Phase Ib Trial of Pentoxifylline and Ciprofloxacin in Patients Treated with Interleukin-2 and Lymphokine-activated Killer Cell Therapy for Metastatic Renal Cell Carcinoma

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ABSTRACT

The dose of interleukin 2 (IL-2) which can be administered to cancer patients is limited largely by a capillary leak syndrome. Pentoxifylline (PTX) is a methylxanthine which reduces IL-2 toxicity in animals. Ciprofloxacin (Cipro) modifies the metabolism of methylxanthines and, when coadministered with PTX, increases levels of PTX and certain of its metabolites. We conducted a phase Ib trial in patients receiving IL-2 and lymphokine-activated killer cell (LAK) cell therapy for metastatic renal cell carcinoma to identify the maximum tolerated dose of PTX which could be coadministered with Cipro in this setting. Eighteen patients received IL-2 (Roche) by continuous infusion at 6 × 10⁶ units/m²/day on days 1–5 and underwent leukapheresis on days 7–9. LAK cells were infused on days 12–14. IL-2 was administered at 2 × 10⁶ units/m²/day on days 10–20. Cohorts of patients received PTX at 2.5 (n = 3), 3.1 (n = 6), 3.9 (n = 6), and 4.9 (n = 3) mg/kg by 30 min i.v. infusion every 4 h on days 0–5 and 10–20 and Cipro (500 mg p.o. every 12 h) on days 1–5 and 10–20. Toxicity was compared with that observed in 33 historical control patients who received 37 cycles of an identical regimen of IL-2/LAK without PTX/Cipro.

PTX at 2.5–3.9 mg/kg and Cipro were well tolerated. The maximum tolerated dose of PTX was 3.9 mg/kg. Dose-limiting emesis (n = 1) and atrial fibrillation (n = 2) occurred at 4.9 mg/kg and were reversible. Two complete, one partial, and one minor, responses were observed. Patients treated with 3.9 mg/kg PTX and Cipro received 95.0% of the planned dose of IL-2 as compared to 72.8% in the control patients (P < 0.025), primarily due to a lower incidence of azotemia and metabolic acidosis in PTX/Cipro recipients than had been seen in the historical control patients. The results of this study demonstrate that PTX/Cipro can be administered to patients receiving IL-2/LAK without apparent loss of therapeutic efficacy. Moreover, PTX/Cipro recipients exhibited less toxicity than historical controls. Therefore, treatment with PTX/Cipro may allow delivery of higher doses of IL-2, which might induce more responses in IL-2-responsive tumors and regression of tumors unresponsive to conventional doses of IL-2.

INTRODUCTION

Therapy with high-dose IL-2 alone or in conjunction with LAK cells can induce objective remissions, including durable complete remissions, in patients with metastatic RCC (1, 2). The antitumor effect of IL-2 in animal models is related to the dose of IL-2, with higher doses being more effective (3, 4). Clinical regimens of IL-2 ± LAK which have been associated with the highest rates of complete remission involved IL-2 at or near the maximum tolerated dose (1, 2, 5–9). However, the ability to administer higher doses of IL-2 is limited by the capillary leak syndrome, which is characterized by hypotension, oliguria, renal dysfunction, and interstitial edema. This syndrome is mediated in part by secondary cytokines, including TNF, γ-interferon, and interleukin-1 (10–13).

One strategy to increase the antitumor activity of IL-2 is to escalate IL-2 doses beyond the conventional MTD by pharmacologically inhibiting the mechanism(s) of IL-2-induced capillary leak. Such a strategy would be advantageous only if it did not abrogate antitumor effector mechanisms and, ultimately, tumor responses. PTX is a methylxanthine which has been shown to reduce the hypotension, microvascular protein leakage, and decreased microvascular blood flow induced by IL-2 in animal models (14, 15). In one murine tumor therapy model, parenteral administration of PTX significantly reduced the toxicity of high-dose IL-2 without decreasing its antitumor efficacy (16). Inhibition of TNF secretion is one mechanism proposed to explain the reduction in IL-2 toxicity by PTX (17, 18). Preclinical studies with human peripheral blood mononuclear cells showed that PTX, at concentrations achievable in vivo, did not significantly inhibit the generation of LAK cytotoxicity (19).

