

A Randomized Controlled Trial of Pentoxifylline for the Prevention of Regimen-Related Toxicities in Patients Undergoing Allogeneic Marrow Transplantation

By R.A. Clift, J.A. Bianco, F.R. Appelbaum, C.D. Buckner, J.W. Singer, L. Bakke, W.I. Bensinger, R.A. Bowden, G.B. McDonald, M. Schubert, A.F. Shields, J.T. Slattery, R. Storb, L.D. Fisher, M. Mori, E.D. Thomas, and J.A. Hansen

This study evaluated the effect of pentoxifylline (PTX) on the incidence of regimen-related toxicity in patients receiving allogeneic marrow transplants from related donors. All patients received a regimen of methotrexate and cyclosporine as prophylaxis against acute graft-versus-host disease (GVHD). Patients were randomized to receive PTX or a placebo for 70 days and the outcome was examined in a blinded fashion. Forty-four patients were evaluable in each study arm. PTX had no significant effect on engraftment, the incidence of GVHD, venoocclusive disease of the liver,

infection, the need for oxygen, posttransplant survival, or the duration of hospitalization. Patients receiving PTX were significantly more likely to develop major elevations of serum creatinine levels. PTX was poorly tolerated and induced significantly more vomiting than the placebo. PTX as administered in this randomized study was associated with significant toxicity and offered no benefit in reducing transplant-related morbidity or mortality.

© 1993 by The American Society of Hematology.

ORGAN DAMAGE caused by cytoreductive therapy (regimen-related toxicity [RRT]) is an important cause of treatment failure for patients with hematologic malignancy undergoing allogeneic marrow transplantation. In addition to a direct effect on survival, RRT¹ is a major obstacle to the delivery of regimens that result in a reduced probability of post-transplant relapse, and it also impedes the delivery of effective prophylaxis against graft-versus-host disease (GVHD).^{2,3}

Bianco et al⁴ have reported a phase 1-2 trial of pentoxifylline (PTX) [3,7-dimethyl-1-(5-oxo-hexyl)-xanthine] (Trental; Hoechst-Roussel Pharmaceuticals Inc, Somerville, NJ) for the prevention of transplant-related toxicities after bone marrow transplantation. The incidence of posttransplant complications was compared between 30 consecutive adult recipients of allogeneic (n = 26) or autologous (n = 4) marrow who received PTX and a historical control group of 20 consecutive patients receiving HLA-identical transplants for chronic myeloid leukemia (CML) in chronic phase (CP). This was a dose escalation study with patients receiving 1,200 mg, 1,600 mg, or 2,000 mg/d orally from day -10 through day 100 posttransplant. When compared with the historical control group, PTX recipients experienced a lower frequency of mucositis, hepatic venoocclusive disease (VOD), renal insufficiency, and acute GVHD, and they required significantly fewer days of total parenteral nutrition and of hospitalization. PTX administration at doses greater than 1,200 mg/d further reduced the severity of mucositis and the duration of hospitalization compared with patients receiving 1,200 mg/d.

Encouraged by these observations, we undertook a prospectively randomized study designed to define the value of prophylactically administered PTX to patients receiving allogeneic bone marrow transplants. We now report the results of this study.

MATERIALS AND METHODS

Study Design

Patients were eligible for this study if they received allogeneic marrow transplants from related donors and cyclosporine (CSP) and methotrexate (MTX)⁵ for prophylaxis against acute GVHD. There were no restrictions on the degree of HLA matching with the donor, on disease or phase, or on the pretransplant treatment regimen. Patients were randomized to receive PTX or placebo begin-

ning at a minimum of 3 days before commencing the preparative regimen for transplantation. Patients received treatment until day 70 after transplantation, at which time dose tapering was initiated. The objective of the study was to evaluate the effect of PTX on the incidence of RRT (specifically mucositis, renal dysfunction, and VOD) in patients undergoing marrow transplant.

