Phase I-II Trial of Pentoxifylline for the Prevention of Transplant-Related Toxicities Following Bone Marrow Transplantation

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Disease relapse and transplant related toxicities have limited the application of bone marrow transplantation (BMT) in the treatment for hematologic malignancies. Because elevated levels of tumor necrosis factor alpha (TNF-α) have been correlated with the development of transplant related complications, we conducted a phase I-II trial of pentoxifylline (PTX), a xanthine derivative capable of down-regulating TNF-α production, in patients with hematologic malignancies undergoing BMT. Thirty consecutive adult patients (median age, 34) were entered and received either an allogeneic (n = 26) or autologous (n = 4) BMT. Patients were enrolled at increasing dose levels (1,200, 1,600, and 2,000 mg/d) from day −10 through day +100 posttransplant. PTX was well tolerated with no significant adverse side effects noted at any of the dose levels administered. The actuarial day 100 survival for these 30 patients was 90% (95% confidence interval 79% to 100%). When compared with a good risk control group, PTX recipients experienced less mucositis (3.7 ± 1.1 *v* 18.7 ± 1.1 days, *P* = .004), less hepatic venocclusive disease (10% *v* 65%, *P* = .001), a lower incidence of renal insufficiency (3% *v* 65%, *P* = .0003), required less days of total parenteral nutrition (TPN) (24.0 ± 1.3 *v* 35.0 ± 2.4, *P* = .001) and were discharged from the hospital earlier than controls (day 26.0 ± 1.8 *v* 37.0 ± 3.8, *P* = .01). In addition the incidence of graft-versus-host disease (GVHD) ≥ grade II was also reduced among the PTX recipients (35% *v* 68%, *P* = .03). PTX at doses in excess of 1,200 mg/d further reduced the severity of mucositis, and TPN requirements resulting in earlier hospital discharge than patients receiving 1,200 mg/d of PTX. In this study oral administration of PTX in doses up to 2,000 mg/d was well tolerated and associated with a reduction in morbidity and mortality in patients undergoing BMT. Prospective randomized trials are currently in progress to test these preliminary observations.

DISEASE RELAPSE and toxicities directly or indirectly due to the preparative regimen remain leading causes of treatment failure in patients treated for hematologic malignancies with bone marrow transplantation (BMT). Although increases in radiation dose can decrease relapse frequency, the lower relapse rates have been offset by increases in non-relapse deaths, suggesting that the limits of nonhematopoietic organ toxicity have been reached. At our institution, 57% of all patients undergoing allogeneic BMT develop some evidence of hepatic venocclusive disease (VOD) with 15% of all cases being severe (McDonald, personal communication). Similarly, the incidence of renal insufficiency is over 50% in allograft recipients.[1] Recent interest has focused on the role of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) in the clinical expression of a variety of posttransplant syndromes. Elevated plasma levels of TNF-α have been correlated with both the development and severity of graft-versus-host disease (GVHD), VOD, and diffuse noninfectious, idiopathic pneumonia (IP).[2-4]

Recently, the hemorrheologic agent pentoxifylline (PTX) [3,7-dimethyl-1-(5-oxo-hexyl)-xanthine] (Trental; Hoechst-Roussel Pharmaceuticals Inc, Somerville, NJ) has been shown to have a marked effect on cellular mediators of inflammation and tissue injury.[5-8] PTX has been shown to modulate TNF-α production possibly via inhibition of TNF messenger RNA transcription.[8] Through its effects on cellular levels of cyclic adenosine monophosphate (cAMP), PTX also stimulates vascular endothelial production of noninflammatory prostaglandins of the E and I series (PGI_2, PGE_2), enhancing loco-regional blood flow and promoting thrombolysis.[9-11] These studies suggest that PTX might modify a variety of transplant-related toxicities. We previously demonstrated the ability of this agent to preserve renal function in patients undergoing BMT.[12] The present study was designed to determine the safety and possible efficacy of PTX as a measure to decrease transplant-related toxicities in patients with hematologic malignancies undergoing BMT.

MATERIALS AND METHODS

Study Design

This study was a dose escalation trial in which groups of 10 consecutive patients were enrolled at increasing dose levels. Pentoxifylline was administered at three doses: 1,200 mg, 1,600 mg, and 2,000 mg/d, orally as three, four, and five divided daily doses, respectively from day −10 through day +100 posttransplant. Pills were crushed and mixed with liquid for patients who experienced difficulty swallowing intact caplets. Vomited doses were repeated if vomiting occurred within 30 minutes of administration of a crushed dose or if an intact pill was recovered.