Cipro is a quinolone antibiotic which modifies the metabolism of methylxanthines (20, 21), such that the coadministration of PTX and Cipro results in higher levels of PTX and certain of its metabolites than in the absence of Cipro. The current trial was conducted to determine the maximum tolerated dose of PTX which could be coadministered with Cipro in the context of IL-2/LAK therapy, to compare toxicity in recipients of PTX/Cipro/IL-2/LAK with a group of historical controls treated with the same regimen of IL-2/LAK without PTX/Cipro, and to determine the pharmacokinetics of PTX and its metabolites, specifically the first metabolite M-1, in the presence of Cipro. PTX was administered by intermittent i.v. infusion in an attempt to avoid the possibility of erratic absorption of oral PTX caused by IL-2-induced gastrointestinal dysfunction (22).

MATERIALS AND METHODS

Patient Population and Study Design. Eighteen patients with histologically documented, bidimensionally measurable metastatic RCC were treated according to a protocol approved by the Human Subject’s Review Committee of the University of Washington. All patients met eligibility and performance status criteria as previously described (1). Induction IL-2 (Roche) was administered by continuous i.v. infusion for 120 h at 6 × 10⁶ units/m²/day, beginning at 10 a.m. on day 1 and stopping at 10 a.m. on day 6. Patients underwent leukapheresis on days 7–9, and peripheral blood mononuclear cells were incubated in vitro with IL-2 to generate LAK cells, as previously described (1). LAK cells were infused on days 12–14. Maintenance IL-2 was administered at 2 × 10⁶ units/m²/day by continuous i.v. infusion on days 10–20. Cipro was administered at 500 mg p.o. every 12 h on days 1–5 and 10–20. PTX was administered i.v. as a 30-min infusion every 4 h beginning day 0 at 1 p.m. through day 6 at 9 a.m. and from day 10 at 9 a.m. through day 20 at 9 a.m. Cohorts of 3 patients entered at 4 dose levels of PTX: 2.5, 3.1, 3.9, and 4.9 mg/kg. After we determined the maximum tolerated dose of PTX, six addi-

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tional patients were entered on the study, three at 3.1 and three at 3.9 mg/kg. PTX and Cipro were discontinued for grade III-IV toxicity attributable to PTX.

Clinical results were compared with a group of 33 historical control patients with metastatic RCC who met identical entry criteria and who received 37 cycles of the same regimen of IL-2 and LAK cells without PTX/Cipro at our institution between October 1989 and June 1992. Results of 23 of the historical control cycles were previously published (denoted protocol B in that report; 1) and are extended here with an additional 14 cycles. Patient characteristics are shown in Table 1.

Patient characteristics were obtained from all patients before, at the completion of, and 15, 30, 60, 120, and 240 min after the first PTX infusion on day 0 and the third PTX infusion on day 5. Additional trough and peak levels were obtained on days 12 and 19. The plasma concentrations of PTX and M-1 (1-(5'-hydroxyethyl)-3,7-dimethyloxanthine) were determined by the method of Gairner-Moiroux et al. (23) using high-performance liquid chromatography, as previously described (19). M-1R was quantitated in selected samples following formation of Mosher's esters (24), which were subsequently analyzed by reverse-phase high-performance liquid chromatography.

Lymphokine-activated Killer Cell Cytotoxicity. Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque centrifugation in all patients on day 7 prior to leukapheresis. Peripheral blood mononuclear cells were tested for LAK precursor activity, defined as lysis of Daudi cells in a 4-h 51Cr release assay after 5 days incubation in the presence of 1000 units/ml IL-2, and for LAK effector activity, defined as lysis of Daudi cells in a 4-h 51Cr release assay without in vitro culture in IL-2, as previously described (25).

Plasma Concentration of TNF. Blood samples were collected immediately before starting PTX on day 0 (or before starting IL-2 in historical controls) and on days 5 and 7. Samples were collected in sterile vacuum tubes containing EDTA (1.5 mg/ml blood) and aprotinin (0.67 trypsin inhibitor unit/ml blood; Sigma, St. Louis, MO). Tubes were transported on ice for immediate centrifugation and cryopreservation of plasma at −70°C until assayed. The concentration of TNF was determined by enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN).

Statistical Analysis. Results were compared using Student's unpaired t test or, where indicated in the text, the χ2 test. Computations were performed using the Statview microcomputer software package.