Patients

Between December 21, 1990 and November 26, 1991, 101 patients were registered in this study and 13 were excluded from analysis for reasons stated in Table 1, leaving 44 patients randomized in the PTX group and the same number in the placebo group. Table 2 describes diagnoses, disease status, and recipient/donor histocompatibility matching. There was no difference in age distributions between the PTX and placebo groups (median age, 40 and 38 years; ranges, 8 to 59 and 18 to 65, respectively). Twenty patients in the PTX group and 22 in the placebo group were males. The percentages of patients seropositive for cytomegalovirus (CMV) and of seronegative patients with seronegative donors were not significantly different between the groups. The largest category consisted of patients with CML in chronic phase receiving HLA-identical transplants, in which 16 patients received PTX and 17 received placebo. Table 3 describes the treatment regimens used for patients in this study. The day of marrow infusion was designated day 0. All patients were registered on protocols approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Informed consent was obtained using forms approved by the Insti-

From The Fred Hutchinson Cancer Research Center and the Veterans Administration Medical Center, Seattle, WA.

Submitted February 25, 1993; accepted June 3, 1993.

Supported by Public Health Service Grants No. CA 15704, CA 18029, CA 18221, and CA 09515 awarded by the National Cancer Institute and HL36444 by the National Heart, Lung and Blood Institute, Department of Health and Human Services. E.D.T. is the recipient of a Research Career Award AI 02425 from the National Institute of Allergy and Infectious Diseases.

Address reprint requests to R.A. Clift, FIMLS, The Fred Hutchinson Cancer Research Center, 1124 Columbia St, Seattle, WA 98104-2092.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1993 by The American Society of Hematology.
0006-4971/93/8207-0008\$3.00/0

Downloaded from http://ashpublications.net/blood/article-pdf/82/7/2025/611695/2025.pdf by guest on 03 June 2024

Table 1. Patient Registration and Exclusion

Registrations	No.
Total	101
Change to ineligible protocol*	9
Not receiving transplant	2
Refused randomization	1
Died before PTX	1
Available for analysis	88

* Ineligible protocols were those that did not use MTX + CSP for GVHD prophylaxis.

tutional Review Board of the Fred Hutchinson Cancer Research Center.

Prophylaxis and Treatment of Acute GVHD

All patients were scheduled to receive intravenous MTX, 15 mg/m² on day 1 and 10 mg/m² on days 3, 6, and 11. CSP administration started on the day before marrow infusion (day -1) with a dose of 3.0 mg/kg/d intravenously in two divided doses (1.5 mg/kg each) infused over a period of 1 to 4 hours. Unless toxicities were encountered, CSP was continued at the same dose until day 50. After day 50 the dose of CSP was gradually reduced by 5% per week and the drug was discontinued at approximately 6 months after grafting. Intravenous CSP was discontinued once the patient started to eat and the drug was administered orally at a dose of 12.5 mg/kg/d in two divided doses (6.25 mg/kg each).⁵ Acute GVHD was diagnosed

Table 2. Disease and Transplant Type

Diagnosis	Phase	PTX		Placebo	
		Match	Mismatch	Match	Mismatch
AA	—	1	0	1	0
ALL	REL-1	1	0	1	0
	REL-2	0	0	0	1
	REM-1	1	0	0	0
AML	REM-2	0	2	0	0
	REL-1	0	0	1	1
	REL-2	0	0	0	1
CML	REM-2	0	0	0	1
	Chronic	16	6	17	5
	Accelerated	1	4	1	3
	Blast	0	2	2	0
CMMML	Blast-REM	1	1	0	1
	—	1	0	0	0
HD	REL	0	0	0	1
	REM-2	0	0	1	0
Lymphoma	REL	0	1	0	0
	REM-2	1	0	0	0
MDS	—	4	0	3	0
PNH	—	0	0	1	0
RA	—	1	0	2	0
Totals		28	16	30	14

Abbreviations: AA, aplastic anemia; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CMMML, chronic myelo-monocytic leukemia; HD, Hodgkin's disease; MDS, myelodysplasia; PNH, paroxysmal nocturnal hemoglobinuria; RA, refractory anemia with excess blasts; REL, relapse; REM, remission; Blast-REM, blast phase in remission; Match, HLA genotypically identical; Mismatch, not HLA genotypically identical.

