transplantation of unmanipulated PBSCs.²⁷ Thus, the administration of cyclosporin A for 3 weeks appears to be safer than 4 weeks in this regard.

Eleven of the 19 patients received TBI before PBSCT. The incidence of autologous GVHD in these patients was 64%, which was comparable to that reported previously.^{14,16} Although it is accepted that high-dose chemotherapy is capable of abrogating the autoregulatory system that inhibits autoreactive T cells and thus induce autologous GVHD,^{15,16} the chemotherapy regimen we used may not have been as potent as regimens such as thiopeta, busulfan, and cyclophosphamide. It must be determined whether a regimen including TBI is more effective for the induction of autologous GVHD in PBSCT patients than a pure chemotherapy regimen.

Although all of the patients with NHL who were enrolled in this study had poor prognostic factors, the disease-free survival rate was 63%, which improved to 100% when only the patients who experienced the development of autologous GVHD were assessed. Although the follow-up period was short, these results appear to be better than those for patients with NHL with poor prognostic factors reported previously.^{2,5} It therefore seems possible that the induction of autologous GVHD with cyclosporin A and IFN- γ may benefit patients with refractory NHL. When autologous PBSCT is scheduled for patients with NHL who have poor prognostic factors, the administration of cyclosporin A for 3 weeks coupled with a conditioning regimen including TBI or the use of purified CD34⁺ cells is recommended.

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