RESULTS

Toxicity of PTX/Cipro. Toxicity is summarized in Table 2. The most common side effect attributable to PTX/Cipro therapy was nausea which was maximal shortly after PTX infusions. With antiemetic therapy, PTX was well-tolerated at doses between 2.5 and 3.9 mg/kg i.v. every 4 h. Toxicity which required discontinuation of PTX occurred in two of three patients treated with 4.9 mg/kg and consisted of reversible atrial fibrillation in both patients and intractable nausea in one. These toxicities were attributed to PTX because of the temporal association with onset of toxicity within 30 min of PTX infusion and because of the associated peak plasma concentrations of PTX >7500 ng/ml. The maximum tolerated dose of PTX was determined to be 3.9 mg/kg.

Toxicity of IL-2/LAK. Prior to beginning IL-2 treatment, the average serum creatinine and bicarbonate concentrations were 1.2 mg/dl and 26 mEq/liter, respectively, in patients treated with PTX/Cipro and in historical controls. As shown in Fig. 1, the median (range) peak creatinine (mg/dl) during treatment of PTX/Cipro recipients was 2.25 (1.2—6.1), compared to 4.2 (1.2—8.7) for historical controls (P < 0.005). Similarly, the median (range) nadir serum bicarbonate (mEq/liter) of PTX/Cipro recipients was 20 (15—22), compared to 17 (11—21) for historical controls (Fig. 2; P < 0.005). The peak creatinine and nadir bicarbonate values for patients treated at different dose levels of PTX did not differ significantly. With PTX/Cipro, discontinuation of IL-2 because of renal dysfunction was necessary in only two of 18 cycles (11%), compared to 20 of 37 cycles (54%) with controls (P < 0.01 by χ2).

Toxicities involving other organ systems were also lower in PTX/Cipro recipients than in historical controls. The median (range) peak alkaline phosphatase value (units/liter) with PTX/Cipro was 228 (69—363) compared to 352 (103—969) in controls (P < 0.01). The median (range) peak bilirubin concentration (mg/dl) was 1.9 (0.7—6.9) in recipients of PTX/Cipro and 2.8 (0.5—16.9) in controls (P, not significant). No patient developed bacteremia in the current study, com-
Table 2: Toxicity of PTX/Cipro/IL-2/LAK

<table>
<thead>
<tr>
<th>PTX dose (mg/kg)</th>
<th>2.5 (n = 3a)</th>
<th>3.1 (n = 6)</th>
<th>3.9 (n = 6)</th>
<th>4.9 (n = 3)</th>
<th>Historical controls (n = 37)</th>
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<tr>
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<tr>
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<td>3</td>
<td>5</td>
<td>2</td>
<td>6</td>
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<td>0</td>
<td>0</td>
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<tr>
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<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
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<td>3</td>
<td>0</td>
<td>24</td>
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<tr>
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<td>0</td>
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<td>12</td>
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</table>

- Number of cycles.

PHASE Ib TRIAL OF PTX AND CIPRO

Phase Ib trial of PTX and Cipro.

- 100% of the planned doses of induction IL-2 were administered in all cycles in the current study and in 36 of 37 cycles in historical controls. However, maintenance IL-2 was more often discontinued prematurely because of cumulative IL-2 toxicity and LAK infusions. IL-2 was discontinued prematurely in: 3 of 3 patients at dose level 1 (grade 3 respiratory dysfunction in 2; at patient request because of dyspnea in 1), 3 of 6 patients at dose level 2 (atrial fibrillation in 1; metabolic acidosis and grade 3 respiratory dysfunction in 2), and 2 of 6 patients at dose level 3 (hematocrit in 1; grade 3 respiratory dysfunction in 1). Maintenance IL-2 delivery increased with increasing PTX dose; the mean (±SD) maintenance IL-2 dose deliveries at PTX doses of 2.5, 3.1, and 3.9 mg/kg were 63.3 (±15.2), 78.3 (±25.7), and 95.0% (±8.3), respectively, compared to 72.8 ± 24.7% for historical controls (P < 0.05 for dose level 3.9 mg/kg versus controls). Therapy with PTX at 3.9 mg/kg and Cipro allowed maintenance IL-2 to be given for a longer duration (median, 10 days; 7 days in controls).