Table 3. Transplant Regimens

TBI*	BU†	CY‡	PTX§	Placebo¶	
1.2 × 11		60 × 2	13	13	
1.2 × 12		60 × 2	1	2	
2.0 × 6		60 × 2	12	7	
2.25 × 6		60 × 2	1	0	
2.25 × 7		60 × 2	1	1	
	14	50 × 4	0	1	
2.0 × 6	7	50	5	3	
	16	60 × 2	9	16	
		50 × 4	2	1	
Total no. of patients				44	44

Abbreviations: TBI, total body irradiation; BU, busulfan; CY, cyclophosphamide.

* TBI: 1.2 × 11, 11 fractions each of 1.2 Gy delivered thrice daily; 1.2 × 12, 12 fractions as above; 2.0 × 6, 6 fractions each of 2.0 Gy delivered once daily; 2.25 × 6, 6 fractions each of 2.25 Gy delivered as above; 2.25 × 7, 7 fractions each of 2.25 Gy delivered as above.

† Total dose in milligrams per kilogram administered in 16 equal fractions over 4 days.

‡ Dose is in milligrams per kilogram, fractions are administered once daily.

§ Number of patients who received PTX.

¶ Number of patients who received placebo.

and graded according to published criteria⁶ and was treated with methylprednisolone (2 mg/kg/d for 3 to 4 weeks).⁷

PTX and Placebo

Patients were randomized to receive PTX at a dose of 600 mg orally 4 times daily or placebo beginning a minimum of 3 days before starting the preparative regimen. PTX was dispensed in 600 mg tablets. Both PTX and placebo were prepared in a coded fashion and health care providers did not know which preparation was provided. Patients received PTX or placebo until day 70 after transplant at which time the dose was tapered by 600 mg every 2 days until discontinuation. Patients unable to take the medication for medical reasons had an intravenous preparation substituted at an equivalent dose, with a return to oral medication as soon as possible. Patients who vomited shortly after administration of tablets had the dose repeated only if recoverable tablets were observed. Patients with diarrhea had the preparation crushed and mixed with liquid to facilitate administration and absorption.

Infection

Fever. A day of fever was defined as one on which a temperature of 38.5°C or more was recorded.

CMV infection. Viral cultures included both centrifugation cultures⁸ and inoculation onto layers of human fibroblasts by standard techniques. Viral cultures were obtained from urine, blood, and throat on a weekly basis through day 100 or until leaving Seattle, whichever was longer. Infection was defined as recovery of CMV from the throat, urine, or blood. Disease caused by CMV was defined as recovery of virus from a visceral site (lung, gastrointestinal tissue) or by bronchoalveolar lavage in patients who had signs and symptoms consistent with CMV pneumonia.

Mucositis

The severity of mucositis for days 6 to 12 posttransplant was graded in a 34-item assessment⁹ and an overall index of severity was calculated.

Statistical Analysis

Data from patients receiving PTX were compared with those of patients receiving placebo. Patients with CML in CP receiving matched transplants constituted the largest relatively homogeneous group and an additional comparison was performed including only these patients.

Normally distributed means were compared using the standard *t*-test, and other distributions were compared with the two sample Wilcoxon test.¹⁰ Other comparisons of proportion were performed with Fisher's exact test.¹¹ When the *t*-test failed to show significant differences between means, 95% confidence limits (CL) were calculated as a measure of the power of the test. The endpoint of survival analysis was death from any cause, censored by the end of follow-up. The distributions of survival duration were estimated by the method of Kaplan and Meier¹² and levels of statistical significance for differences between these curves were calculated by the Mantel-Cox statistic.¹³ Events were recorded through December 1992. Durations of follow-up were calculated to the latest date of contact with each patient.

RESULTS

Ciprofloxacin

Only 1 patient (in the PTX group) received ciprofloxacin during the transplant period. This was administered from day 18 to day 27 as part of the treatment of a pseudomonas infection.

Drug Delivery

The percentage of the prescribed dose of each drug received on each day through day 28 posttransplant was calculated for each patient. A significantly larger proportion of patients received 80% or more of the prescribed dose of drug on each day in the placebo arm than in the PTX arm ($P = .05$, Wilcoxon). This difference in compliance between the two arms was also present in the patients with CML in CP receiving transplants from matched siblings ($P = .009$, Wilcoxon).

