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Escalating doses of interferon alpha-2A with cisplatin and concomitant radiotherapy: a phase I study

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Abstract. In this phase I study, we added escalating doses of interferon-alpha2A (IFN) to cisplatin and twice-daily radiotherapy based on the following rationale. Radiation enhancement has been shown for both interferon and cisplatin; in addition, potentiation of the cytotoxic activity of cisplatin by interferon has been demonstrated. A total of 48 patients with advanced solid tumors were treated with radiotherapy in 2 daily fractions of 125 cGy plus cisplatin at 8 – 10 mg/m^2 per day delivered on 3 different schedules (continuous infusion, daily short-term infusion, and single short-term infusion of 50 mg/m^2). IFN was injected s.c. 2 h preceding the first daily fraction of radiation. IFN doses ranged from 0 to 5.0×10^6 U/m^2 per day. All therapy was given over 5 days of every other week until completion of the radiotherapy. Treatment at all dose levels was well tolerated during cycles 1 and 2, with no instance of acute grade 3 or 4 toxicity being noted. However, cumulative myelosuppression in patients receiving more than two treatment cycles was seen at all dose levels and was attributed to the repeated administration of cisplatin. Alteration of the cisplatin schedule did not allow for further dose escalation of cisplatin. Our recommended doses are cisplatin given at 8 mg/m^2 per day as a continuous infusion with IFN at 5.0×10^6 U/m^2 per day. Among 24 patients with non-small-cell lung cancer, 2 had a complete response, 9 had a partial response, and 7 had stable disease. We conclude that this concomitant cisplatin-IFN-radiotherapy regimen is feasible. Activity was seen in non-small-cell lung cancer, and further studies of this regimen in that disease appear indicated.

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Introduction

For many patients with locoregionally advanced solid tumors, current standard therapy consists of surgery and/or radiotherapy. To increase locoregional and distant control rates and, thus, improve survival, the use of concomitant chemoradiotherapy is increasingly under clinical investigation [12, 41, 43, 45, 46]. Randomized studies comparing standard radiotherapy with concomitant chemoradiotherapy have demonstrated improved disease-free and/or overall survival in a number of solid tumor types, including carcinoma of the cervix [20], esophagus [15], lung [35], and head and neck [11, 28, 31, 47, 51].

A number of cytotoxic drugs have been used in this setting, including cisplatin, carboplatin, bleomycin, mitomycin C, and the antimetabolites 5-fluorouracil (5-FU) and hydroxyurea [12, 41, 43, 45, 46]. Cisplatin, in particular, has been frequently investigated. This interest in cisplatin is due to its known activity as a single agent in many solid tumors and its radiation-enhancing potential. Radiation enhancement by cisplatin has been postulated to occur through inhibition of repair of sublethal radiation damage and the killing of hypoxic cells by cisplatin that are less responsive to radiation [2, 21, 22, 27, 36, 39, 40, 52]. Although no clear schedule of administration has been demonstrated to result in maximal single-agent activity, it has been suggested that cisplatin may be more active when given as a continuous i.v. infusion [44]. Regarding its interaction with radiation, animal studies suggest that its administration in divided daily doses prior to radiotherapy may allow for maximal radiation enhancement as compared with large single doses [21, 22, 27, 39].

More recently, biological response modifiers, including interferon, have been investigated as radiation enhancers [8]. In vitro radiosensitization by interferon has been reported for several cell lines, including non-small-cell and small-cell lung cancer cells [10, 13, 18, 23, 25, 29, 32]. The exact mechanisms by which radiosensitization with interferon occurs remain to be established. Chang and Keng [6] demonstrated increased blockage of hypernephroma cells at the G_2-M junction of the cell cycle 24 h after interferon