Patients

From November 1989 to September 1990, 30 consecutive patients were enrolled in this study. Fifteen patients received HLA-identical sibling transplants while three patients underwent mismatched transplants from related donors. Five patient received matched transplants from unrelated donors while three patients were recipients of mismatched unrelated grafts. Four patients

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Submitted October 10, 1990; accepted May 1, 1991.

Supported in part by the Veterans Affairs Medical Center, and Grants No. CA 18029, CA15704, and CA18221 awarded by the National Cancer Institute.

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0006-4971/91/7805-0030$3.00/0

received autologous transplants. All patients were treated on protocols approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center and the Research and Development Committee of the Seattle Veterans Affairs Medical Center (VAMC). Diagnosis, preparative regimen, and disease phase are shown in Table 1.

Prophylaxis and Treatment of Acute GVHD

Prophylaxis of acute GVHD consisted of either cyclosporine (CyA) plus methylprednisolone (MP) or cyclosporine plus short methotrexate (MTX).[13,14] Acute GVHD was diagnosed and graded according to previously published criteria[15] and was treated, in both groups, with MP (2 mg/kg/d for 3 to 4 weeks). The maximum grade of acute GVHD achieved by day 100 posttransplant was recorded.

Posttransplant Supportive Care

All patients were nursed in single reverse isolation rooms and received intravenous (IV) hyperalimentation and *Pneumocystis carinii* prophylaxis (trimethoprim-sulfamethoxazole) along with monthly IV immune globulin at a dose of 500 mg/kg (Sandoglobulin; Sandoz, NJ). Patients were maintained on parenteral nutrition until they were capable of sustaining 100% of their calculated fluid and caloric requirements orally. Twenty-six patients were cytomegalovirus (CMV) seropositive pretransplant and received prophylactic high-dose acyclovir daily until time of discharge,[16] at which time oral acyclovir (400 mg four times daily) was administered until day +75 posttransplant. All patients received prophylactic systemic antibiotics consisting of cefotaxime and mezlocillin if febrile (temperature $\geq$38.5°C) or when their absolute neutrophil count (ANC) was $\leq$500 cells/μL and continued until ANC rose $\geq$500 cells/μL. Patients with unexplained fever for $\geq$48 hours received presumptive antifungal therapy with amphotericin B (0.5 mg/kg IV) until resolution of neutropenia. Weekly rapid diagnostic CMV shell-vial assays were routinely performed beginning day +35 on buffy coat and urine samples in all CMV seropositive patients. Patients excreting CMV were treated with a 1-week course of 1,3 dihydroxy-2 propoxymethyl guanine (DHPG) (10 mg/kg/d IV; Ganciclovir, Syntex, Palo Alto) followed by an additional 4 weeks of five times weekly maintenance therapy (5 mg/kg/d). In addition, 15 patients received recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) at a dose of 250 μg/M^2/d IV over 2 hours, days 0 to 21 (Leukine; Immunex, Seattle, WA).

