Prevention of Regimen-Related Toxicities After Bone Marrow Transplantation by Pentoxifylline: A Prospective, Randomized Trial

By Michel Attal, Francoise Huguet, Herve Rubie, Jean-Paul Charlet, Daniel Schlaifer, Anne Huynh, Guy Laurent, and Jacques Pris

Elevated levels of tumor necrosis factor alpha (TNF-α) have been reported to correlate with the development of transplant-related complications after bone marrow transplantation (BMT). In a recent phase I-II trial, oral administration of pentoxifylline (PTX), a xanthine derivative capable of downregulating TNF-α production in vitro, was reported to reduce morbidity and mortality in patients undergoing BMT. We conducted a prospective randomized trial of PTX therapy among 140 patients undergoing either allogeneic (n = 51) or autologous BMT (n = 89). Patients were randomized to receive (n = 70) or not receive (n = 70) oral PTX, 1,600 mg/d in four divided doses from day −9 until day +100 post-BMT. The incidence of mucositis requiring morphine sulfate (MS04) was similar in both groups (42.9%), with the mean number of days with MS04 being 7.8 (SD = 3.4) in the PTX group versus 8.2 (SD = 3.4) in the control group (NS). The incidence of renal insufficiency was not affected by PTX administration (15.7% in the PTX group vs 21.4% in the control group [NS]) and the highest serum creatinine value during the first 100 days post-BMT was 119 μmol/L (SD = 82.4) in the PTX group versus 103.9 μmol/L (SD = 57) in the control group (NS). The incidence of grade ≥2 graft-versus-host disease was similar in each group (11/25 [44%] in the PTX group vs 12/26 [46%] in the control group). No significant difference was observed in hematologic toxicity, transfusion requirements, duration of fever, and hepatic toxicity between the treatment groups. In conclusion, our study failed to show a prophylactic effect of PTX in transplant-related toxicities after BMT. On the basis of these findings, we cannot recommend that PTX be part of early mortality and morbidity prevention programs after BMT.

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OXICITIES CAUSED BY chemotherapy and radiotherapy used to prepare patients for bone marrow transplantation (BMT) remain a major cause of patient morbidity and mortality after allogeneic or autologous BMT. Indeed, transplant-related mortality associated with allogeneic BMT is still about 30% and varies from 10% to 20% after autologous BMT.1 Recently, the development of various transplant-related complications, including hepatic veno-occlusive disease (VOD), interstitial pneumonitis (IP), endothelial leakage syndrome (ELS), infections and acute graft-versus-host disease (GVHD), has been related with elevated plasma levels of tumor necrosis factor alpha (TNF-α), which suggests a role for this inflammatory mediator in the initiation or amplification of tissue injury after BMT.2,4

Pentoxifylline (PTX) is a xanthine derivative that has been shown to downregulate TNF-α production by monocytes/macrophages in vitro,3 to decrease radiation-induced TNF-α production in experimental models,6 and to decrease endotoxin-induced TNF-α production in healthy volunteers.3 Furthermore, PTX was reported to stimulate vascular endothelial production of prostaglandins (PGs) I2 and E2 enhancing locoregional blood flow in the liver and the kidney and promoting thrombolysis.8,9 Because endothelial production of PGs I2 and E3 has been reported to be depressed following irradiation,10 it was reasonable to speculate that PTX administration could decrease BMT-related toxicities via the inhibition of TNF-α production and/or the stimulation of endothelial production of PGs I2/E2. Recently, Bianco et al reported that oral administration of PTX in doses up to 2,000 mg/d was well tolerated and associated with a reduction in morbidity and mortality after allogeneic or autologous BMT compared with historical control patients.11 The impact of such a prophylactic effect of PTX could be considerable in the BMT setting because PTX would decrease regimen-related toxicities, permit the delivery of higher doses of chemoradiotherapy resulting in a lower relapse rate, and ultimately improve event-free survival after BMT.11 Therefore, a controlled trial was warranted to test the efficacy of PTX in preventing BMT-related toxicities. We report the first trial designed to address this crucial issue. One hundred forty patients were randomized to receive or not receive PTX after either autologous or allogeneic BMT.