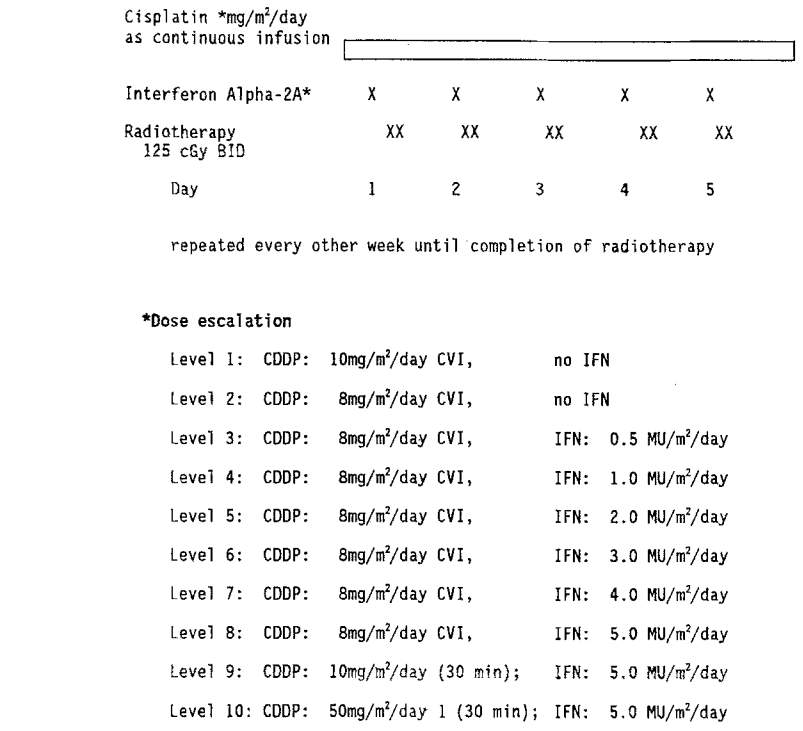

Fig. 1. Regimen. (Levels 1–8). The daily dose of IFN preceded the first daily fraction of radiotherapy by 2 h. The IFN dose was escalated after 3–6 patients had been observed for at least 2 cycles of therapy at a given dose level. When grade 3 toxicity was observed in 1 of 3 patients, a total of 6 patients were treated at that dose level. *CVI*, continuous i.v. infusion; *CDDP*, cisplatin; IFN, interferon alpha-2A

treatment; cells in that phase of the cell cycle have been shown to be more radiation-sensitive.

Recent attention has also focused on the use of interferon in combination with cytotoxic drugs [50]. In particular, its interaction with 5-FU has been studied [49]. Preclinical data also support the combined use of interferon with cisplatin. Carmichael et al. [5] applied weekly doses of cisplatin with human lymphoblastoid interferon to three human non-small-cell cancer xenografts and found a significant potentiation of the cytotoxic activity of cisplatin. Sklarin et al. [37] also observed increased cytotoxicity after adding interferon to cisplatin in a malignant mesothelioma xenograft. In addition, some clinical studies have suggested increased activity when cisplatin is combined with interferon [1, 4, 33, 34].

On the basis of these data, we designed a phase I study testing the concomitant administration of continuous-infusion cisplatin with escalating daily doses of interferon alpha-2A (IFN) and twice-daily radiotherapy in a cohort of patients undergoing palliative radiotherapy. The twice-daily radiotherapy schedule was chosen because of the increased antitumor activity suggested in randomized clinical studies [19]. A protracted chemoradiotherapy schedule involving administration of this therapy every other week was chosen to allow for recovery from toxicities following each cycle of therapy and for the subsequent integration of this regimen with other chemoradiotherapy combinations in a curative-intent treatment setting.

Patients and methods

All patients entered on this study were treated at two participating institutions (University of Chicago Hospitals and Michael Reese Hospital). The objectives of this study were to define the maximal tolerated dose (MTD) of daily IFN given s.c. with continuous-infusion cisplatin and concomitant hyperfractionated radiotherapy every other week and to define the pattern of toxicities observed.

Patient eligibility. Patient eligibility was determined by a team composed of a radiation oncologist and a medical oncologist. Histologic or cytologic documentation of neoplastic disease and predominance of disease in a site amenable to palliative-intent radiotherapy was also required. Measurable disease was carefully recorded prior to the initiation of protocol therapy but was not an absolute requirement. Additional eligibility criteria included a patient performance status of 0 – 2 (Cancer and Leukemia Group B), a platelet count of $\geq 100{,}000/\mu l$, and an initial 24-h creatinine clearance of ≥ 50 ml/min. There was no limitation on prior radiation therapy or chemotherapy. Patients who had received prior therapy with interferon and patients with brain metastases were ineligible for this study. Written informed consent was obtained from all patients prior to the initiation of protocol therapy.