The intravenous preparation of PTX was not available at the beginning of the study, and 6 patients in the PTX arm and 8 patients in the placebo arm could not have received the study drug intravenously for this reason. Eight patients in the PTX group and 13 patients in the placebo group did not require intravenous drug ($P = .31$, Fisher) and the median day of initiating intravenous drug was day 4 in each group. The intravenous administration of study drug was discontinued because of nausea in 8 patients in the PTX group and in 2 patients in the placebo group ($P = .17$, Fisher).

Emesis

The volume of emesis was recorded for each patient during each day of hospitalization. The mean volume of emesis for each group on each day between days -10 and +10 was significantly higher in the population of patients receiving PTX than in those receiving placebo ($P = .01$, Wilcoxon). The mean daily emesis was not different between the arms between days -3 and +1 (the peak period for regimen-induced emesis).

Engraftment

Granulocytes. The first of 3 consecutive days with a granulocyte count $0.5 \times 10^9/L$ or a granulocyte count of $1.0 \times 10^9/L$ were both used as measures of granulocyte engraftment. There was no significant difference between the arms in the days on which these levels were achieved. The mean days of engraftment for the PTX and placebo arms were 20 and 20, respectively, for $0.5 \times 10^9/L$ (CL 18.64, 21.64), and 20.75 and 22.93, respectively, for $1.0 \times 10^9/L$ (CL 20.04, 23.54). The analyses of granulocyte engraftment in patients with CML in CP receiving HLA-identical transplants conformed to the above with no significant differences between the arms in the speed of granulocyte engraftment.

Platelets. The day of platelet engraftment was defined as the first of 7 consecutive days with a platelet count of $20 \times 10^9/L$ or more without platelet transfusion. There was no significant difference between the arms in the rate of platelet engraftment, with the mean days of engraftment being 43.1 in the PTX group and 33.97 in the placebo group (CL 31.30, 45.62). The analysis for patients receiving HLA-identical transplants for CML in CP conformed to the above, with no significant differences between the arms in speed of platelet engraftment. There was no significant difference between the arms in the number of platelet units transfused per patient.

Transplant-Related Toxicity

Weight gain. Weight gain during the transplant period is frequently associated with VOD.¹⁴ There was no significant difference between the arms in the mean maximum weight gain as a percentage of the pretreatment weight, which was 7.54% in the PTX group and 6.83% in the placebo group ($P = .54$; CL 6.07, 8.31). The analysis for patients receiving HLA-identical transplants for CML in CP conformed to the above with no significant difference between the arms.

Creatinine ratios. In all patients there was a consistent decrease in serum creatinine levels between the commencement of cytoreductive therapy and the day of marrow infusion. The maximum serum creatinine during the first 28 posttransplant days was compared with the day 0 creatinine (creatinine ratio). These ratios were significantly higher for patients in the PTX arm (mean, 2.24) than for those in the placebo arm (mean, 1.78; $P = .04$, *t*-test). The proportion of patients with a creatinine ratio of 2 or more was 39% in the PTX group and 36% in the placebo group ($P = .77$, Fisher), but 20% of patients in the PTX group had creatinine ratios of 3 or more, compared with 7% in the placebo group ($P = .01$, Fisher). The mean creatinine ratios for patients with CML transplanted in CP from matched donors were not significantly different between the PTX and placebo groups (1.72 and 1.58, respectively). There was no significant difference between the arms in the day on which the maximum creatinine occurred.

Eighteen patients in each group received amphotericin B. Among these patients, the mean creatinine ratio was significantly higher in the PTX group than in the placebo group (3.20 v 2.17 , $P = .017$).