MATERIALS AND METHODS

Requirements for patient enrollment. All patients admitted to the BMT unit of Purpan Hospital from December 1990 to September 1992, who were to receive unpurged autologous or non–T-depleted HLA genoidentical allogeneic BMT, prepared with standard regimens, were eligible for this study. Standard regimens included (1) cyclophosphamide (CY) (120 mg/kg) and total body irradiation (TBI) (12 Gy); (2) CY (120 mg/kg) and busulfan (Bu) (16 mg/kg); (3) melphalan (MEL) (140 mg/m2) and TBI (8 Gy); (4) CY (6 g/m2), etoposide (1 g/m2), and carbustine (300 mg/m2) (CBV). According to the criteria stated above, 10 patients were excluded for the following reasons: 7 patients had received nonstandard preparative regimens, and 3 patients had received a matched, unrelated allogeneic BMT. Informed consent was obtained either from patients or from one of their parents in accordance with institutional policy.

Patients. One hundred forty consecutive eligible patients were enrolled in the study. Their clinical characteristics are detailed in Table 1. Mean age was 37.4 years (SD = 15.4). Fifty-one patients received allogeneic BMT and 89 received autologous BMT. Pa-
Table 1. Clinical Characteristics of the Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pentoxifylline Group</th>
<th>Control Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>47/23</td>
<td>44/28</td>
<td>91/49</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>38.5 (14.6)</td>
<td>36.2 (16.2)</td>
<td>37.6 (15.4)</td>
</tr>
</tbody>
</table>

Diagnoses

- AML (all/1st CR/2nd CR) 12/11/1
- ALL (all/1st CR/2nd CR) 13/13/0
- CML (chronic phase/blast phase) 10/8/5
- Lymphoma (all/1st response/2nd response) 19/9/5
- Myeloma (all/1st response/2nd response) 14/9/5

Mean interval between diagnosis and BMT in months (SD)

- Autologous 20.6 (28.9)
- Allogeneic 18.9 (28.6)
- Total 19.7 (28.7)

Type of graft

- Autologous 45
- Allogeneic 25
- Total 70

Preparative regimen

- Cy-TBI 31
- Mel-TBI 13
- BU-CY 10
- CBV 16
- Total 80

Number of patients in laminar air flow room

- Total 32

Pretransplant hepatitis B serology

- Negative 60
- Positive 10
- Total 70

Pretransplant CMV serology

- Negative 46
- Positive 24
- Total 70

Pretransplant SGOT value ≤40 IU 67

Pretransplant bilirubinemia value

- <19 μmol/L 66
- >19 μmol/L 4
- Total 70

Pretransplant creatinine value (μmol/L, mean (SD))

- 74.7 (18.6)
- 71.2 (21.3)
- 72.9 (19.9)

None of the characteristics differed significantly between treatment groups.

Patients were treated for the following diseases: 26 for acute myelogenous leukemia (AML), 29 for acute lymphoblastic leukemia (ALL), 17 for chronic myelogenous leukemia (CML), 33 for malignant lymphoma, and 29 for multiple myeloma. Twelve patients (8.5%) had an abnormal aspartate aminotransferase value (SGOT) before BMT (laboratory norms, <40 IU). Seven patients (5%) had abnormal total serum bilirubin before BMT (laboratory norms, <19 μmol/L). None of the patients had positive serology for hepatitis B antigen before BMT. Fifty patients (35.7%) had positive serology for cytomegalovirus (CMV) before BMT.

Study design. Ten days before transplantation, patients were randomized to receive or not receive PTX. The treatment allocation for each patient was assigned via telephone by the biostatistics department, which had prepared before initiation of the trial a computer-generated sequence unknown to the physicians participating in the trial. Randomization was stratified according to the type of graft (allogeneic/autologous). Prophylactic PTX, 1,600 mg, was administered orally in four divided daily doses, starting on the day preparative therapy began until 100 days 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. Omitted pills, if any, were recorded from day −8 until day +45.

PTX procedures. Preparative regimens are detailed in Table 1. Eighty-seven patients (62.2%) received a TBI-containing regimen, 25 patients received a BU-CY regimen (17.8%), and 28 patients received the CBV regimen (20%). Patients received autologous unpurged cryopreserved graft or non-T-depleted allogeneic graft on day 0. Prevention of GVHD was attempted by the administration of methotrexate (15 mg on days +1,+3,+6) plus cyclosporine. Patients were treated in laminar air flow or positive-pressure rooms with usual aseptic precautions. All patients received sterile diet. A total gut decontamination regimen with oral nonabsorbable antibiotics (cephalosporine, gentamicin, bacitracin) was started on day 8 before BMT. Patients received fluconazole for prophylaxis of fungal infections, acyclovir for prevention of herpes infections, and ranitidine for prophylaxis of upper gastrointestinal tract bleeding. Prophylaxis of VOD was attempted by the continuous infusion of low-dose heparin (100 IU/kg/d) from day −8 until day +30 post-BMT in 120 patients (85.7%).12 Blood products were irradiated before transfusion. Neither prophylactic nor therapeutic granulocyte transfusion was used. No prophylactic hematopoietic growth factor was used after BMT. A central venous catheter was inserted surgically 1 week before admission to the sterile unit.