Treatment schema. Patients were hydrated i.v. with 500 ml normal saline (NS) over 3 h prior to the initiation of chemotherapy (Fig. 1). A continuous i.v. infusion of cisplatin was begun on the evening prior to day 1 (usually Sunday) at 10 mg/m^2 per day for 5 consecutive days. One-half of the daily dose was given in 1000 cc of D_5NS over 12 h for a total of ten doses. IFN was given s.c. on days 1 – 5 preceding the first daily fraction of radiotherapy by 2 h. Radiotherapy was delivered in two daily fractions of 125 cGy separated by at least 6 h on days 1 – 5 (Monday through Friday). Following completion of the cisplatin infusion, 500 ml of NS with 20 mEq KCl were given over 2 h, followed by 500 ml D_5W with 4 g of $MgSO_4$ over 2 h. No therapy was given on days 7 – 14. Following dose level 1, the daily dose of cisplatin was decreased to 8 mg/m^2 per day after dose-limiting cumulative toxicity had been observed.

Due to the phase I nature of the study, radiotherapy was variable. All patients were simulated prior to treatment and treatment was delivered with a linear accelerator (>6 MV). However, treatment volumes were highly variable and individualized for each patient. Typical radiation fields encompassed gross disease and included a 2-cm margin. In patients with non-small-cell lung cancer, typical fields included the primary lesion along with the hilar and mediastinal lymph nodes. An AP/PA field arrangement was most commonly used. All fields were treated each day. An oblique field arrangement was employed to boost areas of gross disease in patients receiving >40 Gy and in those who had undergone prior radiation therapy so as to keep the spinal cord dose within tolerance.

IFN dose escalation proceeded from 0 (level 1) to 5×10^6 U/m^2 per day. Further dose escalation of IFN was not attempted in view of its known myelosuppressive and hepatotoxic effects at higher doses. Two alternative schedules of cisplatin were also tested with the highest doses of IFN in the final portion of this study. These cisplatin schedules consisted of 10 mg/m^2 per day given in 200 ml of NS over 30 min on 5 consecutive days, preceding the first fraction of daily radiotherapy by 1 h (dose level 9); and 50 mg/m^2 given on day 2 of each cycle in 250 cc of NS over 30 min (level 10). In this setting, cisplatin was infused after delivery of the second dose of radiotherapy on day 1 of each cycle.

The dose of IFN was escalated after three to six patients had been evaluated at a given dose level. If grade 3 toxicity during cycles 1 or 2 (Common Toxicity Criteria, National Cancer Institute) was observed in one patient, a total of six patients were treated at that dose level. Dose escalation continued until $\geq 50\%$ of the patients (a maximum of three patients) treated on a given dose level developed acute grade 3 toxicity. Dose escalation was to be stopped if any patient developed grade 4 toxicity. Antiemetics were given at the discretion of the attending physician. The introduction of a double-lumen venous access device (e.g., Port-a-cath) prior to the initiation of therapy was recommended.

Patients who experienced grade 3 or 4 toxicity could continue therapy on protocol; however, their doses of IFN and cisplatin were reduced in subsequent cycles. Patients who experienced grade 3 toxicity (except

Table 1. Patients' characteristics

Number of patients	48
Sex:	
M	30
F	18
Age (years):	
Median	63
Range	24–78
Performance status:	
0	2
1	17
2	28
Unknown	1
Prior therapy:	
None	19
Surgery	22
Radiotherapy	7
Chemotherapy	13
Hormonal therapy	1
Primary tumor site:	
Non-small-cell lung	24
Small-cell lung	1
Breast	3
Esophageal	3
Colorectal	5
Melanoma	1
Head and neck	4
Parotid gland	2
Gallbladder	1
Mesothelioma	1
Appendix	1
Pancreas	1
Adenocarcinoma, unknown primary	1

renal toxicity) continued therapy at 75% of the intended doses of cisplatin and IFN. For grade 4 toxicity (except renal toxicity), 50% doses of cisplatin and IFN were given. For grade 3 or 4 toxicity (except renal toxicity) that had not resolved to ≤grade 2 by day 14, the next cycle was postponed by 1 week or until resolution of that toxicity to ≤grade 2.

The dose of cisplatin was reduced to 50% for a calculated creatinine clearance of 30–50 cc/h using the formula of Cockcroft and Gault [7]. No cisplatin was given for a creatinine clearance of <30 cc/h. Determination of 24-h creatinine clearance by a timed urine specimen was performed for an estimated creatinine clearance of ≤30 cc/h.

