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Low-dose Dopamine Induces Early Recovery of Recombinant Interleukin-2—Impaired Renal Function

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Recombinant interleukin-2 (rIL-2) can produce impairment of renal function with hypotension, fluid retention, elevated blood urea nitrogen, oliguria and low fractional sodium excretion; these side-effects are a common cause of reduction or interruption of rIL-2 infusion. The aim of this study was to investigate the control and treatment of renal toxicity induced by rIL-2 therapy. Here we show that dopamine, at a low dose of 2 μg/kg/min, completely prevented renal toxicity induced by rIL-2. While continuing rIL-2 therapy, 24-h continuous infusion of low-dose dopamine produced a rapid normalisation of urine output and a significant decrease in serum creatinine levels and body weight ($P < 0.01$), with an early and complete recovery of the rIL-2—impaired renal function: mean recovery time of renal function in patients treated with dopamine was significantly lower ($P < 0.05$) than in non-treated patients (4.8 days vs. 10 days, respectively).
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INTRODUCTION

IMMUNOTHERAPY WITH recombinant interleukin-2 (rIL-2) has shown antitumour effects in patients with metastatic renal cell carcinoma or melanoma. The best results (35% overall response rate) have been achieved with high dosage of rIL-2 (100 000 Cetus units/kg every 8 h for 5 days, followed by 7–10 days of rest, and a further 5 days of therapy) and reinfusion of *in vitro* activated LAK (lymphokine-activated killer) cells [1, 2]. Results achieved with high-dose rIL-2 alone, without reinfusion of LAK cells, seem comparable, although fewer complete responses have been observed. A 19–20% response rate has also been achieved with rIL-2 alone at a lower dose (3 million Cetus units/m^2/day for 5 days, followed by a 6-day break and a further 4.5 days of therapy), in intravenous continuous infusion [3, 4, 5].

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It must be considered, however, that important side-effects often determine reduction or discontinuation of rIL-2 administration. A major side-effect of rIL-2 therapy is the vascular leak syndrome (VLS), which is due to an increase of vascular permeability and is characterised by hypovolaemia, hypotension, oedema, increase of body weight and acute renal failure [6]. These side-effects are dose-dependent, disappear when rIL-2 treatment is discontinued and can sometimes be extremely severe and life-threatening; continuous patient monitoring or admission to intensive care units is often required.

This report describes a new approach for the achievement of complete control of renal toxicity through the use of low doses of dopamine (2 μg/kg/min).

Dopamine effects are mediated by at least three types of vascular receptors, including adrenergic and dopaminergic receptors, through various dose-related mechanisms [7]. At the dose employed, dopamine does not alter blood pressure, but acts as a renal vasodilator and increases renal blood flow [8, 9], which is often reduced during rIL-2 treatment [10, 11]. Early recovery of renal function can, therefore, be achieved, and dose-reduction of rIL-2 is avoided.

PATIENTS AND METHODS

Over the past 2 years, 2 patients with melanoma and 16 patients with metastatic renal cell carcinoma (all previously nephrectomised at the site of primary cancer), refractory to standard therapy, underwent rIL-2 immunotherapy at our institution (Table 1). All patients had a performance status 0–2 (ECOG criteria) and a life expectancy greater than 3 months. The sites of disease were lung and nodes in melanoma patients, while in patients with advanced renal cell carcinoma, metastatic disease was present in lung (10/16), bone (8/16), nodes (4/16) and liver (3/16); local recurrence was observed in 4/16. Patients not eligible for the use of vasopressor agents, or who presented central nervous system metastasis, or with other primary neoplasms, were not included in this study.

Recombinant IL-2 was administered over 2 consecutive weeks at the dose of 3 million Cetus units/m^2/day (18 million U/m^2/day) by continuous intravenous infusion for 5 days, followed by 2 days of rest and a further 5 days of therapy; after 3 weeks of rest, a second cycle of induction was administered. Haematological and serum biochemical parameters were evaluated daily during rIL-2 treatment. Vital signs, body weight, urine volume, urinary sodium/potassium ratio were also checked daily. Volume expanders (saline or albumin) intended to avoid haemodynamic instability, and paracetamol or indometacine to alleviate fever, chills and malaise were also administered.