Toxicity definitions. Renal insufficiency was defined as a two- to four-fold or more increase in baseline serum creatinine. The diagnosis of hepatic VOD required the presence of hyperbilirubinemia (≥34 μmol/L), weight gain ≥5% of baseline weight, and right upper quadrant pain with hepatomegaly.13 Severity of mucositis was scored in accordance with previously published criteria,14 and the number of days of continuous morphine sulfate (MS04) administration was used to compare treatment groups. A patient was defined to be refractory to platelet transfusions if the platelet count remained below the pretransfusion level 24 hours after platelet transfusions during 5 consecutive days.

Statistical analysis. The proportions of patients with a given characteristic were compared by χ² test or Fischer's exact test. Differences in the means of continuous measurements were tested with Student’s t test, controlled by nonparametric Mann-Whitney U test. All tests were two-sided. PTX has been reported dramatically to decrease four major regimen-related toxicities, including severe mucositis (requiring MS04), renal insufficiency (twofold or more increase in baseline serum creatinine), severe GVHD, and VOD.11 We previously reported that the heparin regimen we used was associated with a low rate of VOD.12 Thus, hepatic dysfunction was not considered as an endpoint in this study. At our institution, the rates of severe mucositis, renal insufficiency, and grades 3 to 4 GVHD are 45%, 25%, and 23%, respectively. According to Bianco et al.,11 the rates of severe mucositis, renal insufficiency, and grades 3 to 4 GVHD were expected to decrease to 20%, 7%, and 1%, respectively, in the PTX group. To ensure a significance level of 5% and a power of 10% to these assumptions, a minimum of 70 patients (including 25 patients undergoing allogeneic BMT) assigned randomly to each treatment arm was required. The study was completed by an enrollment of 140 patients.

RESULTS

Randomization. Seventy patients were randomly assigned to each treatment group. As shown in Table 1, patient characteristics of each group were similar, and no significant differences were found with regard to age, sex, underlying disease, type of graft, preparative regimen, pre-BMT serology of hepatitis B and cytomegalovirus (CMV), and pre-BMT value of SGOT, bilirubin, and creatinine.

PTX tolerance and compliance. No patient experienced adverse side effects related to PTX administration. The compliance was satisfactory. Indeed, all patients received oral PTX with >95% of prescribed doses. During early neutropenia, four patients did not receive the full course of PTX.

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Hematologic toxicity and transfusion requirements. As shown in Table 2, the mean duration of neutropenia (<500/mm³), the mean duration of thrombocytopenia (<25,000/mm³), and the mean number of platelet and RBC transfusions were not affected by PTX administration.

Infections during the first 100 days post-BMT. As shown in Table 2, the mean duration of fever above 38°C during neutropenia was not significantly different between the two groups. Septicemia (two or more positive blood cultures) occurred in 13/70 patients in the PTX group versus 9/70 patients in the control group (NS). One patient died of septicemia (Pseudomonas) in the control group. Among allogeneic patients, the incidence of CMV viremia and interstitial pneumonitis were similar in both groups: 7/25 and 2/25, respectively, in the PTX group versus 9/26 and 4/26, respectively, in the control group (NS).

Organ toxicities during the first 100 days post BMT. As shown in Table 3, no significant differences were found with regard to renal toxicity between the treatment groups. The highest creatinine value and the number of patients with renal insufficiency were similar in both groups. Among allogeneic patients, PTX did not affect the number of patients requiring an interruption of cyclosporine for renal toxicity (creatinine >160 μmol/L): 5/25 in the PTX group versus 6/26 in the control group (NS).

The incidence and severity of mucositis were not decreased by PTX administration. Indeed, 30/70 (42.9%) patients in each group required MS04 for grade II or higher mucositis. The mean duration of continuous MS04 administration was similar in both groups: 7.8 days (SD = 3.4) in the PTX group versus 8.2 days (SD = 3.4) in the control group (NS).