Treatment evaluation. Patients completing at least one cycle (days 1–14) of protocol therapy were evaluable for toxicity. Patients who completed a planned course of radiotherapy on protocol were evaluated for response. A complete response (CR) was defined as the complete disappearance of all detectable tumor for at least 28 consecutive days. A partial response (PR) was defined as a reduction by at least 50% of the products of the longest perpendicular diameters of the most easily measurable or largest tumor mass, usually the lesion undergoing radiation (indicator lesion). At the same time, there was to be no growth of other lesions and no appearance of new lesions for at least 28 consecutive days. Stable disease (SD) defined a decrease of the indicator lesion by <50% or an increase by <25%, and progressive disease (PD) represented an increase by ≥25% of the product of perpendicular diameters at the indicator lesion or the appearance of new lesions.

Results

A total of 48 patients were entered on 10 dose levels in this study. The pretreatment characteristics of the patients are summarized in Table 1. In all, 30 patients were men and 18 women. The median age was 62 years (ranges, 24–78 years). Most patients had a performance status of 1 or 2. Overall, 19 patients had not previously been treated, whereas 29 had previously undergone surgery and/or chemotherapy and radiotherapy. Patients with a variety of solid tumors were treated, but the majority of patients had non-small-cell lung cancer (NSCLC) or colorectal, head and neck, esophageal, or breast cancer.

Toxicities

In this trial, toxicities observed during the first treatment cycle (2 weeks) were used to determine dose-limiting toxicities and the MTD. However, in the administration of a concomitant chemoradiotherapy regimen, it is necessary to give several repeated cycles of therapy so as to deliver the previously determined amount of radiotherapy. Therefore, toxicities occurring during later cycles of therapy may also be of clinical significance. Therefore, we decided to analyze separately as acute toxicities those observed during cycles 1 and 2, corresponding to a customary chemotherapy cycle of 4 weeks, and as cumulative toxicities those observed during the entire treatment course in patients receiving more than two cycles.

The acute toxicities for all ten dose levels are summarized in Table 2 and the cumulative toxicities, in Table 3. Dose levels 1 and 2 utilized continuous-infusion cisplatin without IFN. Although a daily dose of 10 mg/m^2 of cisplatin did not result in dose-limiting acute toxicity, grade 3 cumulative myelosuppression was observed in two of five such patients. Subsequently, we decreased the cisplatin dose to 8 mg/m^2 per day. Again, no dose-limiting acute toxicity was seen, and only one of four patients developed dose-limiting cumulative toxicity.

We subsequently added escalating daily doses of IFN to this lower dose of cisplatin. Doses ranging from 0.5 to 5.0×10^6 U/m^2 per day (dose levels 3–8) were all well tolerated and not dose-limiting as defined in the protocol, although grade 3 neutropenia during cycle 2 was observed in some patients treated with IFN doses of 2.0, 3.0, and 4.0×10^6 U/m^2 per day. Thrombocytopenia exceeding grade 1 was not observed. Similarly, serum creatinine elevation exceeding 2.0 mg/dl was not observed. Grade 2 or 3 hypomagnesemia was seen in several patients. These renal toxicities did not appear to increase in severity with higher doses of IFN. Nausea and vomiting were mild to moderate in the majority of patients.

In our analysis of cumulative toxicities, grade 3 neutropenia was seen in the majority of patients treated for more than two cycles on dose levels 3–8. Although the patient numbers for most dose levels were small, this toxicity occurred at all dose levels and did not appear to be IFN-dose-dependent within the IFN dose range tested in this study. Thrombocytopenia, serum creatinine elevation, and

