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ORIGINAL ARTICLE

Marc Trudeau · Alex Zukiwski · Adrian Langleben
Gerald Boos · Gerald Batist

A phase I study of recombinant human interferon alpha-2b combined with 5-fluorouracil and cisplatin in patients with advanced cancer

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Abstract To determine the maximum tolerated dose (MTD) of escalating doses of interferon-α-2b (IFN, Intron A) with 5-fluorouracil (5-FU) and cisplatin (DDP) in patients with advanced cancer, 15 patients were accrued between May 1990 and July 1991. Primary sites were unknown (3), colorectal (3), head and neck (2), lung (2), gynecologic (1), gallbladder (1), sarcoma (1), anal canal (1) and pancreas (1). IFN was given s.c. on days 1–5 and then three times weekly with DDP (75 mg/m^2, day 1) and 5-FU [750 mg/m^2, days 1–5, continuous infusion (CI) on a 28-day cycle. The first two patients treated at level I (3×10^6 U/m^2 s.c.) experienced possible neurotoxic deaths [massive cerebrovascular accident (CVA) and metabolic encephalopathy], and patient 3 had a grade 4 toxicity of performance status decline. Analysis of these events led us to exclude the enrollment of patients on i.v. morphine and of those with prior exposure to DDP. This resulted in grade 3 toxicity in terms of nausea, vomiting, fatigue and leukopenia but in no further CNS event. All patients were evaluable for toxicity but only ten were evaluable for response. Only two partial responses were seen, one in a patient with an unknown primary tumour and one in a patient with head and neck cancer. The combination of IFN is possible with 5-FU and DDP. The recommended dose of IFN is 2×10^6 U/m^2 s.c. in patients with no prior exposure to DDP or i.v. morphine, given together with 5-FU (750 mg/m^2, days 1–5, CI) and DDP (75 mg/m^2, day 1) on a 28-day cycle.

Key words Cisplatin · 5-Fluorouracil · Interferon

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M. Trudeau · A. Zukiwski[1] · A. Langleben · G. Boos · G. Batist
Section of Experimental Therapeutics, Department of Oncology, McGill University, Montreal, Canada

M. Trudeau (✉)
Montreal General Hospital, 1650 Cedar Avenue, Room D5-515, Montreal, Quebec, Canada H3G 1A4

Present address:
[1] M.D. Anderson Cancer Center, Houston, Texas, USA

Introduction

Interferon (IFN) was characterized in 1957 as a protein elaborated by virus-infected cells that functioned to prevent secondary viral infection [1]. It is now evident that IFN has direct and indirect cytotoxic, cytostatic and immune effects. Response to treatment with IFN has been observed in hairy-cell leukemia, lymphoma, melanoma, Kaposi's sarcoma, renal-cell carcinoma, myeloma and chronic myelogenous leukemia [2].

5-Fluorouracil (5-FU) is a structural analogue of the pyrimidines uracil and thymidine that has a fluorine atom substituted in the 5 position and modulates the enzyme thymidylate synthetase, which in turn blocks the synthesis of DNA. 5-FU, has been used successfully in the treatment of gastrointestinal malignancies, carcinoma of the aerodigestive tract, and breast and bladder cancer.

Several laboratories have shown an in vitro synergistic interaction of IFN and 5-FU [3–5]. The report of earlier phase I trial of the combination of 5-FU and IFN in colon carcinoma has been published [6]. A recent phase II trial of this combination has been reported with very encouraging results [7]. The mechanism of the synergistic interaction of 5-FU and IFN remains unclear. However, evidence indicates that the possible mechanism is an increase in thymidylate synthetase inhibition [8].

Cisplatin (DDP) is an inorganic complex of platinum surrounded by chlorine and ammonia atoms in the *cis* position of the horizontal plane. DDP inhibits DNA synthesis by causing inter- and intra-strand cross-linking. The major clinical indication for DDP use has

included testicular, ovary, bladder, lung, and aerodigestive tract malignancies.

