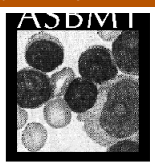

Equivalence of 2 Effective Graft-Versus-Host Disease Prophylaxis Regimens: Results of a Prospective Double-Blind Randomized Trial

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ABSTRACT

We have previously demonstrated a decrease in the incidence of acute graft-versus-host disease (GVHD) with the addition of methotrexate (MTX) to cyclosporine (CSP) and prednisone (PSE) chemotherapy in patients with leukemia. We have now completed a prospective randomized trial comparing the 3-drug regimen (CSP/MTX/PSE, including 3 doses of MTX) to the standard 2-drug regimen (CSP/MTX, including 4 doses of MTX) to investigate the benefit of PSE used up front for the prevention of acute and chronic GVHD. In the trial, 193 patients were randomized and 186 were included in the final analysis. All patients received a bone marrow graft from a fully histocompatible sibling donor. The preparatory regimen consisted of fractionated total-body irradiation (fTBI) and etoposide in all but 13 patients, who received fTBI and cyclophosphamide. The patients were randomized to receive either CSP/MTX/PSE or CSP/MTX. The 2 groups were well balanced with respect to diagnosis, disease stage, age, donor-recipient sex, and parity. In an intent-to-treat analysis, the incidence of acute GVHD was 18% (95% confidence interval [CI] 12-28) for the CSP/MTX/PSE group compared with 20% (CI 10-26) for the CSP/MTX group (P = .60), with a median follow up of 2.2 years. Overall survival was 65% for those receiving CSP/MTX/PSE and 72% for those receiving CSP/MTX (P = .10); the relapse rate was 15% for the CSP/MTX/PSE group and 12% for the CSP/MTX group (P = .83). The incidence of chronic GVHD was similar (46% versus 52%; P = .38), with a follow-up of 0.7 to 6.0 years. Of interest, 21 patients went off study due to GVHD (5 in the CSP/MTX/PSE group and 16 in the CSP/MTX group [P = .02]), and 11 patients went off study because of alveolar hemorrhage (3 in the CSP/MTX/PSE group and 8 in the CSP/MTX group [P = .22]). The addition of PSE did not result in a higher incidence of infectious complications, bacterial (66% versus 58%), viral (77% versus 66%), or fungal (20% versus 20%), in those receiving CSP/MTX/PSE versus CSP/MTX, respectively. These data suggest that the addition of PSE was associated with a somewhat lower incidence of early posttransplantation complications but did not have a positive impact on the incidence of acute or chronic GVHD or event-free or overall survival.

KEY WORDS

Prednisone • Methotrexate • Graft-versus-host disease • Leukemia

INTRODUCTION

Graft-versus-host disease (GVHD) is the result of an intricate immune response to foreign allogeneic stimuli. GVHD is the process caused by the immunologic response of donor T cells infused into an allogeneic recipient [1,2], but removal of T cells that are responsible for GVHD has been associated with a higher rate of graft failure and relapse [3-5]. The use of immunosuppressive drugs is another approach to the prophylaxis of acute GVHD. Many studies have used combinations of immunosuppressive drugs after HLA-identical marrow transplantation. The regimen of methotrexate (MTX) on days 1, 3, 6, and 11, plus a 180-day course of cyclosporine (CSP) twice a day, was compared with either drug used alone [6-9]. The combination regimen

Table 1. *Characteristics of Evaluable Patients**

	CSP/MTX	CSP/PSE/MTX	*P*	
No. of patients	96	90		
Disease				
Chronic myelogenous leukemia				
CP1	39 (41)	36 (40)	.97	†
Beyond CP1	5 (5)	7 (8)		
Acute myelogenous leukemia				
CR1	23 (24)	19 (21)		
Beyond CR1	8 (8)	9 (10)		
Acute lymphoblastic leukemia				
CR1	12 (13)	10 (11)		
Beyond CR1	9 (9)	9 (10)		
Median age in years (range)	34.5 (1-50)	34.5 (2-49)	.78	‡
Donor-recipient sex				
Match	51 (53)	45 (50)	.77	†
Mismatch	45 (47)	45 (50)		
Donor-recipient sex and parity				
Nonparous F/F	6 (6)	3 (3)	.61	†
Nonparous F/M	6 (6)	7 (8)		
Parous F/F	8 (8)	12 (13)		
Parous F/M	15 (16)	9 (10)		
M/F	20 (21)	22 (24)		
M/M	36 (38)	30 (33)		
Unknown parity F/F	1 (1)	0 (0)		
Unknown parity F/M	4 (4)	7 (8)		

