CORRESPONDENCE

PENTOXIFYLLINE DID NOT PREVENT TRANSPLANT-RELATED TOXICITY IN 31 CONSECUTIVE ALLOGENEIC BONE MARROW TRANSPLANT RECIPIENTS

To the Editor:

A recent study published by Bianco et al[1] has suggested that pentoxyifylline [3,7-dimethyl-1-(5-oxo-hexyl)-xanthine] reduces morbidity and mortality in patients undergoing bone marrow transplantation (BMT). When compared with a "good risk" control group, pentoxifylline recipients experienced less mucositis (3.7 *v* 18.7 days, $P = .004$), less hepatic venocclusive disease (10% *v* 65%, $P = .001$), a lower incidence of renal insufficiency (3% *v* 65%, $P = .003$), and less acute graft-versus-host disease (GVHD) greater than grade II (35% *v* 68%, $P = .03$). Based on these encouraging results, we prophylactically administered pentoxifylline to 31 consecutive allogeneic BMT recipients (acute myeloid leukemia [AML], n = 11; acute lymphoblastic leukemia [ALL], n = 5; hybrid leukemia, n = 1; chronic myelogenous leukemia [CML], n = 10; non-Hodgkin's lymphoma [NHL], n = 2; multiple meyloma [MM], n = 2; median age, 32 years [range, 9 to 53 years]; "high risk," 17 of 31 [55%]; "good risk," 14 of 31 [45%]). Twenty-four patients received a transplant from an HLA-identical, MLC-negative sibling, four patients from a 1-antigen–mismatched relative, one patient from a 2-antigen–mismatched relative, and two patients from an HLA-identical, MLC-negative unrelated donor. Pentoxifylline (12 to 30 mg/kg/d by continuous infusion) was started 1 day before conditioning and switched from intravenous to oral administration at the time of discharge; it was discontinued on day 100 posttransplant. Conditioning consisted of either total body irradiation (TBI) plus cyclophosphamide and/or etoposide (n = 15) or busulfan plus cyclophosphamide and/or etoposide (n = 16). For GVHD prophylaxis, either cyclosporine A (CSA) plus short-course methotrexate (n = 22) or CSA plus methylprednisolone (n = 9) was administered. Clinical data were compared with a historical control group of 61 consecutive allogeneic BMT recipients who had undergone BMT between 1988 and 1990 (AML, n = 23, CML, n = 23; ALL, n = 8; NHL, n = 3; myelodysplasia, n = 4; median age, 30 years [range, 8 to 57 years]; "good risk," 35 of 61 [57%]; "high risk," 26 of 61 [43%]; donor status: HLA-identical, MLC-negative sibling, n = 57; 1-antigen–mismatched relative, n = 3; 2-antigen–mismatched relative, n = 1; conditioning: TBI plus cyclophosphamide or etoposide, n = 40; busulfan plus cyclophosphamide and/or etoposide, n = 21). Patients were analyzed for transplant-related toxicities within the first 30 days posttransplant, for day 100 survival, and for overall survival. Pentoxifylline was well tolerated at all dose levels administered and no patient experienced significant adverse side effects. Twenty-seven of 28 evaluable pentoxifylline recipients (97%) engrafted; three patients died too early to be evaluated (on days 13, 15, and 22). All 59 (100%) evaluable control patients engrafted; two patients were not evaluable (died on days 13 and 19). At 100 days posttransplant, 19 of 31 (61%) of pentoxifylline patients were alive compared with 46 of 61 (75%) of the controls. Currently, 17 of 31 pentoxifylline recipients (55%) are alive with a median follow-up of 202 days (range, 55 to 449 days) compared with 34 of 61 control patients (56%) with a median follow-up of 573 days (range, 50 to 1,576 days). Serum bilirubin levels greater than 3 mg% were observed in 20 of 31 pentoxifylline recipients (65%) and in 16 of 61 control patients (26%), respectively. Serum creatinine levels greater than 1.5 mg% were seen in 7 of 31 pentoxifylline recipients (23%) compared with 14 of 61 (23%) in the control group. Acute GVHD II-IV developed in 22 of 31 pentoxifylline recipients (71%) (15 of 22 grade II, 3 of 22 grade III, and 4 of 22 grade IV) and in 24 of 61 control patients (39%) (11 of 24 grade II, 9 of 24 grade III, and 4 of 24 grade IV), respectively. Mucusitis requiring analgetic therapy developed in 21 of 31 pentoxifylline recipients (68%) compared with 21 of 61 in the control group (34%). There was no difference with regard to the days of fever greater than 38.3°C between the two groups (pentoxifylline: median, 2 [range, 0 to 11] *v* control: median, 2 [range, 0 to 17]). Separate comparison of "standard risk" and "high risk" patients of the pentoxifylline group and the control group did not show any difference regarding transplant-related toxicities. In contrast to Bianco et al,[1] who found significantly less toxicity in the pentoxifylline group, which consisted of 40% "high risk" patients even when comparing them with a "good risk" historical control group, we did not observe this advantage for our pentoxifylline patients. Our data show that, despite the parenteral prophylactic administration of pentoxifylline, substantial transplant-related toxicities were observed. To further define the value of a prophylactic use of pentoxifylline in allogeneic BMT recipients, prospective randomized trials are clearly necessary.