Table 2. Acute toxicities, cycles 1 and 2

Dose Level[a]	Patients (*n*)	WBC grade			Plts grade	Creat (mg/dl)	Magnesium (mg/dl)			N/V grade			Mucositis grade			Skin grade		Fever/ chills grade		Total number of cycles				
		0–1	2	3	0–1	≤2.0	≥1.2	1.0–0.8	0.8–0.16	0–1	2	3	0	1	3	0	1	0.1	≥2	1	2	3	4	5
1) CDDP: 10/IFN: 0	6	4	2	–	6	6	6	–	–	5	1	–	5	1	–	5	1	6	–	–	1	–	–	5
2) CDDP: 8/IFN: 0	5	4	1	–	5	5	3[b]	–	1	3[b]	1	–	4	1	–	5	–	5	–	–	1	2	1	1
3) CDDP: 8/IFN: 0.5	3	2	1	–	3	3	3	–	–	2	–	1	1	2	–	3	–	3	–	1	–	–	1	1
4) CDDP: 8/IFN: 1.0	4	2	2	–	4	4	4	–	–	1	2	1	3	1	–	4	–	2	2	1	1	–	–	2
5) CDDP: 8/IFN: 2.0	3	1	1	1	3	3	3	–	–	2	1	–	3	–	–	3	–	2	1	–	1	2	–	–
6) CDDP: 8/IFN: 3.0	5	3	1	1	5	5	4	1	–	4	1	–	3	1	1	3	2	3	2	–	4	–	–	1
7) CDDP: 8/IFN: 4.0	6	1	3	2	6	6	6	–	–	3	2	1	6	–	–	6	–	–	6	–	1	1	1	3
8) CDDP: 8/IFN: 5.0	4	2	2	–	4	4	4	–	–	1	2	1	4	–	–	4	–	2	2	–	2	1	1	–
9) CDDP: 10/IFN: 5.0	4	1	1	2	4	4	3	1	–	3	1	–	4	–	–	3	1	1	3	1	–	–	–	3
10) CDDP: 50/IFN: 5.0	8	3	1	4	8	8	7	1	–	6	2	–	8	–	–	8	–	–	8	–	3	–	4	1

Worst toxicities observed in all patients during cycles 1 and 2. PLTS, Platelets; Creat, creatinine; N/V, nausea/vomiting; CDDP, cisplatin; IFN, interferon alpha-2A

[a] CDDP doses are expressed in mg/m^2 per day and IFN doses, in ($\times 10^6$) U/m^2 per day

[b] Data on one patient are missing

Table 3. Cumulative toxicities, all cycles

Dose level[a]	Patients (*n*)	WBC grade				Plts grade			Creatinine (mg/dl)		Magnesium (mg/dl)	
		0–1	2	3	4	0–1	2	3, 4	≤2	2.1–2.5	>1.2	1.1–0.9
1) CDDP: 10/IFN: 0	5	1	2	2	–	5	–	–	5	–	5	–
2) CDDP: 8/IFN: 0	4	2	1	–	1	3	–	1	3[b]	–	2[b]	1
3) CDDP: 8IFN: 0.5	2	–	–	2	–	2	–	–	2	–	2	–
4) CDDP: 8/IFN: 1.0	2	–	–	2	–	1	1	–	2	–	1	1
5) CDDP: 8/IFN: 2.0	2	–	–	1	1	2	–	–	2	–	2	–
6) CDDP: 8/IFN: 3.0	1	–	–	1	–	1	–	–	1	–	–	1
7) CDDP: 8/IFN: 4.0	5	–	1	4	–	4	–	1	5	–	2	3
8) CDDP: 8/IFN: 5.0	2	–	1	1	–	2	–	–	2	–	2	–
9) CDDP: 10/IFN: 5.0	3	–	–	2	1	2	–	1	1	2	1	2
10) CDDP: 50/IFN: 5.0	5	–	2	3	–	5	–	–	5	–	2	3

Worst toxicities observed during all cycles in patients receiving more than two cycles. Plts, Platelets; CDDP, cisplatin; IFN, interferon alpha-2A

[a] CDDP doses are expressed in ng/m^2 per day and IFN doses, in ($\times 10^6$) U/m^2 per day

[b] Data on one patient are missing

hypomagnesemia were again mostly mild in degree when all treatment cycles were analyzed. Similarly, mucositis and in-field dermatitis were graded as 0 or 1 in most patients (data not shown). On the basis of these data, we identified dose level 8, corresponding to a cisplatin dose of 8 mg/m^2 per day and an IFN dose of 5.0×10^6 U/m^2 per day, as our recommended dose level since it resulted in no dose-limiting acute toxicity and in cumulative toxicity that did not appear to be IFN-dose-dependent.

We were interested to know whether the dose of cisplatin could be escalated to 10 mg/m^2 per day (or 50 mg/m^2 per cycle) if a shorter infusion schedule were applied. Therefore, two additional dose levels were tested with a fixed dose of IFN at 5.0×10^6 U/m^2 per day as used on dose level 8. We tested the administration of a short-term daily infusion of cisplatin at 10 mg/m^2 per day over 30 min given 1 h prior to one daily dose of radiotherapy (level 9) as well as its administration only once per cycle at 50 mg/m^2 on day 1 over 30 min.