**Data are n (%) unless otherwise indicated. CP1 indicates first chronic phase; CR1, first complete remission.*

†*Fisher exact test.*

‡*Wilcoxon rank sum test.*

was shown to reduce GVHD and improve survival. This regimen remains the most widely used for the prophylaxis of acute GVHD.

In 1976, we began a series of sequential trials for the prophylaxis of acute GVHD. In a prospective randomized study, CSP combined with prednisone (PSE) was demonstrated to reduce the incidence of GVHD from 47% to 28% compared with the combination of MTX with PSE [10]. This regimen was subsequently modified by increasing the dose of PSE and starting it on day 7 rather than on day 15, resulting in a further reduction in the incidence of acute GVHD (K.G.B., S.J.F., unpublished data). Based on this encouraging information, we conducted a randomized study to determine whether the addition of 3 doses of MTX (days 1, 3, and 6) to the CSP and PSE regimen would further decrease the incidence of acute GVHD. The results of this prospective study demonstrated that the combination of CSP, MTX, and PSE was more effective in preventing acute GVHD than the combination of CSP and PSE without MTX in a selected group of optimal bone marrow transplantation (BMT) candidates, ie, those in early stages of their leukemia [11].

Based on these results, we decided to perform a prospective randomized double-blind study to test this regimen of CSP, MTX, and PSE compared with the standard widely used regimen of CSP and MTX. The regimen of CSP was identical in both arms; however, in the 3-drug arm, 3 doses of MTX were administered on days 1, 3, and 6, whereas the 2-drug regimen used 4 doses of MTX on days 1, 3, 6, and 11.

PATIENTS AND METHODS

Patients

All clinical protocols were approved by the Institutional Review Boards at Stanford University Medical Center (Stanford, CA), City of Hope National Medical Center (Duarte, CA), and Duke University Medical Center (Durham, NC). The risks and benefits of the treatment regimens were explained in detail to each patient during at least 2 outpatient visits and again on the day of admission. Written informed consent was obtained from all patients and, if the patient was a minor, from a parent or guardian. Between 1992 and April 1998, 193 patients were entered into this trial. Five patients were not evaluable for GVHD (they died between days 19 and 29 before engraftment: 3 of multiorgan failure, 1 of graft failure, and 1 of diffuse alveolar hemorrhage) but were included in the toxicity analyses, and 2 patients were deemed ineligible (abnormal pretransplantation liver function tests and the use of a different preparatory regimen). The results presented are based on 186 evaluable patients. To be eligible for the study, patients had to receive a bone marrow graft from a histocompatible sibling donor for the treatment of acute leukemia in first or second remission or first relapse or chronic myelogenous leukemia in first or second chronic phase or accelerated phase. Patient characteristics are described in Table 1. Patients were well balanced in terms of disease and stage, age, donor-recipient sex, and donor parity.

Preparatory Regimens

The preparatory regimen was fractionated total-body irradiation (fTBI) and etoposide in all but 13 patients, who received fTBI and cyclophosphamide (7 in the 3-drug regimen; 6 in the 2-drug regimen). fTBI consisted of 1320 cGy given in 11 fractions on day –7 through –4. Etoposide was given intravenously as a single dose of 60 mg/kg over 4 hours on day –3 [12]. Cyclophosphamide was given at a dose of 60 mg/kg/day over 1 hour on days –3 and –2. All patients received bone marrow only, infused on day 0.

