Cancer Chemother Pharmacol (1989) 24: 135–136

Cancer Chemotherapy and Pharmacology

Short communication

Pharmacokinetics of cisplatin in patients receiving interleukin-2-containing treatment regimens*

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Summary. Plasma cisplatin pharmacokinetics were determined in 6 patients enrolled in a phase I trial of combined high-dose cisplatin and Interleukin-2 (IL-2) therapy. Cisplatin (100 mg/m^2) was given in 3% saline as a 3-h infusion on days 1 and 8 of each 28-day cycle; IL-2($2\text{-}4 \times 10^6$ units/m^2) was given as an i.v. bolus on days 15–19 in a dose escalation trial. Peak total and ultrafiltrate plasma platinum concentrations were 1.15 and 0.172 μg/ml for cycle 1 and 1.2 and 0.124 μg/ml for cycle 3, respectively. The AUCs for total and ultrafiltrate plasma platinum were 7.33 and 0.965 μg/ml per hour for cycle 1 and 8.48 and 0.924 μg/ml per hour for cycle 3, respectively. Total body clearances for total and ultrafiltrate platinum were 0.051 and 0.525 ml/h for cycle 1 and 0.042 and 0.443 ml/h for cycle 3, respectively. These data demonstrate no significant effects of IL-2 on the plasma pharmacokinetics of cisplatin in the dose schedule given and support the feasibility of this combined modality therapy.

Introduction

Recent reports synergistic cytotoxicity obtained in murine models by the combination of adoptive immunotherapy with standard chemotherapeutic agents have stimulated interest in exploring this approach in selected human tumors [8]. In particular, Papa et al. [8] have described markedly enhanced activity of the combination of interleukin-2 (IL-2) and the alkylating agent cyclophosphamide in both immunogenic and non-immunogenic tumors in mice. By comparison, cisplatin is an important chemotherapeutic agent with a broad range of antitumor activity, including that against tumor types unresponsive to standard alkylating agents, such as head and neck cancer and non-small-cell lung cancer.

The usual dose-limiting toxicity of cisplatin is renal insufficiency. Changes in platinum pharmacokinetics may result in increased toxicity due to either higher peak levels or the accumulation of toxic ultrafiltrate platinum species [2, 4]. IL-2 itself commonly results in a self-limited period of renal dysfunction, with a return to baseline within 2 weeks in the majority of patients treated [1]. To determine whether IL-2 alters the pharmacokinetics of cisplatin, we evaluated six patients enrolled in a phase I trial of combined cisplatin and IL-2 therapy, comparing the values obtained during cycle 1 (pre-IL-2) to those recorded during cycles 2 and 3 (post-IL-2).

Materials and methods

Plasma cisplatin pharmacokinetics were determined during three consecutive cycles of therapy in six patients enrolled in a phase I study of the combination of cisplatin/5-fluorouracil (5-FU) and IL-2. The treatment schedule consisted of 100 mg/m^2 cisplatin in 3% saline as a 3-h infusion on days 1 and 8; 1,000 mg/m^2 5-FU daily as a continuous infusion on days 1–5; and $2\text{-}4 \times 10^6$ units/m^2 IL-2 daily on days 15–19 of each 28-day cycle. Therefore, cisplatin levels for cycle 1 were pre-IL-2, and those for cycles 2 and 3 were post-IL-2 administration. Pre- and post-cisplatin hydration and laboratory monitoring were carried out as previously reported [4].

Plasma samples were collected at multiple time points (0, 15, and 30 min and 1, 2, and 4 h) after each 100 mg/m^2 dose of cisplatin. Plasma and plasma ultrafiltrates were prepared for platinum analysis and stored at −20° C as previously described [3]. Atomic absorption spectrometry was carried out on a Perkin Elmer Model 2280 atomic absorption spectrometer (Norwalk, Conn) equipped with an HGA 400 graphite furnace. The oven was programmed for the following steps: (1) drying, 40 s at 110° C; (2) charring, 45 s at 1,500° C; (3) cooling, 15 s at 20° C; (4) atomization, 5 s at 2,500° C; and (5) cleaning, 3 s at 2,650° C. Each sample (20 μl) was pipetted by hand into a pyrocoated graphite tube and run in triplicate. The spectrophotometer was set to measure absorbance at 265.9 nm and deuterium background correction was used. The spectrophotometer was calibrated daily with standard solutions of cisplatin, with a sensitivity of approximately 5 ng and a correlation of coefficients of >0.990; in addition, standards were periodically run to check within-day variations.