Table 1. Characteristics of Patients

UPN	Age (y)	Sex	Disease	Disease Status	Preparative Regimen	HLA Identity	GM CSF*	GVHD Prophylaxis	PTX Dose†
5362	41	M	CML	CP	CY/1200	M	–	CyA/MTX	1,200
5448	23	M	ALL	1 CR	CY/1440	M	+	CyA/MTX	1,200
5469	35	M	CML	CP	CY/1320	1 Ag	–	CyA/MTX	1,200
5517	24	M	CML	CP	CY/1200	URD	+	CyA/MTX	1,200
5549	37	M	CML	CP	CY/1200	URD	+	CyA/MTX	1,200
5300	42	M	MM	REL	BU/CY	M	+	CyA/MP	1,200
5360	42	M	CML	CP	CY/1200	M	–	CyA/MTX	1,200
5265	23	M	ALL	3 REL	CY/1440	M	+	CyA/MTX	1,200
5591	28	F	NHL	1 CR	BCV	AUTO	–	NA	1,200
5421	30	F	ALL	2 CR	CY/1320	AUTO	–	NA	1,200
5456	41	M	NHL	3 REM	BCV	M	+	CyA/MP	1,600
5420	37	M	NHL	2 REM	CY/1440	M	+	CyA/MP	1,600
5518	36	M	MM	REM	BU/CY	M	+	CyA/MP	1,600
5299	44	M	PLL	REL	CY/1320	M	+	CyA/MP	1,600
5554	43	M	CML	CP	CY/1200	M	–	CyA/MTX	1,600
4791	41	M	NHL	2 REL	CY/1200	M	–	CyA/MP	1,600
5552	23	M	AML	1 CR	CY/1200	M	–	CyA/MP	1,600
5653	26	M	CML	CP	CY/1200	M	–	CyA/MTX	1,600
5697	54	M	CML	CP	CY/1200	URD	+	CyA/MP	1,600
5706	30	M	CML	CP	CY/1200	URD	+	CyA/MTX	1,600
5622	33	M	NHL	3 REL	BCV	1 Ag	–	CyA/MP	2,000
5635	33	M	CML	AP	BU/CY/1200	M	–	CyA/MP	2,000
5489	33	M	NHL	3 REL	CY/1440	AUTO	–	NA	2,000
5514	23	M	ALL	2 REL	CY/1320	mURD	+	CyA/MTX	2,000
5716	27	M	CML	CP	CY/1200	mURD	+	CyA/MTX	2,000
5715	22	M	ALL	3 REL	CY/1440	1 Ag	–	CyA/MP	2,000
5705	46	M	CML	AP	CY/1320	URD	+	CyA/MTX	2,000
5740	36	F	CML	CP	CY/1200	M	–	CyA/MTX	2,000
5748	37	M	CML	AP	CY/1320	mURD	+	CyA/MTX	2,000
5074	25	M	HD	3 REL	BCV	AUTO	–	NA	2,000

Abbreviations: UPN, unique patient number; CML, chronic myelogenous leukemia; ALL, acute lymphocytic leukemia; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; PLL, prolymphocytic leukemia; HD, Hodgkin's disease; CP, chronic phase; AP, accelerated phase; Rem, first, second, or third remission; Rel, first, second, or third relapse; CY, cyclophosphamide; 1200, total body irradiation (cGy); Bu, busulfan; BCV, cyclophosphamide, carmustine, VP-16; M, matched related donor; 1 Ag, 1 antigen (A, B, or DR) mismatched; URD, matched unrelated donor; mURD, mismatched unrelated donor; CyA, cyclosporine; MTX, methotrexate; MP, methylprednisolone; NA, not applicable.

*250 μg/M^2/d IV days 0 to 20.

†Pentoxifylline, milligrams per day orally.

Toxicity Definitions

Acute toxicity was judged according to published criteria.[17] Renal insufficiency was defined as a doubling of the baseline (day 0) serum creatinine (Scr); renal failure was defined as a Scr ≥ 3.0 mg/dL with a blood urea nitrogen (BUN) ≥ 80.0 mg/dL. The diagnosis of hepatic VOD required the presence of hyperbilirubinemia (≥ 3.0 mg/dL), weight gain $\geq 2.5\%$ of baseline weight and right upper quadrant pain, with or without the presence of hepatomegaly.[18] Severity of mucositis was scored in accordance with previous published criteria.[14] In this analysis grade II or higher severity was considered a toxicity. The number of days of continuous morphine sulfate (MSO_4) administration was used as an objective parameter for severity of mucositis.

Blood Samples

TNF-α. Blood samples (7 mL) were collected in sterile, vacuum blood collection tubes containing EDTA (1.5 mg/mL of blood) to which aprotinin (0.67 trypsin inhibitor units [TIU]/mL of blood; Sigma, St Louis, MO) was added. The tubes were placed on ice and centrifuged within 2 hours of collection (400*g* for 10 minutes). The plasma was removed without disturbing the buffy coat, aliquoted in 1.5 mL microfuge tubes and spun at 10,000 *g* at 4°C for 1 minute. Platelet-free plasma was transferred to new microfuge tubes and frozen at −70°C until assay. Blood samples were obtained before starting PTX, then on days 0, 7, 14, and 21 posttransplant. Levels were drawn 2 hours after PTX dosing.

PTX levels. Blood samples (4.5 mL) were collected in citrated anticoagulated tubes, platelet free plasma separated as described above, aliquoted, and frozen to −70°C until assay. Blood samples were obtained 2 hours after dosing pretransplant, and then on days 0, 7, 14, and 21 posttransplant.