Clinical Response. Two complete, one partial, and one minor response were observed (Table 3). Responses were observed at PTX doses (mg/kg) of 2.5 (one CR, one minor remission), 3.1 (CR), and 3.9 (PR). The PR may become a CR with longer follow-up in that metastatic disease before IL-2 consisted of a lytic lesion to the ilium with an extensive soft tissue component. The measurable soft tissue lesion has completely regressed, and partial remineralization of the ilium has occurred 1 month after PTX/Cipro/IL-2/LAK. Additional radiographic improvement is possible, but response cannot be considered complete until complete remineralization of lytic defect is documented.

Fig. 1. Peak serum creatinine (mg/dl) in 37 cycles of IL-2/LAK in historical controls and in 18 cycles of PTX/Cipro/IL-2/LAK. Bars, medians.

Fig. 2. Nadir serum HCO₃⁻ (mEq/liter) in 37 cycles of IL-2/LAK in historical controls and in 18 cycles of PTX/Cipro/IL-2/LAK. Bars, medians.

- 5 of 37 control patients with bacteremia (P, not significant, \( \chi^2 \)). Weight gain of >10% occurred in 2 of 18 (11%) cycles of PTX/Cipro/IL-2/LAK and in 10 of 37 (27%) cycles in historical controls (P, not significant, \( \chi^2 \)).

Five of the 18 patients treated with PTX/Cipro required ICU support for the management of severe toxicity. Two of these 5, who received PTX at 4.9 mg/kg, experienced toxicity which was thought to be PTX related (i.e., atrial fibrillation and intractable nausea/vomiting). Three of 15 (20%) PTX/Cipro recipients, who received doses of PTX at or below the MTD, required ICU care for toxicity that was clearly IL-2 related for 1, 2, and 2 days. In comparison, 12 of 37 (32%) historical control cycles required ICU support for a median of 2 days.

IL-2 delivery (administered dose/planned IL-2 dose × 100%) was analyzed to determine whether the reduction in IL-2 toxicity observed with PTX/Cipro permitted longer duration of IL-2 therapy. One hun-
Plasma PTX and M-1. Plasma concentrations of PTX, M-1, and M-1R on day 5 are summarized in Table 4. Concentrations of PTX and M-1 reached values on day 5 of 1361 and 2324 ng/ml, respectively, at a dose of 2.5 mg/kg, and 6767 and 5886 ng/ml at 4.9 mg/kg. The peak PTX concentrations measured on days 12 and 19 (data not shown). Mean peak concentrations of M-1R on day 5 ranged from 253 to 627 ng/ml and did not increase with increasing dose of PTX. The peak PTX concentrations in the two patients who experienced PTX dose-limiting toxicity (atrial fibrillation and intractable nausea) were 7918 ng/ml (30 ±6aM) and 8256 ng/ml (30 ±6aM). These were the highest levels observed in this study, suggesting that the arrhythmia and nausea were attributable, at least in part, to PTX. The peak concentrations of PTX in the clinical responders were 2001 (patient 02), 794 (patient 03), 1286 (patient 06), and 1757 ng/ml (patient 17).

Immunomodulatory Effects. PTX/Cipro did not inhibit IL-2-induced rebound lymphocytosis or the number and cytolytic activity of adoptively transferred LAK cells. The mean ± SD IL-2-induced rebound lymphocytosis at PTX doses of 2.5, 3.1, 3.9, and 4.9 mg/kg was 9,853 ± 6,697, 10,212 ± 3,665, 9,598 ± 2,346, and 11,670 ± 2,122, respectively, which was not significantly different from 66 ± 44 in historical controls. Similarly, the total lytic units infused (median) in PTX/Cipro recipients at doses of 2.5, 3.1, 3.9, and 4.9 mg/kg were 948, 3899, 2323, and 2248, respectively (range, 108–7832 lytic units for PTX/Cipro), which were somewhat lower than in historical controls (median, 4459 lytic units; range, 1–125,868 lytic units), but the difference was not statistically significant.

To test for a potential effect of PTX/Cipro on in vivo LAK activity, LAK effector activity was measured on day 7 in 12 PTX/Cipro recipients and 14 historical controls. LAK effector activity was detected in all historical control patients but the mean (± SD) lytic activity at an effector:target ratio of 50:1 was only 16 (±19%). The mean lytic activity in PTX/Cipro recipients at an effector:target ratio of 50:1 was 15 (±12%), a difference that was not statistically significant.