Results

Table 1 summarizes the pharmacokinetics of plasma platinum, including peak plasma platinum concentrations, AUCs, platinum clearance, and creatinine clearance values for three consecutive high-dose cisplatin cycles. Mean

* Supported in part by Cetus Corporation, Emeryville, California
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Table 1. Pharmacokinetic parameters of high-dose cisplatin with IL-2

	Peak platinum levels (μg/ml)[a]	AUC (μg/ml · h)	CL (ml/h)	Creatinine clearance (ml/min)[b]
Cycle 1				
Total	1.148 (0.091)	7.33 (0.733)	0.051 (0.008)	
UF	0.172 (0.172)	0.965 (0.619)	0.5255 (0.308)	82 (56–108)
Cycle 2				
Total	1.544 (0.218)	9.45 (1.75)	0.038 (0.009)	
UF	0.177 (0.072)	1.01 (0.462)	0.3925 (0.152)	
Cycle 3				
Total	1.197 (0.24)	8.48 (4.51)	0.042 (0.005)	
UF	0.124 (0.062)	0.924 (0.415)	0.4428 (0.175)	53 (35–67)

[a] SDs are noted in parentheses
[b] Ranges are noted in parentheses
UF, ultrafiltrate platinum

pretreatment serum creatinine and creatinine clearances were 1.05 mg/dl and 82 ml/min, respectively. Following cycle 3, mean serum creatinine and creatinine clearances were 1.57 mg/dl and 53 ml/min, respectively. Peak plasma platinum concentrations, AUCs, and total body clearances of total and ultrafiltrate platinum were not affected by the administration of IL-2 on this (days 1 and 8) cisplatin treatment schedule.

Discussion

IL-2, either alone or in combination with lymphokine-activated killer (LAK) cells, has recently been shown to have therapeutic benefit in the treatment of patients with several types of advanced metastatic cancer [7, 9]. In a murine model, Papa et al. [8] observed synergistic effects by combining IL-2 with cyclophosphamide. When IL-2 was combined with cyclophosphamide, the median survival of sarcoma-bearing mice increased for all doses of IL-2 tested, despite an apparent decrease in LAK cells generated in vivo. Although the mechanism of synergism remains unclear, it has been speculated to involve the reduction of tumor burden by the chemotherapeutic agent, an increase in the susceptibility of tumors to cellular immune lysis, and a possible decrease in suppressor cell activity by the chemotherapeutic agent. Clinical studies of IL-2, either alone or in combination with LAK cell therapy, have demonstrated changes in renal function consisting of azotemia, oliguria, and low fractional sodium excretion [1]; these effects were transient, with a return to baseline laboratory values in approximately 84% of patients within a 2-week period and in 95% of patients within 4 weeks.

Combinations of various chemotherapeutic agents and IL-2 are now being tested clinically. In malignant melanoma, a regimen of cyclophosphamide plus IL-2 has shown encouraging results, demonstrating the tolerability of this combination [6]. Since cisplatin is an important chemotherapeutic agent with a very broad range of clinical activity, a combination of cisplatin and IL-2 is logical for phase I trials. As the usual dose-limiting toxicity of cisplatin is renal insufficiency, and as other nephrotoxic agents have been reported to enhance this toxicity [5], we evaluated cisplatin pharmacokinetics in patients receiving a combination of the two agents. The results of the current study demonstrate no differences in plasma platinum pharmacokinetics pre- or post-IL-2 therapy. The serum creatinine and creatinine clearance values in these patients, although demonstrating a progressive decline, were not substantially different from those in patients treated with the (days 1 and 8) cisplatin treatment schedule alone [4]. At the dose and schedule of administration of cisplatin and IL-2 in this trial, these data support the feasibility of this combined modality therapy.

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Received October 6, 1988/Accepted November 29, 1988