TNF-α Determinations

Plasma TNF-α concentrations were analyzed using an enzyme immunoassay (ELISA) with an affinity purified murine monoclonal anti-TNF-α as capture antibody and a horseradish-peroxidase-labeled goat polyclonal anti-TNF as conjugate (R&D Systems, Minneapolis, MN). Antibodies are specific for biologically active TNF-α and do not cross react with human lymphotoxin, IL-1, IL-2, IL-6, interferon-α, β, or γ. For the standard curve, human recombinant TNF-α was added to plasma previously determined to be negative for TNF. The ELISA was sensitive to concentrations above 15 pg/mL and linear over the range of 15 to 1,000 pg/mL. From each sample at least two dilutions were analyzed in duplicate. Levels in excess of 30 pg/mL (≥ 2 standard deviations above mean normal control values n = 20) were reconfirmed by repeat assay on a separate date. The interassay variability on repeat determinations was $\leq 10\%$. Mean TNF-α levels were calculated and recorded.

Assay for PTX

The methodology used in the assay of PTX, as well as plasma metabolites IV, and V was that of Burrows.[19] Briefly, the procedure involved a single extraction of all species from plasma into chloroform, derivative formation (the triflouroacetyl derivative in the case of metabolite I, methyl ester derivatives for metabolite V and their internal standard), and capillary gas chromatographic (GC) separation using thermionic specific detection. An analog (one carbon homolog) of PTX (E79-0254; Hoescht-Roussel Pharmaceutical, Somerville, NJ), was used as internal standard for PTX and metabolite I, while 1-(5′-carboxypentyl)-3,7-dimethylxanthine was used as an internal standard for metabolite V.

Statistical Analysis

The incidence of transplant-related complications among PTX recipients was compared with a "good risk" control group made up of the last 20 consecutive patients at our unit who received a matched related transplant for CML-CP. All control patients received CyA and MTX as GVHD prophylaxis in addition to standard supportive care as outlined above. The number of febrile days, analgesia use, peak bilirubin, peak creatinine, parenteral nutrition, day of discharge, and TNF levels was compared using the Wilcoxon rank-sum test.[20] Transfusion requirements during the first 30 days postgrafting was compared using the paired Student's *t* test. Incidence of grade II-IV acute GVHD was compared using the Pearson chi-squared test.[21] Those who died during their initial hospital stay were censored at the day of death. Survival was estimated by the Kaplan Meier method.[22] All *P* values are two-sided.

RESULTS

PTX Toxicity

No patient experienced significant adverse side effects at any of the dose levels administered. Mild gastrointestinal symptoms occurred in two patients, both relieved by administration of oral antacids.

PTX Levels

The mean PTX levels 2 hours post-dosing are shown in Fig 1. The area between the hatched lines represent the expected range of PTX levels obtained from normal volunteers administered a 1,200 mg daily dose. The bioavailability of oral PTX among our patients was within 90% of expected normal values at the 1,200 mg dose. Plasma levels at steady state tended to be higher at the 2,000 mg/d dose than at the 1,600 or 1,200 mg dose level; these differences were not statistically significant at all time points.

TNF-α Levels

TNF levels at each sampling point are shown in Fig 2. TNF levels assayed from control patients (n = 10) not receiving PTX who did not experience significant regimen related toxicities within the sampling period are also shown in Fig 2. With the exception of pretransplant values, TNF

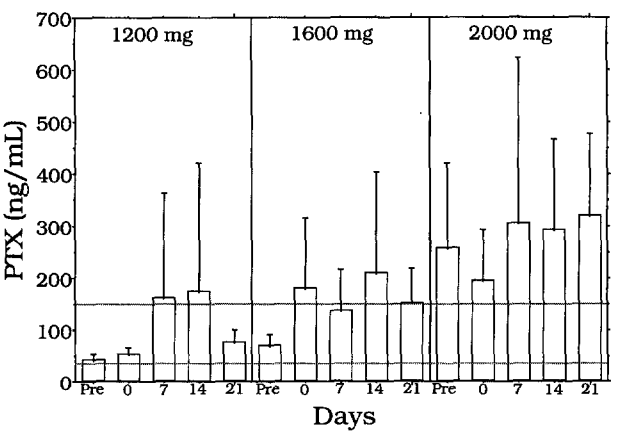

Fig 1. Mean plasma PTX levels (ng/mL)—The area between hatched lines represents the expected range of PTX levels obtained 2 hours after dosing from normal volunteers (n = 23) administered a 1,200 mg/d dose. Data from patients receiving 1,200 mg, 1,600 mg, or 2,000 mg/d is shown. The height of each box represents the mean drug level +1 standard deviation (bar). Bioavailability of PTX among our patients was within 90% of expected normal values at the 1,200 mg/d dose level.