Bilirubin elevations. The maximum serum bilirubin level during the first 28 posttransplant days was compared with the pretreatment bilirubin (bilirubin ratio). Every patient had at least one measured serum bilirubin level that was more than 2.5 times the pretreatment bilirubin. The bilirubin ratios were higher in the patients receiving PTX (mean, 26.60) than in the patients receiving placebo (mean, 23.47), but the differences were not significant ($P = .62$, t -test; CL 18.77, 31.31). There was no difference between the arms in the day on which the maximum bilirubin increase occurred. The analysis of CML CP patients conformed to the above, with no significant differences in bilirubin elevation.

Mucositis. The mucositis index was not available for 6 patients in each arm because of death during the index period in 4 patients, partial data for another 5 patients, and no data for another 3 patients. Patients for whom there were incomplete or no data were not available for assessment at the appropriate times. The median score was 22.11 in the PTX patients and 20.54 in the placebo patients and there was no significant difference between the arms in this score for the patients evaluated ($P = .51$, t -test; CL 19.04, 25.60).

Pain medication. The median number of days on which patients received pain medications was 16.93 in the PTX group, compared with 14.07 in the placebo group; there was no significant difference between the arms in the number of days on which this was administered ($P = .13$, t -test; CL 13.66, 17.34). Three patients in the PTX arm and 8 patients in the placebo arm received no medication for pain relief during the first hospitalization ($P = .1$, Fisher).

Corticosteroid medication. Twenty patients in the PTX group and 22 in the placebo group received no steroids during the first hospitalization. Four patients in the PTX group and 5 in the placebo group received prednisone at a dose of less than 2 mg/kg/d. Prednisone therapy with 2 mg/kg/d or more was administered to 20 patients in the PTX group and 17 in the placebo group. The median duration of such therapy was 11 days in the PTX group and 7 days in the placebo group. The differences between the two arms were not significant.

Infection

Days of fever. Ten patients receiving PTX and 13 receiving placebo had no recorded days of fever during the first hospitalization. The mean number of days of fever was 4.09 for patients in the PTX group and 4.41 for patients receiving placebo; there was no significant difference between the arms for this variable ($P = .78$, t -test; CL 3.19, 5.31).

Amphotericin B. Eighteen patients in each group received amphotericin B and, among the patients with CML in CP receiving matched transplants, 5 patients in each group received amphotericin B.

Positive blood cultures during first hospitalization. Twelve patients in the PTX group and 13 patients in the placebo group had positive blood cultures.

Asymptomatic. In the PTX group, two patients each had a single episode of asymptomatic bacteremia with coagulase-negative staphylococci. In the placebo group, there

were seven episodes of asymptomatic bacteremia in 6 patients. Of these, 5 were caused by coagulase-negative staphylococci and two were attributable to diphtheroids.

Symptomatic. One patient in the PTX group had two separate episodes of bacteremia associated with fever, one caused by coagulase-negative staphylococci and the other by *Enterobacter cloacae*. Nine patients in the PTX group had single episodes of bacteremia associated with fever, and five of these were caused by *Candida* species and four by coagulase-negative staphylococci. Seven patients in the placebo group had single episodes of symptomatic bacteremia, five caused by coagulase-negative staphylococci and two by *Candida* species.

CMV infection. Twelve patients in the study had CMV infections during the period between transplant and day 100. Seven infections occurred in patients receiving PTX (2 in urine, 2 with viremia, 1 in the throat, 1 with a positive culture from broncho-alveolar lavage, and 1 with a positive esophageal culture). Four of these patients had tissue-documented disease (3 with pneumonia and one with esophagitis). In the placebo group, there were 5 CMV infections (2 with viremia, 1 with viruria, and 2, at autopsy, in the kidney and in the lung) and there were 2 cases of CMV disease (1 nephritis and 1 pneumonia, in the patients with the autopsy-discovered infections). There was no significant difference between the arms in the incidence of CMV infection or disease.

Prophylaxis Against Acute GVHD

One patient in the placebo arm died on day 6. The records of the other patients were examined to determine the efficiency with which the regimen for preventing acute GVHD was delivered. There was no statistically significant difference between the arms in compliance with the prescribed regimen of prophylaxis against acute GVHD.