No significant differences were found with regard to hepatic toxicities between the treatment groups. The highest value of bilirubinemia and the incidence of VOD were similar in two groups: 26.4 μmol/L (SD = 31.7) and 3/70 patients, respectively, in the PTX group versus 24.4 μmol/L (SD = 46.1) and 2/71 patients, respectively, in the control group (NS).

The mean duration of hospital admission was similar in both groups: 31.2 days (SD = 6.4) in the PTX group versus 32 days (SD = 7.5) in the control group (NS).

Acute GVHD. As shown in Table 3, the incidence and severity of acute GVHD were not statistically different between treatment groups.

Day 100 survival. Within the first 100 days post-transplant, 6/70 patients died in the PTX group (early relapse, one case; GVHD, two cases; VOD, two cases; CMV pneumonitis, one case) versus 6 of 70 in the control group (GVHD, three cases; septicemia, one case; VOD, one case; CMV pneumonitis, one case).

DISCUSSION

BMT-related mortality has decreased significantly during the last few years. However, the early mortality associated with allogeneic BMT is still about 30% even in “good-risk” patients and varies from 10% to 20% after autologous BMT. Life-threatening toxicities after BMT result not only from infections, bleeding, and GVHD but also from direct organ toxicities of the conditioning regimens, including VOD, ELS, IP, and mucosal toxicities. Recently, several reports have suggested a pathogenetic role of TNF-α in infections, in GVHD, and also in regimen-related toxicities such as VOD, ELS, and IP. Thus, the prophylactic use of agents able to decrease monocyte/macrophage production of TNF-α seemed to be a logical approach to prevent BMT-related toxicities. Recently, Bianco et al, in a phase I/II study, administered PTX in 30 patients undergoing allogeneic/autologous BMT. These investigators reported a highly signif-

### Table 2. Hematologic and Infectious Toxicities During BMT

<table>
<thead>
<tr>
<th></th>
<th>Pentoxifylline Group (n = 70)</th>
<th>Control Group (n = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of neutropenia (&lt;500/mm³) in days (SD)</td>
<td>20.13 (6.3)</td>
<td>21 (7.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of thrombocytopenia (&lt;25,000/mm³) in days (SD)</td>
<td>18.9 (6.2)</td>
<td>20.5 (8.3)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients refractory to platelet transfusions (%)</td>
<td>14.6 (11.7)</td>
<td>14.9 (12.9)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients refractory to platelet transfusions (%)</td>
<td>28 (40)</td>
<td>29 (41.4)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of RBC transfusions in the first 100 days post-BMT, mean (SD)</td>
<td>12.9 (13.9)</td>
<td>10.4 (7.9)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of days with fever (above 38°C), mean (SD)</td>
<td>4.9 (4.2)</td>
<td>6.1 (3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Septicemia (%)</td>
<td>Gram-positive</td>
<td>5 (7.1)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>8 (11.4)</td>
<td>6 (8.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>13 (18.5)</td>
<td>9 (12.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

### Table 3. Organ Toxicities During the First 100 Days Post-BMT

<table>
<thead>
<tr>
<th></th>
<th>Pentoxifylline Group (n = 70)</th>
<th>Control Group (n = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest creatinine value (μmol/L), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous BMT</td>
<td>114 (64.7)</td>
<td>105.7 (62.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Allogeneic BMT</td>
<td>127.5 (108)</td>
<td>101 (47.7)</td>
<td>NS</td>
</tr>
<tr>
<td>All patients</td>
<td>119 (82.4)</td>
<td>103.9 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients with 100% increase in baseline serum creatinine (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>4 (8)</td>
<td>5 (11.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>7 (28)</td>
<td>10 (38.4)</td>
<td>NS</td>
</tr>
<tr>
<td>All patients</td>
<td>11 (15.7)</td>
<td>15 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients requiring MS04 for mucositis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>30 (42.9)</td>
<td>30 (42.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>3 (4.3)</td>
<td>3 (4.3)</td>
<td>NS</td>
</tr>
<tr>
<td>All patients</td>
<td>10 (38.4)</td>
<td>10 (38.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Grades 3–4</td>
<td>5 (20)</td>
<td>6 (23.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>
icant decrease in BMT-related toxicities, including renal insufficiency, hepatic dysfunction, mucositis, and GVHD, compared with 20 historical control patients. In a subsequent study, Bianco et al reported that PTX administration to patients with lymphoma undergoing autologous/allogeneic BMT prepared with CBV, was associated with a reduction of day 100 nonrelapse mortality compared with historical control patients. The interest of such an effective and inexpensive prophylaxis of BMT-related toxicities would be considerable. However, the apparent beneficial effects of PTX have only been observed when compared with historical control groups of patients. Thus, prospective randomized studies are required to confirm these observations.