The combination of IFN and DDP has demonstrated synergistic cytotoxicity in a number of pre-clinical systems [9, 10]. A phase I study of IFN with dose escalation of DDP has been reported [11]. The maximum tolerated dose was determined to be IFN, 5 million units/m^2 given s.c. three times weekly; and DDP, 25 mg/m^2 given weekly.

The combination of 5-FU and DDP has also demonstrated synergistic effect when tested in vitro [12]. Also, clinical studies have demonstrated the synergistic interaction of DDP and 5-FU. The most encouraging results have been observed in using the combination for the treatment of tumours of the upper aerodigestive tract, where the frequency of responders has been reported to be in the 60%–80% range [13–17]. The combination has also been utilized in non-small-cell lung carcinoma [18], colorectal carcinoma [19] and breast cancer [20].

Therefore, the combination of the three agents 5-FU, DDP and IFN may lead to a greater therapeutic effect if there is an increase in the response rate, including the complete response rate and the median duration of response, that when the agents are used alone or in the combination described above.

The objective of this study was to determine the maximum tolerated dose (MTD) of the combination of 5-FU, DDP and IFN; to determine the qualitative and quantitative toxicity and the reversibility of toxicity of this combination; and to document any observed antitumour activity.

Patients and methods

Patients

Patients must have fulfilled all the following criteria to be eligible for this study:

1. A primary diagnosis of histologically proven cancer for which standard therapy is not of proven benefit or for which the established standard therapy has proved unsuccessful in that patient
2. An age of 18 years or more and an ambulatory performance status of above 60% on the Karnofsky scale (KS).
3. Normal cardiac function, preserved hepatic and renal functions and normal blood counts.
4. A minimal life expectancy of 3 months was required as well as the ability to understand and sign a written informed consent form.

Patients were excluded if they had prior treatment with IFN, brain metastases or a known seizure disorder. Treatment with chemotherapy (6 weeks in the case of mitomycin C or the nitrosourea), immunotherapy or radiotherapy at less than 3 weeks prior to entry was not acceptable, nor was ongoing treatment with corticosteroids.

Patients needed to have evaluable disease, but not necessarily measurable disease. Patients were assessed for toxicity every 4 weeks before the next cycle of chemotherapy. The National Cancer Institute toxicity criteria [21] were used, and assessment of response was performed following every two cycles of chemotherapy. Responses were defined as complete (CR) if there was complete disappearance of measurable disease for 4 weeks, as partial (PR) if a decrease of 50% or more in the size of the tumor was observed for 4 weeks and as no response (NR) if no impact of the chemotherapy was found.

This protocol was approved by the Institutional Review Board as well as by the Clinical Trial Committee of the McGill Cancer Center before treatment began.

Treatment plan

Each patient received a fixed dose of the combination of 5-FU, DDP and IFN. No dose escalation was allowed within individual subjects. DDP was infused i.v. over 2 h on day 1 of each cycle, after which 5-FU was given by continuous infusion (CI) over 24 for 5 consecutive days. Intron A (recombinant human IFN-α-2b, rh-IFN-α-2b; Schering Canada) was given s.c. daily after 5-FU and DDP on days 1–5 and then continued three times weekly (days 8, 10, 12, 15, 17, 19, 22, 24 and 26). Therapy was given on a 28-day cycle. The dose-escalation schema is shown in Table 1.

The rationale for the dose and dose schedule used for the single agents and the combination mimics pre-clinical models. These models showed synergy for concurrent exposure to IFN and DDP during the week of chemotherapy since DDP is protein-bound. Thereafter, chronic exposure to IFN is done to avoid tolerance. Treatment cycles were continued until disease progression or unacceptable toxicity occurred. Only patients receiving two or more cycles of chemotherapy were eligible for response analysis.

Three patients were entered on each dose level. For grade 1 or 2 toxicity, the patient was allowed to continue treatment. For any grade 3 toxicity that was felt to be related to 5-FU, DDP or IFN, the treatment was held until recovery from this toxicity. Then the dose of either 5-FU, DDP or IFN was to be reduced by 25% for the next cycle such that the patient could continue on the treatment program. For any grade 4 toxicity, the patient was removed from the study.