GVHD Prophylaxis

All patients received CSP by continuous intravenous infusion with a loading dose starting on day –2 (Figure 1). Serum CSP concentrations were measured 3 times a week by immunoassay (TDx System; Abbott Laboratories, Abbott Park, IL). The patients were randomized to receive either CSP/MTX/PSE or CSP/MTX. Patients randomized to the 3-drug group received a placebo on day 11 instead of MTX. Patients randomized to the 2-drug group received a placebo injection instead of PSE and an oral placebo tablet (sodium bicarbonate) after they were able to take oral medication. The placebo was taken through day 42, at which time the patients were taken off placebo if on the 2-drug arm or continued on PSE as planned on the 3-drug arm. The randomization was blinded to all investigators and was known only to the data management group and the pharmacist.

GVHD Grading

Acute GVHD was graded uniformly by clinical investigators at the 3 study centers according to previously defined criteria [13]. Retrospective chart reviews were also performed by 1 independent investigator at the end of the trial. All patients with a rash suggestive of GVHD underwent a

	Day	Dose	Route		
Cyclosporine	–2 to 3	5 mg/kg	IV q.d. over 20 hours	2-drug regimen	3-drug regimen
	4 to 14	3 mg/kg	IV q.d. over 20 hours		
	15 to 35	3.75 mg/kg	IV q.d. over 20 hours		
	36 to 83	5 mg/kg	p.o. b.i.d.		
	84 to 97	4 mg/kg	p.o. b.i.d.		
	98 to 119	3 mg/kg	p.o. b.i.d.		
	120 to 180	2 mg/kg	p.o. b.i.d.		
	≥181	off			
Methotrexate	1	15 mg/m ^{2}	IV		
	3	10 mg/m ^{2}	IV		
	6	10 mg/m ^{2}	IV		
	11	10 mg/m ^{2}	IV*		
Methylprednisolone (IV)/prednisone (p.o.)					
	7 to 14	0.25 mg/kg	IV b.i.d.		
	15 to 28	0.5 mg/kg	IV b.i.d.		
	29 to 42	0.4 mg/kg	p.o. b.i.d.		
	43 to 56	0.25 mg/kg	p.o. b.i.d.		
	57 to 119	0.1 mg/kg	p.o. b.i.d.		
	120 to 180	0.1 mg/kg	p.o. q.d.		
	≥181	off			

Figure 1. *Schema of the 2 prophylactic regimens. *Note that the day-11 methotrexate dose in the 3-drug arm was a placebo.*

skin biopsy to document involvement with GVHD. Biopsies of the liver or gut were performed as clinically indicated; however, the ultimate grading was based on the clinical signs and symptoms.

Dose Adjustment

If a patient developed clinical acute GVHD, the investigators could place the patient on PSE (intravenous formulation) at 1 mg/kg for up to 3 days while the skin or tissue biopsy was obtained to document GVHD histologically. If the biopsy did not confirm the diagnosis, the investigators could resume the PSE/placebo administration. If the diagnosis was confirmed, the code was broken. If the patient was not on the PSE-containing arm (ie, had been taking placebo), PSE was continued at 1 mg/kg; if the patient was already on PSE, the dose was increased to 2 mg/kg. The amount of each drug actually administered was determined by a review of records and expressed as a percentage of planned doses.

Supportiv e Care

All patients were hospitalized in private rooms with high-efficiency particulate air filtration systems. Strict hand washing was implemented with all patients. Broad-spectrum antibiotics were used to treat initial episodes of fever, and beginning on day 1, low-dose amphotericin B (0.15 mg/kg) was given to all patients as prophylaxis for fungal infections [14]. All blood products were irradiated at 2500 cGy. All patients received intravenous immunoglobulins every other week at a dose of 500 mg/kg. Patients who were seropositive for cytomegalovirus or received bone marrow from a CMV-seropositive donor were screened weekly for CMV antigen and treated with preemptive ganciclovir if the CMV antigen was detected [15]. Hematopoietic growth factors were not routinely used in these patients.