In our prospective study, 140 patients undergoing BMT were randomized to receive or not receive oral PTX, 1,600 mg, in four divided daily doses from day −8 until day +100. Because of concern about oral administration of placebo pills in informed patients with severe mucositis, our study was not placebo controlled. Therefore, only objectively evaluable endpoints were selected to compare treatment groups. Oral administration of PTX was chosen according to Bianco et al. They demonstrated that all patients tolerated oral PTX with >95% of prescribed dose. Furthermore, they reported that bioavailability of the oral formulation in transplant patients receiving cyclosporine and methotrexate for GVHD prophylaxis was similar to that seen in healthy volunteers. A PTX dosage of 1,600 mg in four divided daily doses was chosen in our trial. Indeed, Bianco et al demonstrated that there were no significant differences in assayable plasma levels of TNF between recipients of 1,600 or 2,000 mg/d. Furthermore, they reported that “there did not appear to be additional benefits from the increased dose when compared with 1,600 mg/d.” Therefore, because of concerns about patient compliance, the dose of 1,600 mg in four divided daily doses rather than 2,000 mg in five divided daily doses was chosen for this trial.

The main objectives of our trial were to evaluate the impact of PTX administration on the incidence of renal insufficiency, severe mucositis, and severe GVHD (see statistical analysis). Our trial failed to observe a prophylactic effect of PTX. Indeed, the incidence of severe mucositis, renal insufficiency, and grade 2 or higher GVHD were 42.9%, 21.4%, and 46.1%, respectively, in the control group versus 42.9%, 15.7%, and 44%, respectively, in the PTX group (NS). These results were confirmed when highest value of serum creatinine, mean number of days with MS04 for severe mucositis, and grades 3 to 4 GVHD were compared between the two groups (103.9 µmol/L [SD = 57], 8.2 days [SD = 3.4], and 23.1%, respectively, in the control group, versus 119 µmol/L [SD = 82.4], 7.8 days [SD = 3.4], and 20%, respectively, in the PTX group [NS]). Furthermore, no significant difference was observed between two groups with regard to duration of fever, hematologic toxicity, transfusion requirements, and day 100 survival. The incidence of VOD was not considered as an endpoint in our study. Indeed, we previously reported that the heparin regimen we used was associated with a low rate of VOD. The present study confirmed our previous findings; namely, only 5/140 patients (3.5%) developed VOD after BMT (2 patients in the control group v 3 patients in the PTX group).

Recently, Kalhs et al reported that continuous infusion of PTX (12 to 30 mg/kg/d) did not decrease regimen-related toxicities in 31 consecutive allogeneic recipients. However, in the latter study, the administration schedule may have hampered the efficacy of PTX. Indeed, Bianco et al have reported that peak plasma (Cmax) and area under curve (AUC) concentration of PTX were lower in patients treated with continuous infusion than in patients treated with oral formulation. Thus, difference in drug delivery resulting in differences in Cmax and AUC could have played a role in the differences in outcome observed between the studies of Bianco et al and Kahl et al. In our study, although PTX was administered orally as recommended by Bianco et al, we failed to observe a prophylactic effect of PTX. The reasons for the discrepancy between our results and those of Bianco et al remain unclear. However, several factors distinguish the two studies. Most of the patients in the study of Bianco et al were considered “high risk,” either because of age, advanced disease, preparative regimen, or donor status, and were compared with a historical “good-risk” group. In our prospective randomized study, patients received conventional chemotherapy regimens, were enrolled at an initial phase of their primary disease, and received autologous or HLA genoidentical allogeneic grafts.

In conclusion, oral administration of PTX was found to be ineffective in the prophylaxis of BMT-related toxicities. On the basis of these findings, we cannot recommend the administration of PTX after BMT. Recently, combined therapy with pharmacologic agents (PTX, ciprofloxacin, prednisone) that inhibit TNF synthesis at different points in the synthetic pathway was reported to reduce regimen-related toxicity and to accelerate engraftment after BMT. The role of such combined therapy could be evaluated in further prospective trials.

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Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial

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