Incidence of Acute GVHD

There was no significant difference between the arms in the incidence of acute GVHD Grades 2 to 4 for patients with HLA-identical related donors. There was a higher incidence of severe acute GVHD (grades 3 or 4) in the group of matched HLA patients receiving PTX (0.42) than in those receiving placebo (0.31), but the difference was not statistically significant ($P = .30$, Mantel-Cox).

Survival

There were 20 deaths in each group and 10 deaths in each group occurred within the first 100 days posttransplant. Within the group of patients with CML in CP transplanted from HLA-identical sibling donors, there were 5 deaths (3 within the first 100 days) in the 16 patients who received PTX compared with 3 deaths (none in the first 100 days) among the 17 patients who received placebo; none of these deaths were associated with posttransplant relapse. Figure 1 describes the survival for patients in both arms of the study.

Causes of Death

Table 4 presents the causes of death for patients categorized by arm of the protocol.

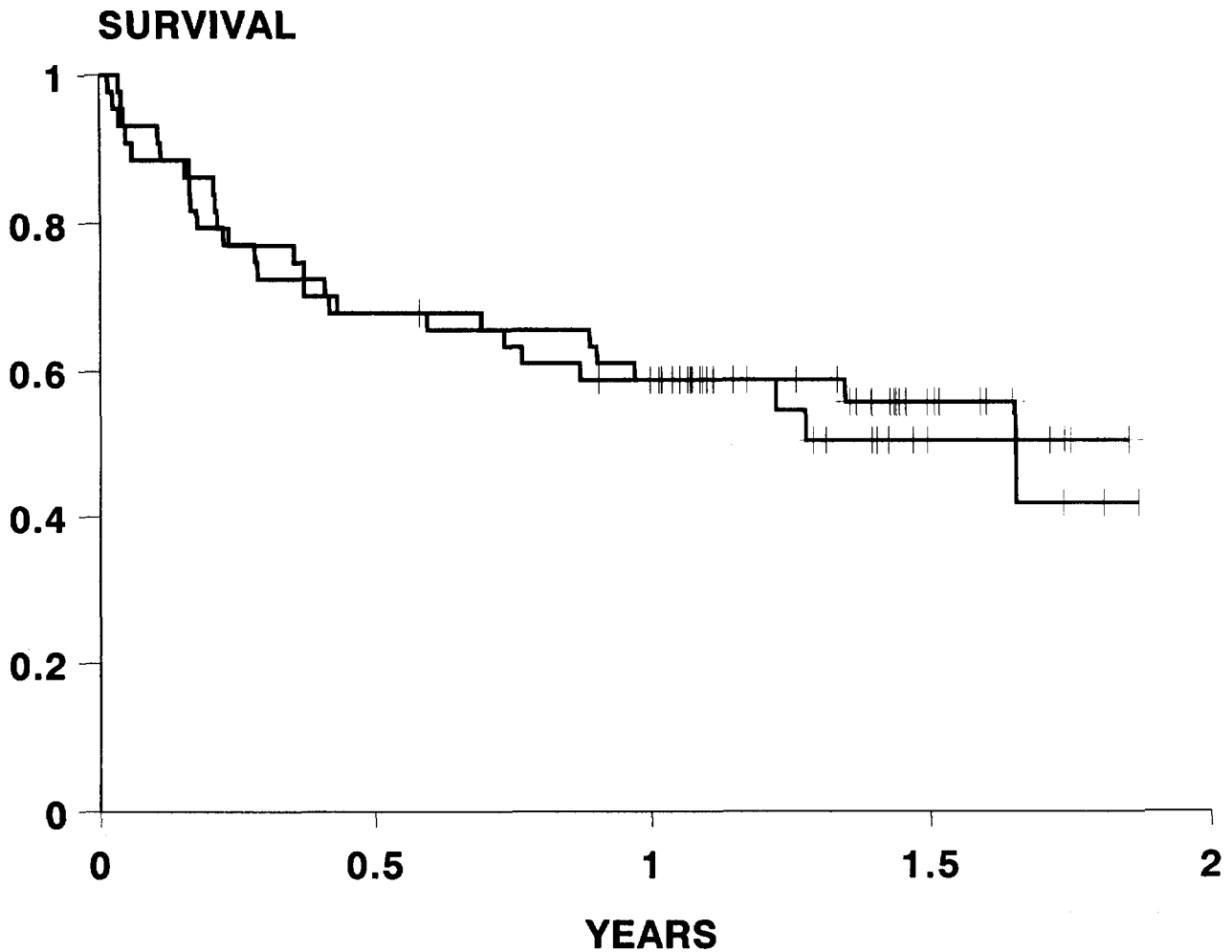


Fig 1. Kaplan-Meier plot of the probability of relapse-free survival for patients in each arm of the study.