Statistical Anal yses

Throughout this study, patients were monitored by a Data and Safety Monitoring Board at predefined intervals. This committee was led by the biostatistics group of the participating centers and included 2 physicians not associated with the trial. The patient accrual goal was based on a 15% incidence of acute GVHD in the 3-drug arm compared with 30% in the 2-drug arm. At the initiation of the trial, 3 interim analyses were planned. At the second interim analysis, after 186 patients had been registered, the Data and Safety Monitoring Board conducted a Monte Carlo simulation based on the current accrual and incidence of GVHD in each of the 2 treatment arms. The conclusion from this analysis suggested that further accrual would not achieve the initially projected end point. Therefore, the study was closed to further accrual and the results were analyzed. Patient characteristics and outcomes in the 2 treatment groups were compared by Fisher exact test and Wilcoxon rank sum test. The significance testing of chronic GVHD was performed using Pearson chi-square test. The Kaplan-Meier method was used to estimate the probabilities of survival, relapse, and acute GVHD over time. The 2 study groups were compared using log rank statistic [16].

RESULTS

Drug Administration

Both groups of patients had similar median serum concentrations of CSP. The median administered dose of MTX was

Table 2. *Patients Receiving Target MTX Dose**

	CSP/MTX	CSP/MTX/PSE
No. of patients	96	90
Day 1	93 (97)	85 (94)
Day 3	93 (97)	87 (97)
Day 6	83 (86)	77 (86)
Day 11	55 (57)	58 (64) †

**Data are n (%).*

†*Placebo.*

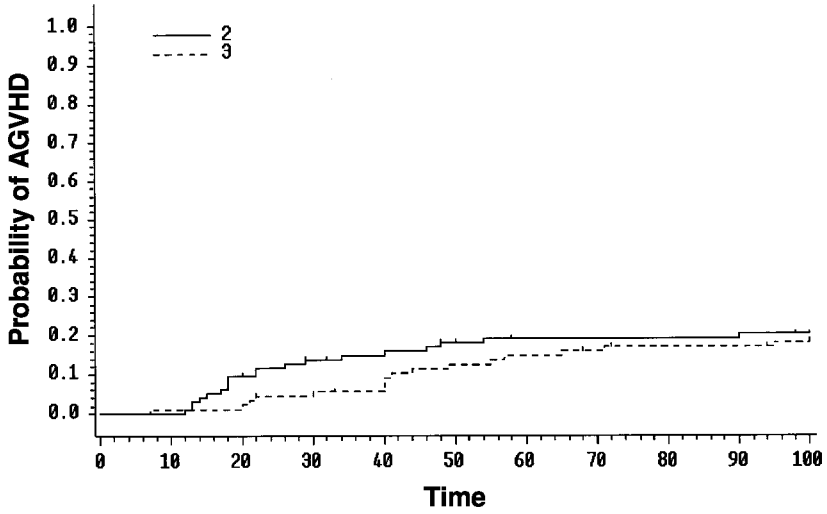

Figure 2. *Incidence of onset of grade II to IV acute graft-versus-host disease (AGVHD) (P = .60).*

100% of the planned dose. Of the patients in the 2-drug arm, 90% received the day 1, 3, and 6 doses of MTX and 57% received the day 11 dose (Table 2). All patients received the target doses of PSE (intravenous or oral) except patients who developed acute GVHD, who received higher doses of PSE.

Engraftment

All 186 patients experienced engraftment with donor cells, according to assays using restriction fragment length polymorphism or other suitable genetic markers. The median time to myeloid recovery (500 granulocytes/μL) was 19 days in the 3-drug arm compared with 21 days in the 2-drug arm ($P = .0001$). The time to platelet transfusion independence (>25,000 platelets/μL sustained for 3 days) was 27 days for the 3-drug group and 30 days for the 2-drug group ($P = .67$).

Table 3. *Graft-Versus-Host Disease (GVHD) Outcome**

	CSP/MTX	CSP/MTX/PSE	*P*
No. of patients	96	90	
Median days to acute GVHD (range)	22 (12-90) (n = 19)	40.5 (7-95) (n = 16)	.02†
Acute GVHD			
Grade 0	58 (60)	60 (67)	
Grade 1	19 (20)	14 (16)	
Grade 2	9 (9)	9 (10)	
Grade 3	5 (5)	1 (1)	
Grade 4	5 (5)	6 (7)	
Grade 0-1	77 (80)	74 (82)	0.73‡
Grade 2-4	19 (20)	16 (18)	
Chronic GVHD			
None	53 (55)	51 (57)	0.39‡
Limited	12 (13)	6 (7)	
Extensive	31 (32)	33 (37)	