In our series 16 patients had been previously nephrectomised and 6 also had moderately high pretherapy serum creatinine levels (1.2–1.6 mg%). These factors are known to characterise patients at high risk for renal toxicity induced by rIL-2, and are associated with severe changes in renal function and with a prolonged recovery [12]. Therefore, renal toxicity was carefully monitored, and in 9 patients, a continuous infusion of dopamine at the dose of 2 μg/kg/min was administered when at least one of these alterations could be detected: urinary sodium/potassium ratio inversion, urine output lower than 350 ml/day, increase of creatinine levels higher than 100% of baseline, increase of body weight higher than 5% of baseline.

Statistical analysis

Paired non-parametric test (Wilcoxon signed-rank test) was used to compare peak/nadir and postdopamine treatment data. The Wilcoxon two-sample test was used to compare differences in renal function recovery between high risk not treated or dopamine treated patients.

Table 1. Characteristics of patients with advanced cancer receiving rIL-2

Characteristics	Patients
Sex	
Males	12
Females	6
Age (years)	
Range	40–77
Mean	55.5
Cancer	
Renal carcinoma	16
Melanoma	2
Tumour sites	
Lung	10
Liver	3
Local recurrence	4
Bone	8
Nodes	4

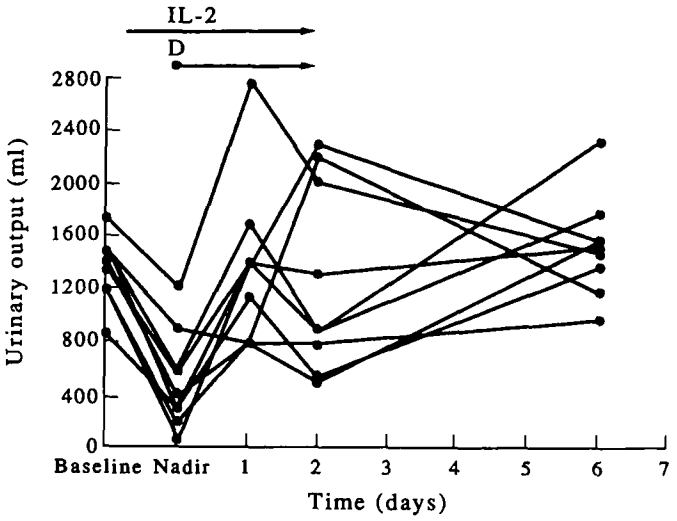

Fig. 1. Effects of 2 μg/kg/min dopamine (D) infusion on urinary output in rIL-2 treated patients.

RESULTS

In the 9 patients treated, urine volume returned to normal values after 24 h of continuous infusion of low-dose dopamine (Fig. 1), with a significative decrease of serum creatinine levels (Fig. 2) and body weight (Fig. 3), without discontinuing rIL-2 infusion ($P < 0.01$). In Table 2 we report median renal function data of the patients at the baseline, at the peak of rIL-2 toxicity and after 24 h of dopamine infusion.

In Table 3 we report the effects of dopamine infusion on renal function in different groups of patients, stratified for baseline serum creatinine levels: pretreatment levels of serum creatinine are predictive of different degrees of renal toxicity [12]. In our experience, a baseline serum creatinine level higher than 1.1 mg/dl characterises patients at "high risk" for renal toxicity by rIL-2. However, the mean recovery time of renal function in "high risk" patients treated with dopamine was significantly lower ($P < 0.05$) than in non-treated patients: 4.8 days against 10 days in non-treated patients. The mean recovery time in "low risk" patients,

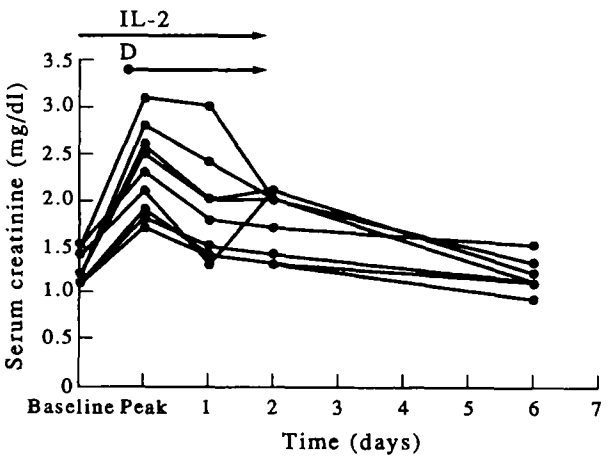

Fig. 2. Effects of 2 μg/kg/min dopamine (D) infusion on serum creatinine in rIL-2 treated patients.