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RESPONSE

In the study reported by Kalhs et al, the oxoalkyl-substituted methylxanthine, pentoxifylline (PTX), was prophylactically administered by continuous infusion to a heterogeneous group of 31 allograft recipients without demonstrable benefit, in contrast to preliminary data reported from Seattle.[1]

There are two important differences between the two studies.

First, in the study by Kalhs et al, PTX was administered parenterally via continuous infusion (0.5 to 1.25 mg/kg/h) at total daily doses ranging from 840 mg to 2,100 mg, assuming a maximum weight of 70 kg. At discharge, PTX was administered orally. By contrast, the Seattle study used a marketed 400 mg oral formulation, administered 3, 4, or 5 times daily. In addition, pills were crushed and mixed with liquid for patients who experienced difficulty swallowing intact tablets. A second difference was the prophylactic use of high-dose dexamethasone as an antiemetic in the majority of patients in that trial, an agent that may have altered the metabolism of PTX.

The pharmacokinetic profiles differ significantly between oral and parenteral routes of administration.[2,3] For example, orally administered, PTX undergoes extensive first-pass metabolism with a plasma half-life of approximately 1 hour. A 400 mg oral solution or capsule formulation results in peak plasma (Cmax) and area under curve (AUC) concentrations for PTX and its first metabolite (metabolite I) of 1,791 and 1,875 ng/mL and 1,196 and 3,690 ng/mL/h, respectively. Conversely, continuous parenteral infusion of PTX results in less first-pass metabolism and lower maximum concentrations of both PTX and metabolite I.[4] For example, we have shown that continuous infusion rates of 1.5 mg/kg/h (2,500 mg/d) results in Cmax levels of only 300 to 500 ng/mL and 300 to 700 ng/mL for PTX and metabolite I, respectively (unpublished observations).

Our initial rationale for prophylactically administering PTX to marrow transplant recipients stemmed from observations that tumor necrosis factor-α (TNF-α) may mediate regimen-related toxicities (RRT) and from in vitro data demonstrating the ability of PTX to inhibit TNF production in response to a variety of stimuli.[5-7] Because TNF inhibition was dose-dependent and only observed at millimolar concentrations of PTX, we chose to administer PTX as an oral solution or via a rapid parenteral infusion aiming to achieve a higher Cmax. Attempts at escalating dose rate or total dosage were often limited by gastrointestinal intolerance, nausea, and, in some instances, CNS and cardiac toxicities. Given the disparity between in vitro millimolar concentrations at which PTX has shown anti-TNF activity and the concentrations clinically achievable (nanomolar to micromolar), we reasoned that inhibition of TNF production by the parent compound would not likely be the mechanism for the observed benefit in our study patients. In addition, it appeared likely that metabolites of PTX may be more active than the parent compound.[8]

We have subsequently reported that the potential beneficial effects of PTX and certain xanthines may result from their ability to modulate a phospholipid signaling pathway coupled to inflammatory and immune cytokine responses in addition to abnormal cellular proliferation.[9,10] Based on clinical observations and an evolving understanding of this novel pathway, we have recently characterized a unique metabolite (CT-1501R) that appeared in the plasma of patients receiving PTX coadministered with certain cytochrome p 450 inhibitors, such as corticosteroids or quinolone antibiotics (eg, ciprofloxacin) (unpublished data). This unique metabolic product was notably absent in patients receiving PTX alone. Ongoing and recently completed clinical trials designed to pharmacologically manipulate the metabolism of PTX to CT-1501R have suggested the ability to reduce regimen-related toxicities in interleukin-2/LAK recipients, as well as among bone marrow transplant patients (J. Thompson, personal communication, September 1992; and Bianco et al[11]). In addition to an apparent reduction in RRT, transplant recipients coadministered PTX and ciprofloxacin demonstrated rapid trilineage engraftment in both autologous and allogeneic recipients (manuscript in preparation).

Differences in drug delivery, maximal peak concentrations, and the concomitant use of other medications that may alter the metabolic profile of PTX may have played a role in the differences in outcome observed between the two study groups. As in any treatment regimen, controlling for such variables is essential for drawing comparisons. Thus, before attempting to define the potential value of compounds such as PTX in randomized trials, a better definition of the pharmacology and mechanisms of actions for such agents is clearly required. As our understanding of the signaling mechanisms uncovered by Bursten et al[9] unfolds, new agents such as CT-1501R can potentially be applied to pharmacologically manipulate the immune and hematopoietic system.

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