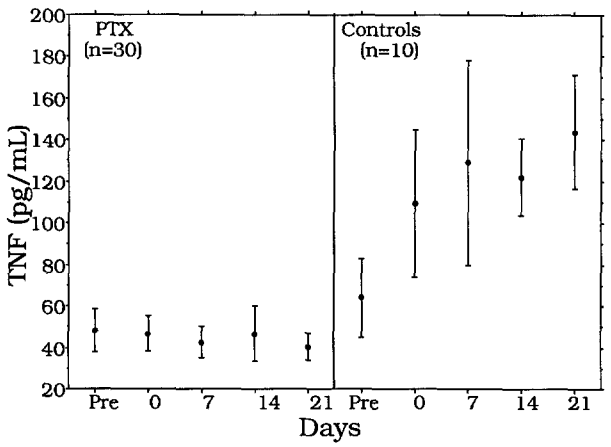

Fig 2. TNF levels (pg/mL)—The closed circle represents the mean TNF level ± the 95% confidence interval (bars). When compared with a control group composed of patients who experienced little toxicity posttransplant, with the exception of pretransplant values, TNF-α levels were significantly lower among PTX recipients.

levels were significantly lower among PTX recipients than controls at each time point sampled (P = .008, .0076, .01, and .04, respectively). There were no significant differences in assayable plasma levels of TNF between recipients of 1,200, 1,600, or 2,000 mg/d.

Day 100 Survival

Within the first 100 days posttransplant, three patients in the study group died, one patient each from infection, diffuse alveolar damage and disease relapse giving a day 100 actuarial survival of 90% (95% confidence interval, 79% to 100%, see Fig 3).

Transplant-Related Toxicities

Three patients (10%) developed mild hepatic VOD with no patient experiencing more than 2.5% increase in basal body weight during the first 21 days. Only one patient (3%) developed renal insufficiency. UPN 5552 received 4.5 grams amphotericin B pretransplant for hepato-splenic candidiasis and received an additional 1.0 grams of amphotericin B prophylactically during the first 30 days of his transplant course. Nine (30%) patients experienced mucositis that required analgesia. The overall incidence of fever (temperature ≥38.3°C) was 45% with 14 patients experiencing fever for a mean of 2.9 ± 0.7 days. Three patients (10%) had a positive blood culture (*Staphylococcus epidermidis* or *S aureus*) during the initial hospitalization period. One patient developed pulmonary aspergillosis and died on day 52 posttransplant. Of the 26 CMV seropositive patients 20 (77%) had evidence of CMV excretion (buffy coat or urine) during the first 100 days posttransplant. No patient developed evidence of CMV tissue infection.

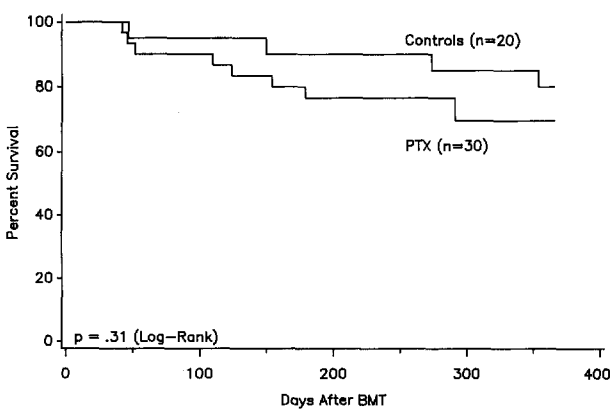

Fig 3. Day 100 and overall survival—A Kaplan Meier estimate of actuarial survival. Estimated overall survival among PTX recipients was comparable with that observed in our good risk control group (P = .31).