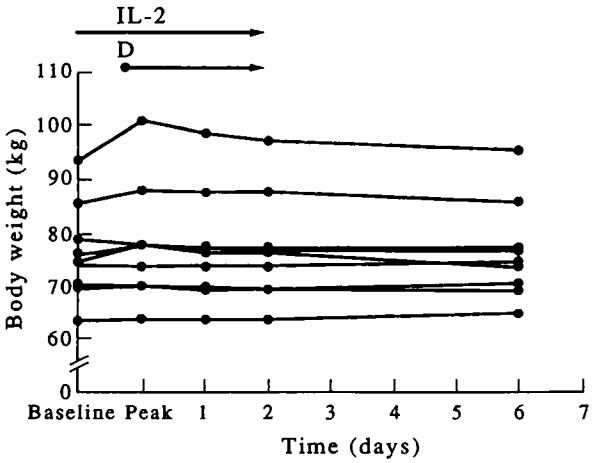

Fig. 3. Effects of 2 μg/kg/min dopamine (D) infusion on body weight in rIL-2 treated patients.

treated with dopamine, was 4.3 days. The mean recovery time of serum creatinine levels in all patients was 5.3 days.

DISCUSSION

It has been reported that renal toxicity is an important cause of interruption or dose reduction of rIL-2 [10, 11]. It is known that rIL-2 induces a direct renal toxic effect by decreasing prostaglandin synthesis, as shown by a reduction of urine prostaglandin E-2 (PGE-2) and 6-keto-PGF-1-alpha excretion [10].

The pathogenesis of acute renal failure during rIL-2 therapy can be attributed to several causes [6]. The hypovolaemia and the hypotension due to the VLS induce a reduction of renal blood flow (RBF), while the rIL-2 itself, by inhibiting renal prostaglandin synthesis, may weaken any possible compensatory mechanism available to the kidney. Moreover, vasoconstriction could promote sodium retention by the renal tubule, an effect also produced by the high levels of aldosterone which have been recorded during rIL-2 therapy [10, 11].

It has to be considered that, during rIL-2 therapy, many patients receive vasopressor agents, most often dopamine at the dose of 10–20 μg/kg/min or phenylephrine hydrochloride, for blood pressure support, and indometacine and other non-steroidal anti-inflammatory drugs (NSAFD) to control fever and chills [10]. It is well known that NSAFD and vasopressor agents induce toxic effects on renal function: NSAFD decrease PG synthesis [11, 13, 14], while vasopressor agents decrease RBF and could, therefore, increase renal toxicity by rIL-2 [10].

Table 2. Effects of low-dose dopamine on body weight, urinary output and serum creatinine in 9 cancer patients treated with rIL-2

Median values	Body weight (kg)	Urinary output (ml/day)	Serum creatinine (mg/dl)
Baseline	74.2	1450	1.2 (106.08)‡
Peak/nadir	77.3	350	2.3 (203.32)‡
24 h*	76†	1275†	1.75† (154.7) ‡

*Hours after beginning of dopamine infusion.
†$P < 0.01$ compared to peak/nadir values, at Wilcoxon's signed-rank test.
‡Values expressed as SI units.

Table 3. Effects of low dose dopamine infusion on serum creatinine levels and on renal function recovery in cancer patients treated with rIL-2

Patients	Number	Mean serum creatinine levels (mg/dl) Baseline	Peak	Mean renal function recovery (days)
"High risk" not treated with dopamine*	3	1.46 (129)‡	4.8 (424.32)‡	10†
"High risk" treated with dopamine*	6	1.3 (114.9)‡	2.6 (229.84)‡	4.8†
"Low risk" treated with dopamine*	3	1.1 (97.24)‡	1.8 (159.12)‡	4.3

*2 μg/kg/min.
†$P < 0.05$ for difference in renal function recovery between high risk not treated or dopamine treated patients, at Wilcoxon two-sample test.
‡Values expressed as SI units.

