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Phase I study of high-dose cisplatin, ifosfamide, and etoposide

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Abstract. To test the feasibility of a regimen of high-dose cisplatin, ifosfamide, and etoposide (VP-16; VIPP regimen), we registered 15 patients with advanced non-small-cell lung cancer in a phase I trial of the Northern California Oncology Group. One cycle of treatment consisted of high-dose cisplatin given at 100 mg/m^2 i.v. on days 1 and 8, VP-16 given at 60–75 mg/m^2 i.v. on days 1–3, plus ifosfamide given at 1.0–1.2 g/m^2 i.v. on days 1–3; cycles were repeated every 28 days. There were 13 men and 2 women; the median age was 59 years (range, 47–72 years). The median Karnofsky performance status (KPS) was 90 (range, 70–100). All patients were assessable for toxicity and response. The median number of cycles delivered per patient was two (range, one to four). Hematologic toxicity was dose-limiting and required de-escalation of the ifosfamide and VP-16 doses. Ten patients developed a white blood count of <1000/mm^3 and seven patients developed a platelet count of $<50{,}000$/mm^3. The duration of cytopenia increased progressively with each subsequent cycle of therapy. Two patients required antibiotics for neutropenic fever with documented infections (pneumonia, bacteremia). Seven patients received red blood cell transfusions for a hemoglobin level of <8 gm/dl. Grade III or IV non-hematologic toxicities were uncommon and involved one patient each with grade 3 ototoxicity and grade 3 neurotoxicity. Five patients developed laboratory evidence of renal salt wasting. The overall response rate was 33% (5/15) with a complete response being achieved by two patients (13%) and a partial response being attained by three (20%). The overall median survival was 44 weeks. We conclude that although this regimen demonstrated activity, hematologic toxicity limited its use in the palliative treatment of non-small-cell lung cancer. Using hemopoietic growth-factor support to permit dose escalation, this schedule of VIPP may be of interest in a number of different chemotherapy-sensitive tumor types.

Key words: Cisplatin – Ifosfamide – Phase I

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Introduction

Dose intensity is a potentially important concept in the chemotherapeutic approach to cancer. For example, in Hodgkins disease, non-Hodgkins lymphoma, and breast cancer, recent studies have suggested the importance of dose intensity in determining the therapeutic outcome [12, 16]. For cisplatin, one of the most important anticancer drugs currently available, in vitro studies have demonstrated steep dose-response relationships in a variety of tumor types [14, 20, 21, 22]. Although previous clinical trials with cisplatin have also suggested a positive dose-response effect, the optimal dose of cisplatin for the treatment of many malignancies remains undefined [6, 20], largely because cisplatin also has a steep dose-response relationship for toxicity. In particular, dose-limiting renal toxicity limited early attempts at cisplatin dose escalation. More recently, several strategies have been developed that demonstrate satisfactory nephroprotective effects, allowing dose escalation from a projected cisplatin dose intensity of 25 mg/m^2 per week to that of 50 mg/m^2 per week [6].

On the basis of pharmacokinetic findings, we developed a divided dose schedule, 100 mg/m^2 given on days 1 and 8 of a 28-day schedule, designed to deliver a high cisplatin dose intensity while avoiding the accumulation of potentially toxic plasma platinum species [7]. In clinical trials, this regimen has proved to be tolerable and active in a number of different tumor types [6, 8, 18].

This report describes a phase I trial of the Northern California Oncology Group (NCOG) evaluating high-dose cisplatin in combination with two other active chemotherapeutic agents, ifosfamide and etoposide (VP-16). This

combination regimen is based on the single-agent activity of each agent plus their relatively nonoverlapping toxicity patterns and the preclinical findings of synergism between cisplatin and the two other agents [11, 14]. The purpose of this study was to assess the feasibility and tolerability of this combination regimen and to determine the optimal dose of ifosfamide and VP-16 for this VIPP regimen.