We evaluated the incidence of complications among PTX-treated patients and compared results with those seen in a retrospective control group made up of the last 20 consecutive patients undergoing allogeneic transplants for CP-CML on our unit (Table 2). The PTX group had significantly less mucositis requiring analgesia, took oral caloric requirements earlier and spent significantly less days in hospital than controls (see Table 2). In addition, the incidence of VOD and renal insufficiency was significantly reduced in the PTX group (P = .001 and P = .0003, respectively). The overall incidence of grade II-IV acute GVHD was lower among PTX recipients than controls (35% *v* 68%, P = .03) (Fig 4). None of the PTX recipients experienced grade III-IV acute GVHD, whereas three of 19 (16%) of controls developed multisystem GVHD (P = .07). When the data were adjusted for age the relative risk of developing grade II-IV acute GVHD was 2.16 times greater for the control group than the PTX group.

In order to determine if a dose-response relationship was present, we compared the incidence of complications in the first 10 patients receiving 1,200 mg/d of PTX with the subsequent 20 patients receiving daily doses in excess of 1200 mg. That comparison is shown in Table 3. At doses of 1,600 and 2,000 mg/d patients had significantly less mucositis, requiring analgesia for a mean of 1.7 days compared with 7.7 days in the 1,200 mg/d group (P = .04). Similarly, TPN requirements were substantially lower with patients

Table 2. Comparison of Transplant-Related Complications Among PTX Recipients and Good Risk Controls

Complication	Control (n = 20)	PTX (n = 30)	P*
Mucositis (days MSO4)†	18.7 ± 1.1	3.7 ± 1.1	.004
TPN	35.0 ± 2.4	24.0 ± 1.3	.001
Hepatic dysfunction‡	65%	10%	.001
Renal insufficiency§	65%	3%	.0003
GVHD ≥ II	68%	35%	.03
Day discharged	37.0 ± 3.8	26.0 ± 1.8	.01

The control group is made up of the last 20 consecutive patients undergoing a matched related transplant for chronic phase CML on our unit.

Abbreviation: TPN, total parenteral nutrition.

*Wilcoxon analysis.

†Morphine sulfate.

‡Bilirubin ≥3.0 mg/dL + weight gain ≥2.5% baseline + hepatomegaly.

§Doubling of baseline Scr first 28 days post-BMT.

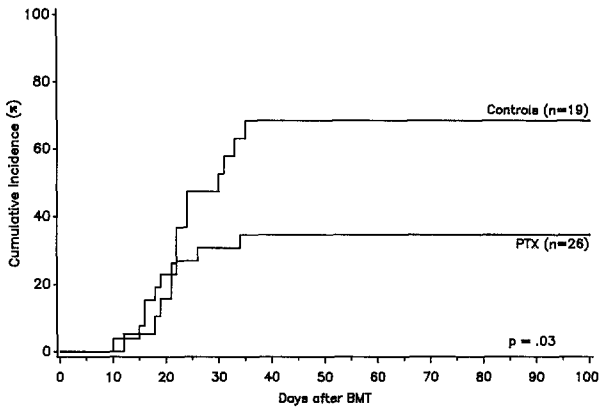

Fig 4. Acute GVHD grade II-IV—Cumulative age adjusted incidence of acute GVHD grade II-IV in patients who received PTX compared with the historical control group (P = .03). Three of 19 (68%) control patients developed grade III GVHD compared with none of 26 PTX recipients (P = .07).

receiving higher PTX doses (P = .02). PTX doses in excess of 1,200 mg/d did not appear to have a further impact on the incidence of either VOD, renal insufficiency, or significant GVHD. This was likely due to the already low incidence of these complications at the 1,200 mg dose level. However, patients receiving the higher dose regimen were discharged from the hospital at a mean of day 25 posttransplant compared with a mean of day 32 for the lower dose recipients (P = .03).

GM-CSF

Because GM-CSF may have contributed to the observed reduction in transplant morbidity, we compared the incidence of transplant associated toxicities among PTX recipients receiving GM-CSF with those PTX recipients not receiving GM-CSF. That comparison is shown in Table 4. There were no significant differences in maximum bilirubin, maximum creatinine, number of febrile days, time to engraftment, TPN requirements, or day of discharge between the two groups.

Transfusion Requirements

We examined the transfusion requirements among PTX recipients not receiving GM-CSF. In the first 100 days posttransplant, PTX recipients required significantly fewer platelet (48.5 ± 11.8 *v* 104 ± 18, P = .05) and red cell transfusions (14.25 ± 2.5 *v* 24.4 ± 3.5, P = .05) than control patients respectively (values are mean ± SEM).