Plasma TNF determinations were performed for all patients in the current study and in 8 historical control patients (Fig. 3). The 2 groups differed in that pretreatment TNF levels were elevated in 12 of 18 recipients of PTX/Cipro compared to only 1 of 8 historical controls. The small number of patients tested and the variability of TNF levels limited the ability to detect an effect of PTX/Cipro. There was no statistically significant correlation between peak TNF levels and either peak creatinine or nadir bicarbonate concentration.

DISCUSSION

Treatment with high-dose IL-2, with or without infusion of LAK cells, has induced durable objective responses in patients with advanced renal cell carcinoma (1, 2, 5, 9). The antitumor effects of IL-2 in preclinical models are dose dependent, with higher doses being more effective (3, 4, 26). No plateau in the dose-antitumor response curve for IL-2 has been described. Escalation of IL-2 doses above the current MTD might be associated with an increase in response rates, but such a strategy would be advantageous only if approaches were developed which reduced IL-2 toxicity without abrogating antitumor effects (19). Treatment with PTX has been shown to decrease the toxicity of IL-2 in animal models (14, 15), without apparent reduction in the antitumor activity of IL-2 (16). The current study demonstrates that treatment with PTX at 2.5–3.9 mg/kg and Cipro was well tolerated in patients undergoing high-dose IL-2 and LAK cell therapy for metastatic renal cell cancer.

The addition of PTX/Cipro did not eliminate the antitumor activity of IL-2 and LAK. Objective responses were observed in 4 of 15
patients treated with PTX at doses up to and including the MTD, for a response rate of 27% (confidence interval, 4–49%). In our historical control group, 8 responses (5 CR + 3 PR) were observed in 33 patients treated with the same regimen of IL-2/LAK without PTX/Cipro, for a response rate of 24% (confidence interval, 9–39%). Thus, the response rate in the small number of patients in the current study does not differ significantly from historical controls or from trials of IL-2/LAK reported by other investigators (5–7).

Compared to historical controls, patients treated with PTX/Cipro experienced less severe IL-2 toxicity. Discontinuation of IL-2 because of severe azotemia or metabolic acidosis (pH < 7.2) was necessary in 20 of 37 treatment cycles in historical controls, compared to only 2 of 18 cycles with PTX/Cipro (P < 0.01). Similarly, ICU care for IL-2-related toxicity was required in 12 of 37 (32%) historical control cycles, compared to 3 of 15 (20%) cycles in which PTX/Cipro was administered at or below the MTD for PTX. Although not statistically significant, the difference in ICU care suggests that patients who receive Cipro and PTX may experience life-threatening IL-2 toxicity less frequently. Significantly more IL-2 was delivered to patients who received 3.9 mg/kg PTX than to historical controls. The delivery of more IL-2 with less toxicity suggests that, at a PTX dose of 3.9 mg/kg, escalation of the IL-2 dose could be explored.

IL-2 toxicity may be mediated through a variety of mechanisms, including the secretion of secondary cytokines (10, 11, 27), LAK cell-mediated endothelial damage (28), and/or the synthesis of nitric oxide (29). Administration of neutralizing anti-TNF antibody reduced the toxicity of high-dose IL-2 in one murine model (13). PTX administration was associated with lower TNF levels and toxicity in another murine model of IL-2 immunotherapy (16). In cancer patients treated with IL-2, serum TNF levels correlated with toxicity in one study (27) but not in others (30, 31). PTX levels of 250–500 μM are required to inhibit TNF secretion in vitro (17, 32), concentrations far higher than the highest achieved in the current study. Because of the small number of patients and variability of TNF levels in this phase I study, definitive conclusions about the effects of PTX/Cipro on plasma TNF levels must await additional trials. PTX/Cipro had no consistent effect on circulating TNF, despite clear evidence for reduced IL-2 toxicity. This observation suggests that plasma concentrations of PTX were too low to inhibit TNF secretion, that the number of patients tested was too small to detect an effect of PTX/Cipro on TNF secretion, and/or that mechanism(s) other than inhibition of TNF release exist through which PTX/Cipro may mediate the reduction in IL-2 toxicity. An alternate hypothesis is that PTX and/or its metabolites may inhibit intracellular signal transduction triggered by the binding of TNF to its receptor. Recent studies indicate that TNF may mediate cytotoxicity by signaling through an intracellular lipid second-messenger pathway involving unique species of phosphatidic acid and diacylglycerol (33).