If two instances of grade 3 or 4 toxicity were observed during the course of treatment on the same dose level, a total of six patients would be placed on that dose level. If three or more instances of grade 3 or 4 toxicity were observed during the course of treatment on the same dose level, accrual into the trial at that dose level would be terminated and the next lower level would be declared the MTD. The MTD was defined as the highest dose producing toxicity that was not greater than or equal to grade 3 in more than two patients.

Results

Patients' characteristics

A total of 15 patients, including 9 women and 6 men, were accrued between May 1990 and July 1991 (Table 2); 8 patients had received prior chemotherapy. The age ranged from 22 to 76 years (median, 58 years). Primary cancers were: unknown, 3; colorectal, 3; head and neck, 2;

Table 1 Dose–escalation schema

Dose level	5-FU CI, days 1–5 (mg/m^2)	Cisplatin bolus, day 1 (mg/m^2)	rh-IFN-alpha-2b, days 1–5, followed by 3 x weekly (U/m^2)	Number of patients
-I	750	75	2.0×10^6	6
I	750	75	3.0×10^6	9

Table 2 Patients characteristics

Patients accrued	15
M	6
F	9
Age (years):	
Range	22–76
Median	58
Previous therapy ($n = 8$ patients):	
Radiotherapy	1
Chemotherapy	5
Chemotherapy/radiotherapy	3
Primary cancer:	
Unknown Primary	3
Colorectal	3
Head and neck	2
Lung	2
Gynecologic	1
Gallbladder	1
Sarcoma	1
Anal canal	1
Pancreas	1

lung, 2; gynecologic, 1; gallbladder, 1; sarcoma, 1; anal canal, 1; and pancreas, 1. All 15 patients were evaluable for toxicity, but only 10 were evaluable for response since 5 did not complete 2 cycles of chemotherapy.

Toxicity

The trials started on level I, which is IFN given at 3 million units/m^2 (Table 3). On that level, the first two patients experienced probable neurotoxic deaths. The first patient, who had a cancer of unknown origin, experienced tonic-clonic generalized seizures on day 8 of cycle 2 and did not recover. This was attributed to metabolic encephalopathy secondary to her disease and was exascerbated by the treatment, since computed tomography (CT) scans of the brain and electroencephalography (EEG) showed non-specific abnormalities. The second patient had non-small-cell lung carcinoma of stage IV. He suffered a massive cerebrovascular accident (CVA) on day 3 of cycle 1 and died. The third patient treated on level I had a grade 3 toxicity in terms of performance status (it declined from KS 1 to KS 4) after 1 cycle. Indeed, a weight loss of 35 lbs. in 1 month and severe anorexia leading to dehydration prompted the patient's admission for i.v. support.

On the basis of these events, accrual into the study was temporarily halted. We decided to re-open accrual that excluded the enrollment of patients on i.v. morphine, which was the case for the first two patients, and to exclude patients with prior exposure to DDP, which was the case in the third patient.

The study was restarted at level -I and six new patients were enrolled. This resulted in grade 3 toxicity

Table 3 Toxicities encountered at dose level I—IFN: 3×10^6 U/m^2

Toxicity	Grade				
	1	2	3	4	5
Nausea	2	5	0	0	0
Vomiting	2	5	0	0	0
Mucositis	1	2	2	0	0
Diarrhea	0	3	1	0	0
Fever/chills	2	3	4	0	0
Fatigue/malaise	1	1	1	0	0
Leukopenia	2	1	2	0	0
Anemia	3	1	1	1	0
Thrombocytopenia	0	0	1	0	0
CNS	0	0	0	0	2[a]
Decline in PS	0	0	0	1	0
Hematuria	2	0	0	0	0
Skin rash	3	0	0	0	0
Proteinuria	3	0	0	0	0

[a] Probable neurotoxic deaths (see Results)

Table 4 Toxicities encountered at dose level -I—IFN: 2×10^6 U/m^2

Toxicity	Grade			
	1	2	3	4
Fever	0	4	0	0
Nausea	0	4	1	0
Vomiting	0	3	2	0
Mucositis	2	3	0	0
Diarrhea	1	1	0	0
Fatigue/malaise	2	0	2	0
Leukopenia/neutropenia	1	0	3	1
Anemia	1	2	1	0
Thrombocytopenia	1	0	1	0
Skin rash	1	0	0	0
Proteinuira	1	0	0	0

in terms of nausea and vomiting, fatigue and leukopenia (in less than 50% of patients) but in no further CNS event. Escalation back to level I resulted in grade 3 and 4 myelosuppression, even in patients previously untreated with chemotherapy. Because four of five patients experienced such toxicity, the study was closed and this level was declared the MTD.