Relapse

Six patients in each arm relapsed after transplant. Among the patients with CML in CP transplanted from HLA-identical siblings, there were 2 relapses (both in patients receiving PTX). This variable was not submitted to statistical examination because of the heterogeneity of relapse risk associated with diagnosis and phase in this study.

Miscellaneous Variables

Oxygen therapy. Nineteen patients in the PTX group and 21 patients in the placebo group received oxygen therapy during the first hospitalization.

Duration of hospitalization. There were no significant differences between the arms with respect to the duration of first inpatient admission, the total number of inpatient days, or the total number of outpatient days.

DISCUSSION

PTX was not well tolerated by patients in this study. The proportion of patients who received 80% or more of the prescribed dose was significantly higher in the placebo

group than in the PTX group and this may be related to the significantly increased nausea and vomiting in the PTX group. The intravenous preparation of PTX was not well tolerated and had to be discontinued more frequently than intravenous placebo.

PTX administration had no demonstrable effect on the speed or incidence of engraftment. PTX administration had no demonstrable effect on the development of VOD as measured by weight gain, bilirubin elevation, or death from VOD. There was no difference between the arms in the need for pain medication or for steroid administration. There was no significant effect on the incidence of infection as measured by days of fever, the incidence of symptomatic or asymptomatic bacteremia, the need for amphotericin B administration, or death from infection.

An unexpected finding was that patients receiving PTX were significantly more likely to develop a major elevation of serum creatinine. This effect was not present in the subpopulation of patients receiving HLA-identical transplants for CML in CP, but was strong in patients at greater risk of developing RRT. Not only did PTX provide no protection against renal toxicity in patients receiving amphotericin B,

Table 4. Causes of Death

Cause of Death	PTX	Placebo
No. of patients who died	20	20
No. who died after relapse	4	2
With acute GVHD		
CMV IP	3	1
Idiopathic IP	1	1
ARDS	1	2
Myocardial infarction	0	1
Infection	6	5
Epstein-Barr virus lymphoma	0	1
VOD of liver	2	0
Bronchiolitis obliterans	1	0
Hepatic failure	0	1
Without acute GVHD		
Infection	2	3
ARDS	0	1
Bronchiolitis obliterans	0	1
VOD of liver	0	1

Abbreviations: IP, interstitial pneumonitis; ARDS, adult respiratory distress syndrome.

but patients receiving both PTX and amphotericin B had significantly higher creatinine ratios than patients receiving placebo and amphotericin B.

There was no difference in survival, days of hospitalization, the institution of oxygen therapy, or the number of platelet units transfused.

We conclude that PTX, administered as described in this study, offers no benefit in reducing transplant-related morbidity and mortality, and may be associated with significantly increased toxicity. In recently published correspondence, Kalhs et al¹⁵ presented data showing no benefit with respect to transplant-related toxicities in marrow transplant recipients who had received parenteral prophylactic PTX. In the ensuing correspondence, Bianco and Singer¹⁶ discussed several possible reasons why this experience differed from that published in their report of a phase I-II study of PTX including the fact that most of the patients in the phase I-II study received dexamethasone as an antiemetic and noting that PTX was administered intravenously in the Kalhs trial and orally in the Bianco study. The present report, of a prospectively randomized placebo controlled trial, reinforces the findings of Kalhs et al. The reasons for the difference between the findings of this study and the published findings of the preliminary phase I-II study are unclear, but the speculations offered by Bianco and Singer in commenting on the Kalhs trial may explain some of the differences.