Patients and methods

A total of 15 previously untreated patients with advanced-stage or recurrent non-small-cell lung cancer (NSCLC) were entered into this phase I NCOG pilot study from March 1989 to June 1990. Initial workup included a complete blood cell (CBC) count, chemistry panel, and chest and upper abdomen computed tomographic (CT) scan. The patients characteristics are described in Table 1. Five patients had undergone prior surgery and three had received radiotherapy before entering this trial. None had received prior chemotherapy. The protocol was approved by the Human Investigational Review Boards of the participating institutions. Written informed consent was obtained from all patients.

Study criteria. Histologic or cytologic diagnosis was made from bronchoscopic specimens or fine-needle aspirations in all patients. Stage was assigned according to the international system reported by Mountain (cited in [18]). Assessments of response and toxicity were made using standard cooperative group criteria.

Statistical analysis. Survival duration was measured from the 1st day of treatment until the day of death. Response duration was measured from the date of the first evidence of response until relapse.

Treatment schedule. This phase I trial was designed to determine the maximum tolerated dose of i.v. ifosfamide and VP-16 in this combination regimen. All patients were hospitalized for treatment and received i.v. antiemetics. The planned dose levels of chemotherapy were as follows: VP-16, from 75 mg/m^2 (level 0) to 100 mg/m^2 and then to 120 mg/m^2; ifosfamide, from 1.2 g/m^2 (level 0) to 1.5 g/m^2 and then to 1.8 g/m^2; the cisplatin dose was to remain constant at 100 mg/m^2 on days 1 and 8 of each 28-day cycle. The maximum tolerated dose (MTD) was defined as the dose level that is one dose level below that producing a WBC of $<1000/mm^3$ or a platelet nadir of $<25{,}000/mm^3$ and/or grade 3 or 4 nonhematologic toxicity in more than one-third of the patients treated at that dose level. Intrapatient dose escalations were not planned.

After the first two patients had been enrolled, the doses of both VP-16 and ifosfamide were de-escalated to level −1 due to severe myelosuppression and thrombocytopenia as per the protocol guidelines. Therefore, the planned dose escalations were not possible, and subsequent doses delivered were as follows: ifosfamide was given at a dose of 1.0–1.2 g/m^2 as a slow i.v. infusion over 30 min daily for 3 days, mesna was given at a dose of 1.8 g/m^2 divided into six doses per day (0.3 g/m^2 a 4 h) as a slow i.v. infusion on days 1–4, and VP-16 was given at a dose of 60–75 mg/m^2 in 500 cc normal saline over 2 h, on days 1–3. Cisplatin was given at a dose of 100 mg/m^2 each on days 1 and 8 of each 28-day cycle; it was reconstituted in 3% saline and infused in 250 ml 3% saline over 3 h along with a hydration program as previously described [8]. A maximum of four cycles of therapy per patient was planned.

Table 1. Patients characteristics at study entry

Number of patients registered		15
Age in years:	Mean	59
	Range	47–72
Sex:	F	2
	M	13
Karnofsky performance status:	70%–80%	6
	90%–100%	9
Histology:	Squamous-cell carcinoma	4
	Adenocarcinoma	5
	Large-cell carcinoma	6
Stage:	III (recurrent)	5
	IV	10
Prior surgery:	Yes	5
	No	10
Prior RT to measurable tumor site:	Yes	3
	No	12
Dose level at study entry:	Level 0 Ifosfamide 1.2 g/m^2 VP-16 75 mg/m^2	2
	Level −1 Ifosfamide 1.0 g/m^2 VP-16 60 mg/m^2	13

Results

All 15 patients were assessable for toxicity and survival. As defined by the MTD procedure for ifosfamide and VP-16 doses, after grade IV leukopenia (WBC, $<1000/mm^3$) had developed in the first two patients treated during the first cycle of therapy, the doses of ifosfamide and VP-16 were decreased to 1.0 g/m^2 given i.v. on days 1–3 and 60 mg/m^2 given i.v. on days 1–3 (dose level −1), respectively, whereas the cisplatin dose was maintained at 100 mg/m^2 given i.v. on days 1 and 8. The median number of cycles delivered was two (range, one to four). Six of the 15 patients received more than 2 cycles of therapy.