We have obtained early and complete control of renal toxicity induced by rIL-2, by administering low doses (2 μg/kg/min) of dopamine in continuous infusion, when the first signs of toxicity could be detected; mean recovery time of serum creatinine levels in all patients was 5.3 days. These results appear of interest if we consider that 16/18 patients have been previously nephrectomised and 6 of them also had high baseline serum creatinine levels (1.2–1.6 mg/dl). An elevated baseline serum creatinine level or a previous nephrectomy are very important risk factors for renal toxicity and prolonged recovery of basal renal function [12]. In the latter study, patients with high risk factors recovered in 20 days and 3 patients recovered in more than 30 days.

Dopamine acts with different and dose-related mechanisms through three types of vascular receptors: alpha-adrenoceptor, beta-adrenoceptor and a specific dopamine receptor [7, 15, 16]. Stimulation of the alpha-adrenoceptor with dopamine at "high doses" (> 10 μg/kg/min) generally leads to vasoconstriction; stimulation of the beta-adrenoceptor with dopamine at the dose of 2–10 μg/kg/min leads to increase of cardiac index, whereas stimulation of the specific dopamine receptor with dopamine at "low doses" (1–2 μg/kg/min) usually leads to renal vasodilatation [7]. Dopamine receptors have been found in mesenteric and renal vessels, that appear in fact very responsive to dopamine. Therefore, dopamine at "low doses" acts as a renal vasodilator and increases RBF and natriuresis [8, 9], operating on the intrarenal specific dopamine receptors, via prostacyclin (PGI-2) synthesis, as reflected by increased urinary excretion of its metabolite 6-keto-PGF-1-alpha [17]. Moreover, low-dose dopamine does not alter blood pressure, pulse or cardiac index [18, 19].

Recently, Mercatello *et al.* demonstrated that during IL-2 therapy, renal plasma flow remains constant and the reduction in glomerular filtration rate may be due either to a decrease in efferent to afferent arteriolar resistence ratio, leading to a decrease in glomerular capillary pressure, or to a decrease in ultrafiltration coefficient, or both [20, 21]. These authors suggest that a further reduction in renal vascular resistence with

dopamine might be inefficient and might cause additional damage to tubules and glomeruli and affirm that only potent vasoconstrictor agents might be useful in this clinical situation [22]. These observations contrast with our results: we have in fact demonstrated significant improvement of renal function during "low dose" dopamine infusion in acute renal failure induced by rIL-2.

In conclusion this is the first report which shows that the use of "low dose" dopamine by continuous infusion controls prerenal azotaemia, serum creatinine levels and oliguria in patients who are at high risk and finally develop major rIL-2 induced renal toxic effects and determines an early recovery of the rIL-2—impaired renal function. Administration of low-dose dopamine, therefore, can avoid dose reduction or discontinuation of rIL-2 administration, which could compromise the antitumour effect of rIL-2.

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Phase I Study of WR-2721 and Carboplatin

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Because WR-2721 reduces the toxicity of cisplatin and carboplatin in preclinical systems, we have treated 35 patients in a phase I study of WR-2721 and carboplatin. As the plasma half-life of WR-2721 is short relative to that of carboplatin, WR-2721 was administered in two divided doses. This schedule produced acceptable toxicity in 24 patients treated with carboplatin 400 mg/m² and escalating doses of WR-2721. In the subsequent 11 patients, WR-2721 was fixed at 740 mg/m²/dose and the dose of carboplatin was escalated. With WR-2721, grade 3–4 thrombopenia (platelets $<50 \times 10^9$/l) was produced in 4/5 patients treated with carboplatin 625 mg/m² and in 1/6 patients treated with carboplatin 500 mg/m². Carboplatin pharmacokinetic parameters in 4 patients were similar to those reported for carboplatin alone. These results suggest that WR-2721 might increase the maximum tolerated dose of carboplatin from 400 to 500 mg/m².
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INTRODUCTION

WR-2721 [S-2-(3-aminopropylamino) ethyl phosphorothioic acid, Ethiofos] is a sulfhydryl compound which selectively protects normal tissues from the cytotoxicity of radiation and alkylating agents in animal models [1]. The mechanism by which this selective protection occurs requires further study, but has been attributed to a differential metabolism of the agent by normal and neoplastic tissues [2]. WR-2721 is rapidly converted to the active species, WR-1065 and related disulphides, which are rapidly taken up into normal tissues [3, 4]. *In vitro* studies