REFERENCES

- Bearman SI, Appelbaum FR, Back A, Petersen FB, Buckner CD, Sullivan KM, Schoch HG, Fisher LD, Thomas ED: Regimen-related toxicity and early posttransplant survival in patients undergoing marrow transplantation for lymphoma. *J Clin Oncol* 7:1288, 1989
- Clift RA, Buckner CD, Appelbaum FA, Bryant E, Bearman SI, Petersen FB, Fisher LD, Anasetti C, Beatty P, Bensinger WI, Doney K, Hill RS, McDonald GB, Martin P, Meyers J, Sanders J, Singer J, Stewart P, Sullivan KM, Witherspoon R, Storb R, Hansen JA, Thomas ED: Allogeneic marrow transplantation in patients with chronic myeloid leukemia in the chronic phase. A randomized trial of two irradiation regimens. *Blood* 77:1660, 1991
- Clift RA, Buckner CD, Appelbaum FR, Bearman SI, Petersen FB, Fisher LD, Anasetti C, Beatty P, Bensinger WI, Doney K, Hill R, McDonald G, Martin P, Sanders J, Singer J, Stewart P, Sullivan KM, Witherspoon R, Storb R, Hansen J, Thomas ED: Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission. A randomized trial of two irradiation regimens. *Blood* 76:1867, 1990
- Bianco JA, Appelbaum FR, Nemunaitis J, Almgren J, Andrews F, Kettner P, Shields A, Singer JW: Phase I-II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation. *Blood* 78:1205, 1991
- Storb R, Pepe M, Deeg HJ, Anasetti C, Appelbaum FR, Bensinger W, Buckner CD, Clift RA, Doney K, Hansen J, Martin P, Pettinger M, Sanders JE, Singer J, Stewart P, Sullivan KM, Thomas ED, Witherspoon RP: Long-term follow-up of a controlled trial comparing a combination of methotrexate plus cyclosporine with cyclosporine alone for prophylaxis of graft-versus-host disease in patients administered HLA-identical marrow grafts for leukemia. *Blood* 80:560, 1992 (Letter)
- Thomas ED, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD: Bone-marrow transplantation. *N Engl J Med* 292:832, 1975
- Doney KC, Weiden PL, Storb R, Thomas ED: Treatment of graft-versus-host disease in human allogeneic marrow graft recipients: A randomized trial comparing antithymocyte globulin and corticosteroids. *Am J Hematol* 11:1, 1981
- Gleaves CA, Smith TF, Shuster EA, Pearson GR: Rapid detection of cytomegalovirus in MRC-5 cells inoculated with urine specimens by using low-speed centrifugation and monoclonal antibody to an early antigen. *J Clin Microbiol* 19:917, 1984
- Schubert MM, Williams BE, Lloid ME, Donaldson G, Chapko MK: Clinical assessment scale for the rating of oral mucosal changes associated with bone marrow transplantation. *Cancer* 69:2469, 1992
- Fisher LD, van Belle G: *Biostatistics: A Methodology for the Health Sciences*. New York, NY, Wiley, 1993
- Mehta CR, Patel NR: A network algorithm for performing Fisher's exact test in rxc contingency tables. *J Am Stat Assoc* 78:427, 1983
- Clift R, Goldman J, Gratwohl A, Horowitz M: Proposals for standardized reporting of results of bone marrow transplantation for leukaemia. *Bone Marrow Transplant* 4:445, 1989
- Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 50:163, 1966
- McDonald GB, Hinds MS, Fisher LD, Wolford JL, Banaji M, Hardin BJ, Shulman HM, Clift RA: Venous-occlusive disease of the liver and multi-organ failure after bone marrow transplantation: A cohort study of 355 patients. *Ann Intern Med* 118:255, 1993
- Kalhs P, Lechner K, Stocksclaeder M, Kruger W, Peters S, Zander A: Pentoxifylline did not prevent transplant-related toxicity in 31 consecutive allogeneic marrow transplant recipients. *Blood* 80:2683, 1992
- Bianco JA, Singer JW: Letter of response to Kalhs et al: Pentoxifylline did not prevent transplant-related toxicity in 31 consecutive allogeneic marrow transplant recipients. *Blood* 80:2683, 1992