Toxicity data

The hematologic and nonhematologic toxicities encountered are described in Tables 2 and 3, respectively. Hematologic toxicity was significant and dose-limiting. Leukopenia (WBC, $<1{,}000/mm^3$) occurred in 33% (5/15) of the patients, in two cases at dose level 0 and in three cases at dose level −1; anemia (hemoglobin <8.0 gm/dl) occurred in 54% (8/15) of the patients, in two cases at dose level 0 and in five cases at dose level −1; and grade IV thrombocytopenia (platelets, $<25{,}000/mm^3$) was noted in 27% (4/15) of the patients, in two cases at dose level 0 and in two cases at dose level −1. Only one of the patients had a platelet count of $<20{,}000/mm^3$, which promptly responded to one platelet transfusion. In addition, platelets counts of $<49{,}000/mm^3$ but $>25{,}000/mm^3$ were observed in three patients at dose level −1. The median time to nadir WBC and platelet counts did not change with subsequent cycles (median of 13 days for each). However, the median WBC recovery time (WBC, $>3500/mm^3$) and platelet recovery time ($>100{,}000/mm^3$) increased progressively as subsequent cycles were delivered. The WBC recovery time was 7, 7.5, 14, and 29 days for cycles 1, 2, 3, and 4, respectively. The platelet recovery time was 0, 4.5, 14, and 13.5 days for cycles 1, 2, 3, and 4, respectively. Seven patients received red blood cell (RBC) transfusions.

The nonhematologic toxicities were not severe (Table 3), but 5 of 15 patients (33%) developed renal salt wasting

Table 2. Most severe hematologic toxicities noted

Toxicity		Grade	Total (n = 15)
WBC ($\times 10^3$/mm^3):	3.0–3.9	1	1
	2.0–2.9	2	2
	1.0–1.9	3	5
	<1.0	4	5[a, a]
Platelets ($\times 10^3$/mm^3):	75.0–130	1	1
	50.0–74.9	2	3
	25.0–49.9	3	3
	<25.0	4	4[a, a]
Infection		1	1
		2	1
		3	0
		4	0
Hemorrhage		1	0
		2	1
		3	0
		4	0
Hemoglobin (mg/dl):	M 10–14; F 10–12	1	2
	8.0–10.0	2	5
	6.5–7.9	3	7[a]
	<6.5	4	1[a]

[a] Patient receiving VIPP at dose level 0

Table 3. Most severe nonhematologic toxicities noted

Toxicity		Grade	Total (n = 15)
GI: nausea and vomiting		1	5
		2	5
		3	1[a]
		4	1[a]
Neuro: peripheral neuropathy		1	0
		2	2
		3	1
		4	0
Ototoxicity		1	2
		2	0
		3	1[a]
		4	0
Fever (no infection)		1	1
		2	2
		3	0
		4	0
Creatinine clearance (ml/min):	50–80	1	3
	20–49	2	6[a]
	<20	3	0
		4	0
Hematuria		1	1
		2	0
		3	0
		4	0
Renal salt wasting			5[a]

GI, Gastrointestinal; Neuro, neurotoxicity
[a] Patients receiving VIPP at dose level 0

as previously described [4]. Two patients (who had received dose level 0) required antibiotics for neutropenic fever. There were no drug-related deaths.

Table 4. Overall response status

Detailed overall response	Evaluable patients
Complete response	1
Equivocal complete response	1
Partial response >50%	3
Partial response <50%	1
Mixed response	1
Stable disease	3
Disease progression	5
Overall response rate	**Rate**
Complete response rate (CR + equivalent CR/number evaluable	2/15 (13%)
Partial response rate (PR >50%/number evaluable)	3/15 (20%)
Overall objective response (CR + equivalent CR + PR >50%/number evaluable)	5/15 (33%)

Response and survival data

Table 4 demonstrates that a complete response was documented in 2/15 (15%) patients and a partial response, in 3/15 (20%) patients, for an overall response rate of 33%. The median time to progression was 23 weeks. The median survival was 44 weeks (10.7 months) and all patients enrolled are now deceased. Six patients survived for longer than 1 year after study entry, and the longest-term survivor died at 1.9 years after study entry.