Tables 3 and 4 show the greatest toxicity experienced by each patient on the study in the first two cycles only. Patients may have had more than one grade 3 or 4 toxic episode during their entire treatment on the study. The common symptoms of fatigue, fever and chills from IFN are almost universally found (even if patients are premedicated with acetaminophen), as are nausea and vomiting from DDP (ondansetron was not available at the time) and mucositis and myelosuppression from 5-FU, as felt by the investigators. Episodes of dose modification or delay of treatment because of grade 3 or 4 toxicity happened once for 5-FU and 11 times for IFN. Nine patients were enrolled on level I and six patients on level -I.

Outcome

Because of the toxicity encountered on level I, the MTD of IFN given in this manner was found to be 2 million units/m^2. Responses were seen in two patients. The first patient was a 56-year-old woman with liver metastases form an adenocarcinoma of unknown origin. She had received no previous chemotherapy and had a partial response after six cycles of chemotherapy on level -I that lasted for 6 months. The second patient was a 60-year-old man who had laryngeal cancer and pulmonary metastases that had been treated previously with 5-FU and DDP. He was the third patient treated on dose level I before it was halted temporarily. This patient had a partial response of 2 months' duration after one cycle and declined further treatment after experiencing severe toxicity in terms of performance status.

Discussion

5-FU, DDP and IFN-alpha are chemotherapy agents active against a variety of solid tumours. Since synergy exists amongst most of them, the combination of these three agents may lead to greater therapeutic efficacy. This possibility led to the present phase I dose- escalation study to determine the MTD of this combination. This study shows that this combination chemotherapy is reasonably well tolerated at lower doses, but it appears to be quite toxic at IFN dose levels that are generally considered moderate (dose level I). The usual major toxicities consisting of fever, chills, nausea, vomiting, fatigue and myelosuppression were all found in this trial and could be related to each of the agents 5-FU, DDP or IFN. IFN was the drug whose dose was most frequently modified, and its administration was delayed eight times at dose level I and three times at dose level -I because of unacceptable toxicity. On the other hand, 5-FU and DDP could be delivered at close to 100% of the scheduled dose on each occasion.

In our study, there were two patients who responded to chemotherapy: one had a cancer of unknown origin and the other had cancer of the head and neck. Indeed, in one phase I–II study [22] using the same-combination in head and neck cancers, the MTD was DDP, 105 mg/m^2; 5-FU, 700 mg/m^2 (CI, days 1–5); and IFN, 3×10^6 U/m^2 (s.c., days 1–5); the response rate was 30%. Mucositis and neutropenia were the limiting toxicities. In another phase I trial in head and neck cancer [23], the MTD was DDP, 100 mg/m^2 (day 1); 5-FU, 800–1000 mg/m^2 (CI, days 1–4); and IFN, 3×10^6 U (flat dose, days 1–5). The response rate was 33%. It is possible that these two studies [22, 23] have a higher MTD than our phase I trial because IFN was given only on days 1–5 of the cycle. Other investigators have attempted to increase this combination's activity in head and neck cancer by adding leucovorin [24].

In conclusion, the combination of IFN, 5-FU, and DDP is possible but results in toxicity. It is advisable to avoid treating patients with this combination if they have had prior exposure to DDP or if they are on i.v. morphine. The recommended dose for phase II study is 5-FU, 750 mg/m^2 given on days 1–5 as a CI; DDP, 75 mg/m^2 given on day 1; and IFN, 2 million units/m^2 given on days 1–5 of the first week of chemotherapy and on days 1, 3, and 5 of each week thereafter on a 28-day cycle.

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