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


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 28.0 ± 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 2,800 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. © 1991 by The American Society of Hematology.

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 patients received matched transplants from unrelated donors while three patients were recipients of mismatched unrelated donors. Four patients...
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).\textsuperscript{11,14} Acute GVHD was diagnosed and graded according to previously published criteria\textsuperscript{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 trimethoprim-sulfamethoxazole (Pneumocystis prophylaxis; trimethoprim-sulfamethoxazole) along with mouthy IV immune globulin at a dose of 500 mg/kg (Sandoglobulin; Sandoz, NJ). Patients were maintained on parenteral nutrition with MP (2 mg/kg/d for 3 to 5 weeks). The maximum grade of acute GVHD achieved by day 100 posttransplant was recorded.

Table 1. Characteristics of Patients

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<tr>
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<th>Sex</th>
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<th>Disease Status</th>
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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/d IV days 0 to 20.

**Pentoxifylline, milligrams per day orally.
Toxicity Definitions

Acute toxicity was judged according to published criteria.\textsuperscript{17} Renal insufficiency was defined as a doubling of the baseline (day 0) serum creatinine (Scr); renal failure was defined as a Scr \( \geq 3.0 \) mg/dL with a blood urea nitrogen (BUN) \( \geq 80.0 \) mg/dL. The diagnosis of hepatic VOD required the presence of hyperbilirubinemia (\( \geq 3.0 \) mg/dL), weight gain \( \geq 2.5\% \) of baseline weight and right upper quadrant pain, with or without the presence of hepatomegaly.\textsuperscript{16} Severity of mucositis was scored in accordance with previous published criteria.\textsuperscript{14} In this analysis grade II or higher severity was considered a toxicity. The number of days of continuous morphine sulfate (MSO\textsubscript{S}) administration was used as an objective parameter for severity of mucositis.

Blood Samples

TNF-\( \alpha \). 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, aliquotted 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 \(-70^\circ\)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, aliquotted, and frozen to \(-70^\circ\)C until assay. Blood samples were obtained 2 hours after dosing pretransplant, and then on days 0, 7, 14, and 21 posttransplant.

TNF-\( \alpha \) Determinations

Plasma TNF-\( \alpha \) concentrations were analyzed using an enzyme immunoassay (ELISA) with an affinity purified murine monoclonal anti-TNF-\( \alpha \) 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-\( \alpha \) and do not cross react with human lymphotoxin, IL-1, IL-2, IL-6, interferon-\( \alpha \), \( \beta \), or \( \gamma \). For the standard curve, human recombinant TNF-\( \alpha \) 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 (\( \geq 2 \) 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-\( \alpha \) 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. \textsuperscript{13} Briefly, the procedure involved a single extraction of all species from plasma into chloroform, derivative formation (the trifluorocrotyl derivative in the case of metabolite I, methyl ester derivatives for metabolite V and their internal standard), and capillary gas chromatographic (GC) separation using thimonic 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. \textsuperscript{30} 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.\textsuperscript{31} Those who died during their initial hospital stay were censored at the day of death. Survival was estimated by the Kaplan Meier method.\textsuperscript{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-\( \alpha \) 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
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.

\[ \text{Days} \quad p = .31 \quad (\text{Log-Rank}) \]

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.

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 (\textit{Staphylococcus epidermidis} or \textit{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.

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% vs 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 1,200 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

\[ \text{Table 2. Comparison of Transplant-Related Complications Among PTX Recipients and Good Risk Controls} \]

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<td>3.7 ± 1.1</td>
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<td>65%</td>
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<td>Renal insufficiency§</td>
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<td>GVHD ≥ II</td>
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<td>Day discharged</td>
<td>37.0 ± 3.8</td>
<td>26.0 ± 1.8</td>
<td>.01</td>
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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.
PENTOXIFYLLINE PREVENTS TOXICITY POST-BMT

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 vs 104 ± 18, $P = .05$) and red cell transfusions (14.25 ± 2.5 vs 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. Despite the nonspecific, diverse biologic effects of TNF-α it makes it a prime suspect in either the initiation or amplification of tissue injury following BMT.

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, advanced disease phase, preparative regimen or donor status. 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

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Table 3. Dose-Response Relationship

<table>
<thead>
<tr>
<th>PTX Dose (mg/d)</th>
<th>Maximum Bilirubin (mg/dl)</th>
<th>Maximum Creatinine (mg/dl)</th>
<th>No. Days Days of TPN</th>
<th>Days ANC &gt; 500/μL</th>
<th>Last Day of Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1,200</td>
<td>2.99 ± 0.69</td>
<td>1.1 ± 0.09</td>
<td>3.6 ± 0.9</td>
<td>7.7 ± 2.6</td>
<td>23.8 ± 2.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.4-4.5)</td>
<td>(0.9-1.3)</td>
<td>(1.5-5.7)</td>
<td>(1.7-13.6)</td>
<td>(18.2-29.4)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1,200</td>
<td>2.74 ± 0.45</td>
<td>1.15 ± 0.06</td>
<td>2.6 ± 0.8</td>
<td>1.75 ± 0.8</td>
<td>17.9 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>(1.8-3.6)</td>
<td>(1.02-1.27)</td>
<td>(0.8-4.3)</td>
<td>(0.05-3.4)</td>
<td>(15.3-20.4)</td>
</tr>
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</tr>
<tr>
<td></td>
<td>2.2</td>
<td>1.1</td>
<td>0</td>
<td>18.5</td>
<td>20.5</td>
</tr>
</tbody>
</table>

*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.
The overall incidence of grade II acute GVHD was because there did not appear to be additional benefits from prophylaxis and in patients who did not receive GM-CSF. predominantly involving skin. No patient developed grade received the number of febrile days, duration of mucositis, TF escalation was stopped at the 2,000 mg/d dose level in part because of concerns about patient compliance with requirements, and hospital stay when compared with oral dosing in excess of five times daily. It should be noted that the early modulation of TNF-a may reduce the 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 PGI₂ and PGE₂/E₂, a function that is normally depressed following irradiation. These prostaglandins are responsible for the autoregulation of blood flow in several organs including the liver and kidney promoting diuresis and natureus 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. Alternatively, PTX may have an adjunctive immunosuppressive effect through the enhancement of PGF2α production or by acting synergistically with corticosteroids at inhibiting TNF-α production at separate points in the signaling pathway. In addition, PTX may have immunosuppressive properties independent of its effects on TNF or prostaglandin synthesis. 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.

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.

REFERENCES


4. Piguet PF, Grau GE, Collart M, Aliet B, Vasalli P: Graft vs host reaction induced alveolitis involving tumor necrosis factor alpha. Bone Marrow Transplant 1:111, 1988 (suppl 3)


Phase I-II trial of pentoxifylline for the prevention of transplant-related toxicities following bone marrow transplantation [published erratum appears in Blood 1992 Jun 15;79(12):3397] [see comments]


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