**Data are n (%) unless otherwise indicated. For CGVHD significance testing between arms, "limited" and "extensive" were combined as "yes" (2 × 2 table).*
†*Wilcoxon rank sum test.*
‡*Pearson chi-square test.*

Graft-V ersus-Host Disease

The incidence of grades II-IV acute GVHD was 20% (95% confidence interval [CI] 12-28) for the 2-drug regimen compared with 18% (CI 10-26) for the 3-drug regimen ($P = .60$) in an intent-to-treat analysis. Although the total incidence of acute GVHD was not significantly different, the use of PSE seemed to delay the onset of GVHD (Figure 2). Patients receiving CSP and MTX had a median onset of acute GVHD at 22 days (range 12-90) compared with 40.5 days (range 7-95) for those who also received PSE ($P = .02$). It is important to note that with a follow-up of 0.7 to 6.0 years, the rates of chronic GVHD (limited and extensive) were also equivalent between the 2 treatment arms (Table 3), 45% and 43%, respectively.

Table 4. *Treatment Toxicities**

	CSP/MTX	CSP/MTX/PSE	*P*
No. of patients	96	90	
Mucositis (days of morphine drip)†			
Maximum	48	43	.33‡
Third quartile	25	23	
Median	19	18	
First quartile	15	15	
Minimum	0	0	
Peak creatinine (mg/dL) over 100 days	1.8 (0.6-7.6)	1.8 (0.4-6.2)	.30‡
Peak bilirubin (mg/dL) over 100 days	2.9 (0.8-56)	2.8 (0.6-45)	.90‡
Peak alkaline phosphatase (mg/dL) over 100 days	194.5 (61-1339)	146 (56-1271)	.002‡
Peak AST (U/L) over 100 days	102 (40-3711)	106 (25-662)	.76‡
Peak ALT (U/L) over 100 days	149.5 (29-3154)	232 (29-2030)	.01‡

**Data are median (range) unless otherwise indicated. AST indicates aspartate transaminase; ALT, alanine transaminase.*
†*One patient from each group had missing mucositis data.*
‡*Wilcoxon rank sum test.*

Table 5. *Infectious Complications Between the 2 Treatment Groups**

	CSP/MTX		CSP/MTX/PSE	
	Documented Infections (n)	Patients (n)	Documented Infections (n)	Patients (n)
Bacterial infections	112	56	88	48
Gram positive	52	35	44	34
Gram negative	44	30	36	23
Others	16	16	8	8
Viral infections	97	69	83	63
Cytomegalovirus	57	56	47	46
Herpes simplex	25	23	25	25
Herpes zoster	10	10	6	6
Varicella	1	1	0	0
Other	4	4	5	5
Fungal infections	16	16	15	13
Aspergillus	10	10	7	7
Candida	5	5	5	4
Other	1	1	3	3
Other infections †	3	3	1	1

**Includes 5 patients not evaluable for graft-versus-host disease.*

†*Toxoplasmosis, Pneumocystis carinii, or Mycobacterium.*

Toxicity

Table 4 demonstrates the toxicity associated with these 2 regimens over the first 100 days after allografting. There was no difference in the overall incidence of mucositis between the 2 regimens in spite of 1 arm receiving 4 versus 3 doses of MTX. The median peak serum creatinine and bilirubin levels were likewise similar between the 2 treatment arms. There was a higher median peak alkaline phosphatase level with the 2-drug regimen but higher median alanine transaminase with the 3-drug regimen.

Infections

Infection data were collected prospectively and corroborated with a retrospective review in a blinded fashion. The data collected reflect any infection from the time of admission until 1 year after transplantation. Table 5 summarizes the overall incidence of bacterial, viral, fungal, and other infections. As demonstrated in Table 5, the incidence of infectious complications was not significantly different between the 2 groups, although the 3-drug group tended to have fewer infections. Of note, the addition of PSE did not result in a higher incidence of fungal infections.

Reasons for Removal From Study

Table 6 details the reasons patients went off the study drug within the first 42 days, excluding death as an end point. The results from this analysis demonstrate that a higher number of patients withdrew from the study drug for acute GVHD in the 2-drug versus the 3-drug regimen (16 versus 5 patients, $P = .02$). Moreover, there was a trend toward a higher incidence of diffuse alveolar hemorrhage in those patients not receiving PSE as part of GVHD prophylaxis (8 versus 3, $P = .22$). The other causes for removal from the study were equally distributed between the 2 groups.