Overall Event-Free Survival

With a mean follow-up of 290 days (range, 170 to 443), 22 patients survive; 21 patients are disease free. Causes of death after day 100 included infection (days 124, 154, and 291, n = 3), and relapse (days 102 and 150, n = 2). The estimated 1-year event-free survival among PTX recipients was comparable with that observed in our "good risk" control group (Fig 3, P = .31).

DISCUSSION

Transplant related toxicities are frequent and often life threatening and result not only from infection and GVHD but also from direct organ toxicities of the conditioning regimens. Recently several reports have correlated elevated plasma levels of TNF-α with a number of different toxicities following BMT including GVHD, VOD, IP, and infection.[2-4] The nonspecific, diverse biologic effects of TNF-α make it a prime suspect in either the initiation or amplification of tissue injury following BMT.[23-25]

The purpose of this study was to first determine the tolerability of PTX in BMT patients and second, to estimate if PTX might have an effect on the expression of post-BMT toxicities. Seventy-five percent of patients were considered high risk for transplant related toxicities by virtue of age ≥ 45 years,[26] advanced disease phase, preparative regimen or donor status.[17,27] All patients tolerated oral PTX with >95% of prescribed doses taken with no significant toxicity noted. Bioavailability of the oral formulation in transplant patients was similar to that seen in healthy volunteers receiving similar doses. In addition, there was a strong suggestion that PTX ameliorated transplant-related toxicities. Only three patients developed mild VOD associated with minimal weight gain not requiring therapy, and only one patient experienced mild renal insufficiency. This is in contrast to our historical "good risk" control group, in which 65% developed these complications. Similarly, the incidence of mucositis was also reduced among PTX recipients resulting in their ability to eat sooner and be

Table 3. Dose-Response Relationship

	PTX Dose (mg/d)	Maximum Bilirubin Day 0-21	Maximum Creatinine Day 0-28	No. Days ≥38.3°C Day 0-28	Days MSO4 Required	Day ANC ≥500/μL	Last Day of TPN	Day of Discharge
Mean ± SEM	1,200	2.99 ± 0.69	1.1 ± 0.09	3.6 ± 0.9	7.7 ± 2.6	23.8 ± 2.4	29.3 ± 2.7	32.2 ± 2.8
95% CI		(1.4-4.5)	(0.9-1.3)	(1.5-5.7)	(1.7-13.6)	(18.2-29.3)	(23.0-35.6)	(25.6-38.7)
Median		2.2	1.15	4.0	6.5	23	32	35
	>1,200	2.74 ± 0.45	1.15 ± 0.06	2.6 ± 0.8	1.75 ± 0.8	17.9 ± 1.2	21.4 ± 1.1	25.4 ± 2.3
		(1.8-3.6)	(1.02-1.27)	(0.8-4.3)	(0.05-3.4)	(15.3-20.4)	(19.1-23.7)	(20.5-30.2)
		2.2	1.1	0	0	18.5	20.5	25
P value		.64	.65	.23	.04	.04	.02	.03

The incidence of complications in the first 10 patients receiving 1,200 mg/d of PTX was compared with the subsequent 20 patients receiving daily doses in excess of 1,200 mg/d. Mean ± SEM, mean values ± standard error; 95% CI, 95% confidence intervals; median, 50 percentile; *P* value, Wilcoxon signed rank analysis.

Table 4. Effect of GM-CSF and PTX on Transplant-Related Complications

	PTX (1,200 to 2,000 mg/d)	Maximum Bilirubin Day 0-21	Maximum Creatinine Day 0-28	No. Days ≥38.3°C Day 0-28	Days MSO4 Required	Day ANC ≥500/μL	Last Day of TPN	Day of Discharge
Mean ± SEM	+GM-CSF*	2.98 ± 0.60	1.18 ± 0.07	3.0 ± 0.9	4.5 ± 1.6	19.0 ± 1.4	25.3 ± 2.1	29.8 ± 3.0
95% CI	(n = 15)	(1.7-4.3)	(1.0-1.3)	(1.1-4.8)	(0.9-8.1)	(15.9-22.0)	(20.5-29.8)	(23.2-36.7)
Median		2.3	1.2	2.0	0	19	24	31
	−GM-CSF	2.6 ± 0.46	1.08 ± 0.07	2.9 ± 0.9	2.9 ± 1.5	20.7 ± 2.0	22.8 ± 1.6	25.0 ± 1.9
	(n = 15)	(1.6-3.6)	(0.9-1.2)	(0.8-4.9)	(0.4-6.2)	(16.2-25.1)	(19.1-26.7)	(20.5-29.3)
		1.8	1.1	0	0	21	24	26
P value		.95	.25	.92	.57	.53	.55	.70

The incidence of complications was not significantly different among patients receiving GM-CSF and PTX when compared with those patients receiving PTX alone.

