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The Effects of Oral Pentoxifylline on Interleukin-2 Toxicity in Patients With Metastatic Renal Cell Carcinoma

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Interleukin-2 (IL-2) mediates the regression of metastatic renal cell carcinoma, but clinical application has been limited by associated toxicities. Preclinical studies show that pentoxifylline (PTXF), a methylxanthine derivative, inhibits IL-2 toxicity while preserving anti-tumour efficacy. This study was designed to determine whether oral PTXF would alter IL-2-induced toxicities. Patients with disseminated renal cell carcinoma were treated with continuous infusion of 18 × 10^6 IU/m^2/24 h for 4 days followed by 3 days without treatment, for 4 consecutive weeks. After a 2-week interval, the 4-week treatment cycle was repeated. All patients concomitantly received oral PTXF (2000 mg/24 h) in five divided doses. Despite the co-administration of PTXF, all patients demonstrated a spectrum and severity of toxicities consistent with previous reports of continuous infusion of IL-2 alone. There was considerably more nausea and vomiting associated with the administration of PTXF which improved on withdrawal of PTXF. Oral PTXF in IL-2 therapy did not show any substantiated benefit. Indeed, patients suffered more severe nausea and vomiting than if they had received IL-2 alone, resulting in the early termination of the trial.

Key words: interleukin-2, toxicity, pentoxifylline
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INTRODUCTION

IMMUNOTHERAPY WITH interleukin-2 (IL-2) has been shown to be superior to conventional chemotherapeutic agents in mediating the regression of metastatic renal cell carcinoma [1]. IL-2 therapy is, however, associated with dose-dependent toxicities of sufficient severity to limit therapeutic efficacy [2]. The toxicities of primary clinical significance occur secondary to a "vascular leak syndrome", and are manifest by diffuse tissue oedema, weight gain, decreased systemic vascular resistance with hypotension, acute respiratory distress, and hepatic and renal dysfunction [3]. Several studies have evaluated inhibitors of IL-2 toxicity, but none have been identified in clinical trials which can reduce IL-2 toxicity while preserving anti-tumour efficacy. Non-steroidal anti-inflammatory agents reduce the incidence of fever and chills, but increase nephrotoxicity [4]. Corticosteroids have been the most effective inhibitors of IL-2 toxicity, but these drugs also abrogate anti-tumour efficacy [5].

Several clinical studies have demonstrated the ability of IL-2 to induce tumour necrosis factor-α (TNF-α) production [6], which has been shown to be both detrimental [7] and beneficial [8] to patients receiving IL-2 therapy. Both preclinical and clinical studies have shown that pentoxifylline (PTXF), a phosphodiesterase inhibitor, is capable of inhibiting transcription of TNF-α mRNA [9, 10]. Further preclinical studies have shown that PTXF is capable of suppressing IL-2-induced serum TNF-α levels and ameliorating IL-2 toxicity without decreasing tumour efficacy [11].

The present clinical study was designed to determine the feasibility of giving oral PTXF concomitantly with continuous infusion of IL-2 in patients with metastatic renal cell carcinoma in an attempt to decrease IL-2 toxicity.

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PATIENTS AND METHODS

Patients

Five patients with histologically proven metastatic renal cell carcinoma and measurable disease were studied. All patients were required to have a performance status of greater than 2 by Eastern Cooperative Oncology Group scoring (ECOG) [12], and be free from cerebral metastases and ischaemic heart disease. Serum creatinine, bilirubin and haematological parameters had to be within normal ranges prior to obtaining informed consent and initiating therapy.

Oral PTXF was started immediately prior to the IL-2 infusion at a dose of 400 mg five times per day, and continued throughout both cycles of IL-2 therapy, as well as during the 2-week rest period. This dose of PTXF was chosen as the maximum tolerated dose given in a previous report investigating patients with haematological malignancies following bone marrow transplantation [13], and a more recent study by the same group used the higher dose of 2400 mg/day of PTXF in four divided doses and

noticed a significant increase in emesis volume compared to control [14].

IL-2 was given for 96 h of continuous infusion per week at a dose of 18 × 10^6 IU/m^2/24 h. After 4 weeks, patients had a 2-week rest period with no IL-2, followed by the final 4 weeks of therapy. This regime of IL-2 was based on the protocol by West [15] who found 18 × 10^6 IU/m^2/24 h IL-2 to be the maximum tolerated daily dose. We had hoped that the addition of oral PTXF would allow an escalation in the IL-2 dosage in subsequent patients, and thereby potentially improve therapeutic efficacy, since earlier studies had suggested a dose-dependent tumour response to IL-2 therapy. However, the additional toxicity of the PTXF resulted in early termination of the trial after only 5 patients.

Assessment of toxicity

Daily enquiries about symptoms and daily physical examination for signs of IL-2 toxicity were undertaken. A grading system, based on the WHO criteria was used (1 = mild, 2 = moderate, 3 = severe, 4 = most severe). Blood was drawn on a weekly basis for complete blood count and chemistry to assess liver and kidney function.