Treatment Outcome

As of July 15, 1999, estimated 2-year overall survival was 65% for those receiving CSP/MTX/PSE and 72% for those receiving CSP/MTX ($P = .10$), with a relapse rate of 15% for the CSP/MTX/PSE arm and 12% for the CSP/MTX arm ($P = .83$). There was no significant difference in overall survival, event-free survival, or time to relapse between the 2 groups (Figures 3, 4, and 5). Both groups of patients had a rather favorable outcome from this procedure (Table 7).

DISCUSSION

This report describes our experience with a prospective double-blind randomized study for the prevention of acute GVHD in patients undergoing allogeneic bone marrow transplantation for hematologic diseases. We compared the combination of CSP and MTX developed by the Seattle group with the CSP, MTX, and PSE regimen we had developed. The results of this study demonstrate that the regimens are equally effective in the prevention of acute GVHD.

Table 6. *Reasons for Discontinuing Assigned Therapy*

	CSP/MTX	CSP/MTX/PSE	Total
Graft-versus-host disease	16	5	21
Diffuse alveolar hemorrhage	8	3	11
Adult respiratory distress syndrome	2	1	3
Lung disease	1	0	1
Rising bilirubin	1	0	1
Interstitial pneumonitis	0	1	1
Relapse	0	1	1
Mucositis/sepsis	1	0	1
Other toxicity	1	0	1
PSE for placebo*	0	1	1
Wrong MTX dose	1	1	2
Refused MTX	1	0	1
Accidental unblind	1	0	1
Total	33	13	46

**PSE was substituted for placebo when the patient was diagnosed with graft-versus-host disease.*

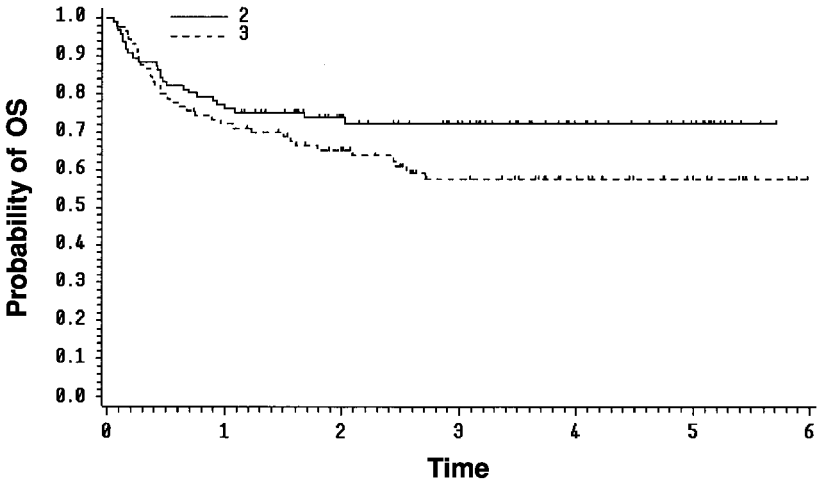

Figure 3. *Overall survival (OS) in the 2 treatment groups (P = .10).*

The combination of CSP and MTX has been shown in several studies to be more effective than single agents in the prevention of acute GVHD. This regimen is the most widely used combination for prophylaxis against acute GVHD. The incidence of grade II to IV acute GVHD is approximately 35% [7,8], and the incidence of chronic GVHD is approximately 40%. When PSE was added to this regimen beginning on day 0, the incidence of acute GVHD increased, possibly because of interference with the immunosuppressive action of MTX by the steroids [17]. The overall survival between those who received steroids and those who did not was similar.