As demonstrated in Tables 2 and 3, both of these dose levels resulted in grade 3 acute neutropenia in 50% of the patients. Similarly, cumulative toxicity exceeded grade 2 in all 3 patients on dose level 9 and in 3 of 5 patients on dose level 10. Therefore, escalation of cisplatin beyond a dose of 8 mg/m^2 per day (or 40 mg/m^2 per cycle) was not feasible and resulted in dose-limiting acute and cumulative toxicity as defined for this study, regardless of its schedule of administration.

Other types of toxicities observed in this study included radiation pneumonitis (three patients) and sudden death in one patient, felt to represent a pulmonary embolus or, possibly, treatment-related cardiac toxicity. An episode of angina in another patient was felt to be possibly IFN-treatment-related [9, 38]. Another patient with a history of coronary artery disease had syncopal episodes that were not felt to represent toxicity. Finally, confusion was noted in 1 patient treated on level 10 and was considered to be possibly IFN-related [3, 14, 24].

Response

A total of 41 patients were evaluated for response within the radiotherapy field (Table 4). Of 24 patients with NSCLC, two had a clinical CR, 9 had a PR, 7 had SD, and 5 had PD. On analysis of the site of first treatment failure, 7 patients with NSCLC were found to have progressed within the irradiated field, whereas 10 progressed outside the irradiated field and 3 progressed both within and outside the irradiated field. The median time to progression was 8 weeks (range, 2 – 42 weeks, with one patient remaining in CR at 186 weeks of follow-up). Nine patients with NSCLC were also evaluated for response outside the irradiated field; of these, one had a PR (this patient had a CR within the radiotherapy field), two had SD, and six had PD. The responses observed for other types of tumors are summarized in Table 4.

Discussion

We investigated the simultaneous use of escalating doses of IFN with continuous-infusion cisplatin and twice-daily radiotherapy and identified recommended doses of 8 mg/m^2 per day for cisplatin and 5.0×10^6 U/m^2 per day for IFN. These doses will result in no severe acute toxicity, although cumulative myelosuppression may be seen and may require dose reductions. Dose escalation to higher doses of IFN was not attempted, given the known myelosuppressive and hepatotoxic effects of IFN at high-dose ranges [3, 14, 24]. Escalation of cisplatin to higher doses, on the other hand, was attempted but found not to be feasible despite the choice of an administration schedule that has been reported to result in less myelosuppression. Since the dose-limiting toxicity consisted exclusively of neutropenia, it is possible that the use of a colony-stimulating factor might permit further escalation of the cisplatin dose. This question is being addressed in an ongoing study at our institution [16].

The use of an alternating-week schedule of chemoradiotherapy in this study was based on a need to observe carefully the interaction and possible toxicities of these drugs when given in combination. Except for the patients developing possible radiation-related pneumonia, there appeared to be no exacerbated in-field toxicity (e.g., mucositis, dermatitis), although the latter has been suggested by other investigators [17, 26, 30, 42]. This would suggest that when cisplatin and IFN are used with concomitant radiotherapy, an interruption of the radiotherapy to allow for normal tissue recovery from in-field toxicity as performed in this trial may not be necessary. This is an important finding, given the loss of activity observed on the interruption of radiotherapy as a single-treatment modality [43].

Of interest is the lack of severe renal toxicity noted for cisplatin and IFN in this study. This finding is in contrast to the results of another study conducted at our institution that utilized higher doses of cisplatin (100 mg/m^2) with continuous-infusion fluorouracil (5-FU), high-dose oral leucovorin, and interferon alpha-2b [48]. In that study, a significant loss of serum electrolytes, including magnesium, sodium, potassium, and calcium, was observed. It is possible that the different extent of nephrotoxicity seen in these two studies relates to the higher doses of cisplatin or to the additional use of 5-FU/leucovorin in the previous study. The possible cardiac toxicity observed in the present study is compatible with previous observations with interferon [9, 38].