RESULTS

The toxicities seen with the co-administration of PTXF and IL-2 were consistent with previous studies using 18 × 10^6 IU/m^2/day continuous Cetus IL-2 alone [15, 16]. Owing to the severity of these toxicities, we were unable to escalate the dose of IL-2, despite the addition of oral PTXF.

All patients experienced mild fever, myalgias, chills and skin rash. Of these general symptoms, only 1 patient developed grade 4 fever with temperature elevations to 40.9°C. The alterations in haematologic parameters with IL-2 and PTXF therapy were similar to those previously reported with IL-2 alone. All patients developed anaemia, thrombocytopenia, leucocytosis, lymphocytosis and eosinophilia (Table 1). Profound lymphocytosis occurred within 48 h of cessation of IL-2 therapy, which is a universal finding in all IL-2 studies, as is eosinophilia.

Gastrointestinal toxicity was considerable and dose limiting. Using our grading system, based on WHO criteria, we found that diarrhoea reached grade IV severity in only 1 patient (defined as requiring treatment for dehydration). However, 4 of 5 patients experienced severe nausea and vomiting of grade IV severity (intractable vomiting requiring in-patient treatment, refractory to medical therapy). This severe nausea and vomiting improved in all 4 patients whenever PTXF was discontinued. Only 1 patient tolerated the combination of IL-2 and PTXF without severe vomiting. An additional patient developed a severe case of necrotising colitis and perforated the transverse colon, requiring emergency colectomy.

Cardiorespiratory toxicity affected 3 of the 5 patients, who developed grade III hypotension (defined by 30–40% decrease in systolic pressure requiring pressor agents), but all were easily manageable with inotropic support. Although tachyarrhythmias have been reported with high doses of methylxanthines, only 1 of 5 patients developed grade IV dysrhythmias with combined IL-2 and PTFX therapy. 3 of the patients developed grade IV "vascular leak syndrome"—defined by anasarca and pleural effusion causing reduced pulmonary function.

Average total protein and albumin decreased to almost 50% of baseline values, indicating a dramatic "vascular leak" with loss of large molecules from the intravascular space into the interstitial space (Table 2). The elevation of blood urea nitrogen resulted from the well-known azotaemia, secondary to the decreased intravascular volume caused by IL-2 induced "vascular leak syndrome". Liver enzymes were significantly elevated, particularly alkaline phosphatase, indicating hepatic injury consistent with the massive lymphocytic infiltration of the liver seen with high dose IL-2 regimes.

PTXF did not, however, interfere with the anti-tumour efficacy of IL-2. 2 patients responded to the IL-2: one complete responder and one partial responder.

DISCUSSION

PTXF was originally developed as an agent for the treatment of peripheral vascular disease, and was thought to act by increasing blood cell deformability by a mechanism involving increased intracellular cyclic AMP [17]. PTXF has also been shown to be capable of inhibiting TNF production by macrophages *in vitro* and *in vivo* [9]. It has been effective in improving survival after lethal injection of endotoxin in mice [18] and beneficial in rodent and swine models of septic inflammation through its effects on decreasing TNF-α production [19–22]. PTXF was also shown to ameliorate lung injury induced by intravenous TNF in an animal model [23]. IL-2 is known to induce the production of TNF, and this increased TNF may be responsible for many of the toxic side-effects of high-dose IL-2 therapy [24]. PTXF has also been found to be beneficial in an animal model of IL-2-induced acute lung injury, which is thought to be secondary to IL-2-induced TNF-α production, by reducing lung oedema and neutrophil accumulation at 8 h [25].

The effects of the IL-2/PTXF combination on the haematological parameters of the patients in this trial are similar to the effect of IL-2 alone reported by Palmer [16] and West [15] (who both also used 18 × 10^6 IU/m^2/24 h of Cetus IL-2). Anaemia was a universal finding in West's series and occurred in 75% of

Table 1. Haematological parameters

	Baseline	Maximum change
Anaemia (haemoglobin, g/dl)	12.5 ± 1.0	8.54 ± 0.6*
Thrombocytopenia (10^3/μl)	303 ± 45	99.4 ± 33*
Leucocytosis (10^3/μl)	8.58 ± 0.7	45.5 ± 10*
Lymphocytosis (%)	18.8 ± 5.5	60.6 ± 4.5*
Eosinophilia (%)	1.2 ± 0.4	59.4 ± 12*

Baseline blood counts were taken prior to the start of IL-2 therapy; the maximum change from this baseline for each patient was taken and the means expressed above ± S.E.M. Statistical significance was determined by paired *t*-test (* $P < 0.05$).

Table 2. Blood chemistry

	Baseline	Maximum change
Total protein (g/dl)	7.0 ± 0.3	4.5 ± 0.2*
Albumin (g/dl)	3.6 ± 0.3	1.9 ± 0.1*
Bilirubin (mg/dl)	0.6 ± 0.1	2.4 ± 0.7*
Lactate dehydrogenase (U/l)	184 ± 57	282 ± 46
Alkaline phosphatase (U/l)	121 ± 16	478 ± 122*
Blood urea nitrogen (mg/dl)	20 ± 4.5	35 ± 5.1*
Bicarbonate (mmol/l)	24.0 ± 1.1	18.0 ± 0.58*

Baseline serum levels were drawn prior to the start of IL-2 therapy; the maximum change from this baseline for each patient was taken and the means expressed above ± S.E.M. Statistical significance was determined by paired *t*-test (* $P < 0.05$).