Discussion

The importance of drug dose for the response to cancer chemotherapy is intuitive and continues to be extensively studied [6, 9, 12, 21]. The concept of dose intensity emphasizes the dose per unit time of drug delivery. For combination chemotherapy regimens, the clinical outcome depends on the complex interaction between each drug dose per unit time, drug disposition, the resulting toxicity profile, and inherent tumor-cell sensitivity.

Previous studies evaluating a day-1 and -8 high-dose cisplatin regimen demonstrated its feasibility, without evidence of severe myelosuppression or neuropathy, and activity in NSCLC, melanoma, and other tumor types [6, 8, 18]. To explore further the dose potential of cisplatin, we designed a combination regimen with the agents ifosfamide and VP-16, taking into consideration their single agent activity, mechanism of action, toxicity profile, and resistance patterns [1–5, 15, 16, 25, 26]. In addition, synergistic in vitro activity between cisplatin and these two agents has been reported.

Although relatively nonoverlapping toxicity for this combination was anticipated, the degree of hematologic toxicity observed with this VIPP regimen precluded the planned dose escalation. Other investigators have reported a variety of VP-16, ifosfamide, and cisplatin combinations [10, 17, 19, 24], but none of these studies incorporated a day-1 and -8 regimen of high-dose cisplatin administration.

Loehrer et al. [17] evaluated the efficacy and toxicity of a VP-16/ifosfamide/cisplatin (VIP) or a vinblastine/

ifosfamide/cisplatin (VeIP) regimen in patients with recurrent germ-cell tumors. The doses were etoposide given at 75 mg/m^2 per day, ifosfamide given at 1.2 gm per day, and cisplatin 20 mg/m^2 per day for 5 days for the VIP regimen, and (substituting for VP-16) vinblastine given at 0.11 mg/kg on days 1 and 2 for the VeIP regimen. Thus, the cumulative doses of VP-16, ifosfamide, and cisplatin delivered per treatment cycle were 450 mg/m^2, 6 g/m^2, and 100 mg/m^2, respectively. Treatment courses were repeated at 21-day intervals. In spite of the overall activity of this regimen, hematologic toxicity was severe, with the median leukocyte nadir being 1.3×10^6/l and the median platelet count nadir being 28×10^9/l. In that study, 22/56 patients (39%) developed granulocytopenic fever, including 6 (11%) who developed sepsis.

In a study by Ghosn et al. [10], 21 patients with refractory germ-cell tumors were treated with VP-16 at 75 mg/m^2 per day (days 1–5), ifosfamide at 3 g/m^2 per day (days 1 and 2), and high-dose cisplatin at 40 mg/m^2 per day (days 1–5). The cumulative doses of the three agents per cycle were 450 mg/m^2, 6 g/m^2, and 200 mg/m^2, respectively. Severe myelosuppression was observed with approximately 50% of the patients developing a leukocyte nadir of $< 0.5 \times 10^6$/l and a platelet count of $< 20 \times 10^9$/l. Six patients (28%) developed documented sepsis.

In a study by Shirinian et al. [24], the cumulative doses per cycle of VP-16, ifosfamide, and cisplatin were 240 mg/m^2, 5.4 g/m^2, and 60 mg/m^2, respectively. Significant myelosuppression was also observed, with 65% of 20 evaluable patients having a WBC of $< 0.5 \times 10^6$/l following the first cycle of chemotherapy.

In our phase I trial, nonhematologic toxicity was mild at the doses tested, but laboratory evidence of renal salt wasting was documented in 5/15 patients. This incidence (33%) was higher than that previously reported in patients receiving cisplatin [8, 13]. This finding may reflect our careful monitoring of toxicity; however, an alternative explanation may be synergistic renal damage from ifosfamide and cisplatin. We did not observe any of the other renal, cardiac, or neurologic side effects previously associated with ifosfamide therapy [20, 23].

In conclusion, although this regimen demonstrated antitumor activity in patients with advanced NSCLC, myelosuppression prevented the dose escalation planned for ifosfamide and VP-16. The use of hematopoietic growth factors may allow further exploration of this dose-intensive combination regimen in chemotherapy-sensitive tumor types.

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