We had previously tested a regimen consisting of CSP, 3 doses of MTX, and PSE beginning on day 7 in a uniform group of patients with leukemia [11]. These patients were optimal candidates for allogeneic BMT. All were in first complete remission of their acute leukemia or in first chronic phase of chronic myeloid leukemia, and all received the same preparatory regimen consisting of fTBI and etoposide. In that study, we compared the 3-drug regimen to CSP and PSE. The results demonstrated a low incidence of acute GVHD of only 9% in patients receiving the 3 drugs. Moreover, whereas the overall incidence of chronic GVHD was approximately 60%, the incidence of extensive chronic GVHD was not excessive, resulting in an overall Karnofsky performance status of at least 80% in the majority of patients. The 3-drug combination as tested was not simply the addition of steroids to the conventional 2-drug regimen of CSP and MTX; it used only 3 doses of MTX given on days 1, 3, and 6 with the steroids beginning on day 7. MTX was given for only 3 days because prior studies had suggested that many patients were not able to receive the day 11 dose.

The present study demonstrates an equivalent incidence of acute GVHD of 18% to 20% with either regimen. The incidence of acute GVHD was higher than we had predicted with the 3-drug regimen and lower than predicted with the standard CSP/MTX regimen based on our experience and results published in the literature. The

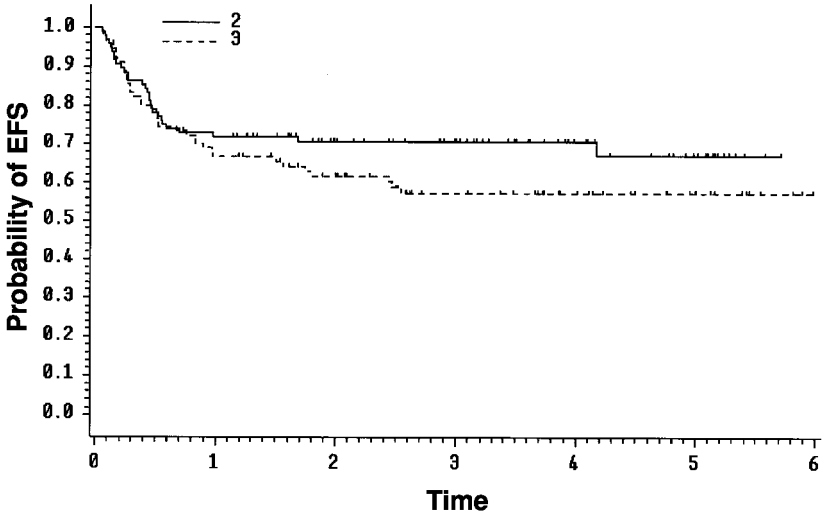

Figure 4. *Event-free survival (EFS) in the 2 treatment groups (P = .18).*

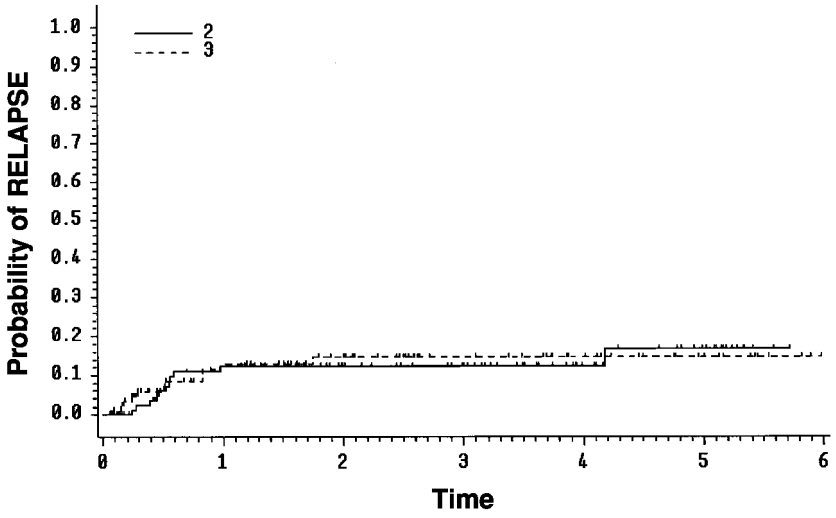

Figure 5. *Probability of relapse in each of the treatment arms (P = .83).*

difference in the incidence of acute GVHD using the 3-drug regimen in this study and our previously published observations may be explained by differences in patient population. Whereas the previous study randomized only optimal candidates, the current study allowed for patients with more advanced leukemias. Other reports have demonstrated that advanced leukemia is an independent risk factor for acute GVHD [18]. Therefore, the higher incidence of acute GVHD in this study was not surprising; the lower incidence of acute GVHD with the 2-drug regimen was unexpected, however. In this study, the majority of patients received the target doses of MTX (nearly 90% received the day 6 dose and 60% the day 11 dose), and dose reductions in MTX on days 6 and 11 have been associated with a higher incidence of acute GVHD. Most of the patients had the later doses of MTX delayed for either severe mucositis or azotemia. Therefore, the commitment of the investigators to deliver the target doses may have led to this lower incidence of acute GVHD in the group receiving CSP/MTX compared with the published data. In the Seattle experience, 26% of patients did not receive MTX at all on day 11 [18]. The difference between the ability to deliver the full day 11 dose of MTX may explain the lower incidence of acute GVHD in the 2-drug arm compared with previously published experience.