Palmer's patients, which concurs with our own findings. Chemical analysis of the patients' serum revealed a highly significant decrease in total serum proteins and albumin due to leakage of these large molecules from the intravascular compartment. Hypoalbuminaemia was a universal finding in West's series [15], although only 13% had a greater than 10% gain in weight. Palmer [16] did not report changes in serum albumin, but less than 10% had pulmonary or peripheral oedema, although 25% had a significant weight gain. In our series, marked weight gain occurred in all patients, despite significant vomiting in all but one. Oral PTXF was clearly unable to effectively inhibit the vascular leak syndrome, indeed it may have worsened it. Abnormal liver function tests were found in almost 50% of the patients in Palmer's series [16], which is consistent with our findings.

Nausea and vomiting is a known side-effect of both PTXF and IL-2. West's series had a 30% incidence of nausea, and nausea and vomiting was a significant problem in over half the patients in Palmer's series. All our patients experienced nausea and vomiting, which was the most prominent side-effect of the combined treatment. This nearly completely resolved upon withdrawal of PTXF in 2 patients for the last 2 weeks of IL-2 therapy, implying that PTXF was a major contributor to the nausea and vomiting in our patients at the dose used in our study. The route of administration of PTXF may be very important in the prevention of toxicities. The recently approved intravenous PTXF did reduce the side-effects of azotaemia and metabolic acidosis without interfering with the anti-tumour efficacy of IL-2/lymphocyte-activated killer (LAK) cell therapy [26], when combined with oral ciprofloxacin (500 mg every 12 h) to increase the active metabolites of PTXF.

There were no treatment-induced fatalities in our series, although 2 patients became comatose during the therapy (both made a full recovery on cessation of the infusion) and 1 patient suffered a perforated colon. This complication rate is comparable with Palmer's series, which had no deaths attributed to IL-2, and West's series [15], which had a single death from septicaemia and a 15% rate of admission to the intensive care unit.

Oral PTXF does not appear to affect the anti-tumour efficacy of IL-2, as one complete response and one partial response out of 5 patients is as good or better than the expected response rate to IL-2 therapy alone. Palmer reports an overall 16% response rate, with a complete response rate of 5%, and West a 33% partial response rate, with no complete responses.

In summary, this study shows that oral PTXF is not well tolerated in patients receiving IL-2 therapy, indeed the combination of IL-2/PTXF results in a greater degree of nausea and vomiting than would be expected with continuous IL-2 treatment alone. Oral PTXF does not appear to diminish the anti-tumour effects of continuous IL-2 therapy.

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High-dose Carboplatin and Etoposide for Salvage Chemotherapy of Germ Cell Tumours

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We evaluated high-dose carboplatin and etoposide with autologous bone marrow stem cell support in the salvage treatment of patients with metastatic germ cell tumours who had failed previous chemotherapy. The treatment programme comprised initial conventional dose chemotherapy. 23 patients received a first cycle of high-dose treatment, and 12 who showed no evidence of progression had a second cycle 2–3 months later. 8 of the 23 patients treated with high-dose chemotherapy are alive in remission 4–29 months from the start of high-dose treatment. 3 of these 8 required further treatment for recurrence. In the initial part of the study, the dose of carboplatin was escalated in successive patients. Grade 3/4 treatment-related toxicity occurred in 4 of 18 patients (1 fatal) who received carboplatin doses to give a AUC (area under the serum concentration/time curve) of 30 mg.min/ml or less and 3 of 5 patients (2 fatal) who received higher doses. We, therefore, recommend 30 mg.min/ml for further evaluation in chemotherapy sensitive patients.

Key words: chemotherapy, bone marrow transplantation, testicular neoplasm, carboplatin, etoposide
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INTRODUCTION

CISPLATIN-BASED combination chemotherapy, followed by surgery if necessary, is successful in the management of more than 80% of patients with metastatic non-seminomatous germ cell tumours [1]. For those who do not respond to primary chemotherapy or relapse after treatment, the prognosis is poor [2]. In relapsed patients, the combination of etoposide, ifosfamide and cisplatin can be curative [3]. To overcome drug resistance, increased doses of these drugs were evaluated in several protocols [4, 5]. When supported by autologous bone marrow transplantation (ABMT), the dose-limiting side-effects are mucositis for etoposide, renal toxicity for ifosfamide, especially in cisplatin pretreated patients, and nephro- and neurotoxicity for cisplatin.

Carboplatin was developed as a cisplatin-analogue showing no significant neuro- or nephrotoxicity, and its dose-limiting effect is mainly myelotoxicity particularly thrombocytopenia which can be calculated from the area under the serum concentration/time curve (AUC) [6]. While carboplatin may be slightly less active than cisplatin in standard treatments [7], it allows major dose intensification [8].

We now report a phase I/II study of high-dose carboplatin and etoposide with ABMT for patients who failed initial chemotherapy. This study contained initially a dose escalation of carboplatin.