Few additional studies have reported on the clinical interaction of interferon with cisplatin or radiotherapy. A phase I study by Torrisi et al. [42] identified a dose of $2 - 5 \times 10^6$ U/m^2 given three to five times per week during radiotherapy as the MTD. Increased normal tissue effects

Table 4. Response

Disease	Patients (*n*)	Response					Site of failure				Median time to progression in weeks (range)
		CR	PR	SD	PD	N/A	In field	Out of field	Both	Unknown	
NSCLC	24	2[a]	9	7	5	1	7	10	3	3[a]	8 (12–186+)
SCLC	1	–	–	–	–	1	1	–	–	–	18
Breast	3	–	–	–	1	2	1	1	–	1	4 (4–8)
Esophageal	3	–	–	2	–	1	1	2	–	–	20 (12–23)
Colorectal	5	–	1	2	2	–	–	2	1	2	7 (3–20)
HNC (SCCA)	4	–	1	–	2	1	3	–	–	1	4 (2–22)
Parotid	2	1	–	1	–	–	–	1	1	–	16, 43
Melanoma	1	–	–	–	1	–	–	–	1	–	1
Adenocarcinoma	1	–	–	–	–	1	–	–	–	1	6
Gallbladder	1	–	–	1	–	–	–	–	–	1	–[b]
Mesothelioma	1	–	–	1	–	–	1	–	–	–	–[b]
Appendix	1	–	–	1	–	–	–	–	–	1	–[b]
Pancreas	1	–	–	1	–	–	1	–	–	–	–[b]

NSCLC, Non-small-cell lung cancer; SCLC, small-cell lung cancer; HNC, head and neck cancer; SCCA, squamous-cell carcinoma; N/A, patient not evaluated for response

[a] One patient remains failure-free at 186 weeks

[b] Data not available

in the radiation field were reported as dose-limiting. Holsti et al. [17] observed activity for interferon and radiotherapy in small-cell lung cancer. Whether the addition of IFN results in an improved treatment outcome remains to be investigated in phase III studies.

More recently, this group of investigators reported on a trial of hyperfractionated radiotherapy [125 cGy twice daily) to 60 Gy with or without natural leukocyte interferon alpha at 3×10^6 U s.c. in the morning prior to radiotherapy and at 1.5×10^6 U via inhalation through jet nebulizer 30 min before each radiotherapy dose [30]. A total of 20 patients with inoperable NSCLC were treated. In all, 5 of 10 patients in the radiotherapy arm and 6 of 10 patients in the radiotherapy/interferon arm responded. Pneumonitis and esophagitis were reported as being more severe in patients receiving the combined therapy.

The interaction of cisplatin and interferon has been investigated in other studies. Bowman et al. [4] gave 100 mg/m^2 of cisplatin every 3 – 4 weeks with interferon alpha-2b to 68 patients with NSCLC. The overall response rate in 60 evaluable patients was 30%; 11 of 24 [46%) patients with squamous-cell carcinoma responded. No potentiation of hematologic, renal, or neurologic toxicity was seen. Rosell et al. [33] gave 50 mg/m^2 of cisplatin on days 1 and 8 of a 28-day cycle with interferon alpha-2b at 5×10^6 U three times weekly for a maximum of 2 months and reported a 13% response rate in 30 patients with NSCLC. Toxicities were judged to be not significant. Ardizzoni et al. [1] reported a response rate of 19% in 34 patients with previously untreated NSCLC treated with cyclophosphamide, epirubicin, and cisplatin together with interferon alpha-2b. The median progression-free survival and overall survival were 20 and 37 weeks, respectively. Finally, Rosso et al. [34] have reported preliminary data on a subsequent randomized study of cyclophosphamide, epirubicin, and cisplatin with or without interferon alpha-2b. The overall response rates were 11% (95% confidence interval, 5% – 21%) vs 22% (95% confidence interval, 9%–33%) in favor of the interferon group. Toxicities were also more severe in that group of patients, including interferon-related flu-like symptoms and fatigue, stomatitis, and myelosuppression.

In conclusion, we identified the MTDs of cisplatin and IFN given with concomitant radiotherapy. Activity was seen in patients with NSCLC, which was the largest group of patients treated in this phase I study. Further phase II investigation of this regimen in that group of patients may be warranted. On the other hand, it may be possible to intensify this regimen further by utilizing colony-stimulating factors and intensifying the radiotherapy schedule. This strategy might succeed in further increasing the potential of this regimen to improve the therapeutic outcome in patients with NSCLC and other malignancies.

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