Although the overall incidence of acute GVHD between the 2 arms was not different by day 100, there were differences within the first 100 days. The median time to acute GVHD was 22 days for CSP/MTX compared with 40.5 days for CSP/MTX/PSE. Moreover, as demonstrated in Table 6, more patients in the CSP/MTX arm compared with patients in the 3-drug arm went off the study because of the development of acute GVHD. That effect was only temporary, however, and by day 100, the incidence of acute GVHD was similar (Figure 2). The incidence of diffuse alveolar hemorrhage was also higher in the patients receiving only CSP/MTX. These data hint at the possibility that steroids will blunt the initial (possibly cytokine-related) toxicity associated with high-dose radiation and chemotherapy.

The occurrence of acute GVHD also predicts the development of chronic GVHD. There have been concerns that the use of PSE may actually increase the incidence of chronic GVHD. In this randomized study, we could not detect a difference in the incidence or severity of limited or extensive chronic GVHD. Relapse rates were also similar in the 2 groups of patients. The relatively low relapse rate may be partly explained by the combination of the preparatory regimen with the incidence of chronic GVHD, ie, graft-versus-leukemia effect.

A previous retrospective study from Seattle suggested that there was an increased risk of infection in marrow transplantation patients receiving PSE for GVHD prevention [18]. In our study, using an intent-to-treat analysis, we did not detect any significant difference in overall incidence or types of infectious complications in the 2 treatment groups, with more than 1 year of minimum follow-up. In fact, the overall number of bacterial infections was lower in the patients on PSE compared with those who did not receive PSE (Table 5). It is not clear whether this comparable immunosuppression is due to the delivery of day 11 MTX in the 2-drug arm or whether the infectious prophylaxis measures have improved since the previously reported Seattle experience. These results suggest that the addition of PSE did not result in a deleterious effect on infectious complications.

Table 7. *Treatment Outcomes**

	CSP/MTX	CSP/PSE/MTX	*P*	
No. of patients	96	90		
Follow-up (months)				
Total	28 (0.7-69)	25 (0.7-72)	.64	†
Alive only	38 (14-69)	44 (9-72)	.44	†
Patients alive ‡	70 (72; 63-81)	54 (65; 55-75)	.10	§
Leukemic recurrence §	11 (10; 2-22)	11 (15; 7-23)	.83	§

**Data are median (range) or n (%; 95% CI).*

†*Wilcoxon rank sum test.*

‡*Kaplan-Meier 2-year estimates.*

§*Log rank statistic.*

These results are also in contrast to a previous report comparing the 2 regimens in which the 3-drug regimen was associated with a lower incidence of acute GVHD, but again, no difference in disease-free or overall survival [19]. Differences between these 2 studies may be secondary to patient selection, numbers of patients enrolled, or differences in the grading of acute GVHD. Moreover, our study blinded the methylprednisolone and the fourth dose of MTX to prevent potential investigator biases.

In conclusion, our study demonstrates that both prophylactic regimens are associated with acceptable rates of acute GVHD. Likewise, the treatment-related toxicities, relapse rate, disease-free and overall survival, and incidence of chronic GVHD were not statistically different. There was a suggestion that the addition of steroids may have been associated with a lower incidence of early complications.

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