PTX undergoes keto reduction in vivo to form a chiral secondary alcohol (1-((5′-hydroxyethyl)-3,7-dimethylxanthine), denoted M-1, and subsequent oxidation to form other metabolites (34). Recent in vitro studies using human liver microsomes suggest that this reduction occurs predominantly stereoselectively to form the S enantiomer of M-1 (M-1S). In the presence of Cipro, the pattern of PTX metabolites in the plasma is altered (20, 21), allowing the appearance of the R enantiomer of M-1 (M-1R) (35, 36). The concentration of PTX required to inhibit intracellular phosphatidic acid signaling is relatively high (IC₅₀ 30 μM) (37) and was achieved in only one patient. In contrast, the concentration of M-1R required to inhibit phosphatidic acid signaling (IC₅₀ 0.26 μM) is 100-fold lower than for PTX (37). Plasma M-1R concentrations of 264–627 ng/ml (0.9–2.2 μM) were detected in the current study, which exceed the IC₅₀ severalfold.

Plasma levels of PTX and M-1 increased in a PTX dose-dependent fashion. PTX dose-limiting toxicity was associated with PTX levels in excess of 7500 ng/ml. However, concentrations of M-1R did not increase with increasing doses of PTX. Thus, the quinolone-PTX interaction appears to be saturable. If M-1R is a mediator of the apparent effect of PTX/Cipro, administration of purified M-1R represents an alternative approach to the use of PTX/Cipro which could be explored in an effort to reduce IL-2 toxicity and which might avoid some of the side effects of high plasma levels of PTX.

Other approaches which have been explored in an effort to reduce the toxicity of IL-2 include the use of corticosteroids (38) and N⁵⁰-monomethyl-L-arginine (29). Dexamethasone administration in patients treated with high-dose bolus IL-2 was associated with a reduction in TNF levels and toxicity (38, 39) and permitted a 3-fold escalation in the IL-2 dose over that possible without dexamethasone (38). Objective tumor responses were reported in some recipients of dexamethasone and high-dose bolus IL-2 (38). However, steroids reduced the antitumor effectiveness of IL-2 in animal models (40) and possibly in cancer patients (39). Nitric oxide synthesis is upregulated by bolus IL-2 in part via secondary TNF secretion and may mediate the vasodilation and hypotension which are frequent dose-limiting toxicities of bolus IL-2 regimens (41). N⁵⁰-monomethyl-L-arginine inhibits nitric oxide synthesis and has the potential to attenuate the hypotension of bolus IL-2 regimens (29), although the effect of N⁵⁰-monomethyl-L-arginine on the toxicity and antitumor activity of IL-2 has not yet been determined. Ciprofloxacin at high concentrations has been reported to inhibit TNF and IL-1 secretion in vitro, but the effects of ciprofloxacin alone on IL-2 toxicity in vivo have not been tested (42). Although the difference in documented bacteremia between PTX/Cipro recipients and historical controls in the current study was not statistically significant, a decrease in subclinical bacteremia may have occurred in recipients of Cipro and may have contributed to the reduction in IL-2 toxicity.

A randomized controlled trial will ultimately be required to determine conclusively whether the toxicity of IL-2 and LAK cells is reduced by treatment with PTX/Cipro. If a reduction in toxicity by treatment with PTX/Cipro is confirmed, additional trials are indicated to redefine the MTD of IL-2 in the presence of PTX/Cipro. If the use of PTX/Cipro permits significant escalation of IL-2 doses or longer infusions of high-dose IL-2, the response rate of such a regimen should be determined in patients with metastatic RCC. If therapy with PTX/Cipro reduces IL-2 toxicity, a response rate superior to that of IL-2 administered at the conventional MTD, the results would have important implications for other settings in which IL-2 has shown efficacy, including melanoma, acute myelogenous leukemia, and lymphoma (43–45), and may justify phase II trials in other solid tumors which have not been responsive to conventional doses of IL-2.

REFERENCES


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