*GM-CSF, 250 μg/M² IV days 0-21.

discharged from the hospital earlier than control patients. This apparent benefit was seen among PTX recipients who received CyA and either prednisone or MTX as GVHD prophylaxis and in patients who did not receive GM-CSF. The overall incidence of grade II acute GVHD was 37%, predominantly involving skin. No patient developed grade III-IV acute GVHD. There was a suggestion that pentoxifylline doses in excess of 1,200 mg/d appeared to further lessen the number of febrile days, duration of mucositis, TPN requirements, and hospital stay when compared with results in patients receiving the 1,200 mg/d dose. The dose escalation was stopped at the 2,000 mg/d dose level in part because there did not appear to be additional benefits from the increased dose when compared with 1,600 mg/d and in part because of concerns about patient compliance with oral dosing in excess of five times daily. It should be emphasized that these apparent beneficial effects are seen compared with a nonrandomized control group and that prospective randomized placebo-controlled trials are required to confirm these observations.

In this study the oral administration of PTX up to doses of 2,000 mg/d appeared to be well tolerated with no adverse side effects observed. Unlike other methylxanthine derivatives, PTX lacks much of the cardiovascular side effects, a finding supported by this phase I-II study. One concern is that the early modulation of TNF-α may reduce the antileukemic efficacy of the preparative regimen resulting in higher relapse rates. To discern such an effect would be difficult with such a small sample size and diverse disease groups. Only four relapses were observed in the entire group and those were among patients at high risk for relapse. As for the possible beneficial effects of PTX, a randomized trial will be necessary to determine if PTX adversely affects relapse rates.

There are various ways in which PTX might work. In addition to modulating TNF-α production, PTX enhances endothelial cell production of PGI_2, and PGE_1/E_2, a function that is normally depressed following irradiation.[28] These prostaglandins are responsible for the autoregulation of blood flow in several organs including the liver and kidney promoting diuresis and naturesis and maintenance of blood flow. The preservation of hepatic and renal function in the early posttransplant period may be responsible for the low incidence of significant acute GVHD. PTX patients received ≥85% of the recommended doses of immunosuppression in the first 35 days posttransplant. This is in marked contrast to reported studies in which less than 60% of patients tolerated 80% or more of the recommended dose.[29] Alternatively, PTX may have an adjunctive immunosuppressive effect through the enhancement of PGE_1/E_2 production[30,31] potentiating CyA's immunosuppressive effects[32] or by acting synergistically with corticosteroids at inhibiting TNF-α production at separate points in the signaling pathway.[8] In addition, PTX may have immunosuppressive properties independent of its effects on TNF or prostaglandin synthesis.[33,34] The ability to block TNF-α makes the combination of PTX and GM-CSF also attractive; in vitro, PTX has been shown to suppress GM-CSF induction of TNF without inhibiting GM-CSF-induced myeloid proliferation.[35]

Whatever the mechanism, compared with recent historical control patients, PTX appeared to reduce morbidity and mortality in patients undergoing BMT. If, in fact, PTX does ameliorate transplant-related toxicities without an increase in relapse rates, then the use of PTX alone or in combination with cytokines like GM-CSF may permit the delivery of higher, more effective doses of chemoradiotherapy resulting in lower relapse rates and improved overall event-free survival. Prospective randomized studies are currently in progress to test these preliminary observations.

ACKNOWLEDGMENT

The authors acknowledge the dedication and commitment to clinical research and patient care by the nursing and pharmacy staff on the BMTU at the Veterans Affairs Medical Center. We would also like to thank Dr Patrick Davis, University of Texas at Austin for PTX determinations, Paul Brown for expert assistance in assaying TNF-α, Motomi Mori for her statistical advice, and Mary Pettinger for survival statistics.

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