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A phase I trial of concomitant chemoradiotherapy with cisplatin dose intensification and granulocyte-colony stimulating factor support for advanced malignancies of the chest

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Abstract Concomitant chemoradiotherapy with cisplatin and combination chemotherapy in the neoadjuvant setting have both shown promising results. *Purpose:* To identify a locally and systemically active concomitant chemoradiotherapy regimen incorporating high-dose cisplatin, interferon alfa-2a (IFN), fluorouracil (5-FU), hydroxyurea (HU) and radiotherapy. *Methods:* Phase I cohort design establishing the maximal tolerated dose (MTD) of cisplatin with and without granulocyte colony stimulating factor (GCSF). For the first six dose levels, a 4-week cycle consisted of escalating doses of cisplatin during weeks 1 and 2, IFN (week 1), and 5-FU and HU (week 2) with single daily radiation fractions of 200 cGy during days 1–5 of weeks 1–3 and no treatment in week 4. When dose-limiting neutropenia was encountered, GCSF was added during weeks 1, 3, and 4. Finally, to decrease esophagitis, the radiotherapy schedule was altered to 150 cGy twice daily during weeks 1 and 2, followed by a 2-week break (level 7). *Results:* Forty-nine patients with refractory chest malignancies were treated. The MTD of this regimen without GCSF was cisplatin 50 mg/m^2 in weeks 1 and 2, IFN 5 million Units (MU)/m^2 per day on days 1–5 in week 1, 5-FU 800 mg/m^2 per day for 5 days by continuous infusion, and HU 500 mg every 12 h for 11 doses during week 2. The addition of GCSF during weeks 1, 3, and 4 allowed for escalation of cisplatin to 100 mg/m^2 during weeks 1 and 2, with a decreased dose of IFN at 2.5 MU/m^2 per day to avoid renal toxicity. Dose-limiting toxicity (DLT) included severe neutropenia, thrombocytopenia, and esophagitis in 5 of 13 patients. Increased thrombocytopenia in patients receiving GCSF was not observed. During hyperfractionated radiotherapy (level 7) chemotherapy doses were as above except for a reduction of 5-FU to 600 mg/m^2 per day. While severe esophagitis was reduced, grade 4 thrombocytopenia became more prevalent and was seen in 6 of 7 patients. In-field tumor responses were observed in 17 of 28 evaluated patients with non-small-cell lung cancer. The median times to progression and survival were 4 and 6 months, respectively. When only patients with all known disease confined to the radiotherapy field were considered the corresponding times were 6 and 15 months, respectively. Most treatment failures occurred outside of the irradiated field. *Conclusions:* (1) This intensive multimodality regimen can be given with aggressive supportive care incorporating GCSF. The recommended phase II doses for a 4-week cycle are cisplatin 50 mg/m^2 week 1, and 100 mg/m^2 week 2, IFN 2.5 MU, HU 500 mg every 12 h × 11 and 5-FU 800 mg/m^2 per day with single fraction radiotherapy during weeks 1–3 and GCSF during weeks 1, 3, and 4. (2) GCSF can be safely administered and provides effective support of neutrophils when administered simultaneously with IFN, cisplatin, and chest radiotherapy. (3) There is synergistic renal toxicity when high doses of IFN and cisplatin are given together. (4) Hyperfractionated radiotherapy decreases the severity of esophagitis but increases thrombocytopenia. (5) Although highly toxic, response rates, time to progression and survival figures with this regimen are encouraging and support its investigation in the phase II setting.

Key words Concomitant chemoradiotherapy
Dose intensity · Granulocyte-colony stimulating factor
Interferon · Lung cancer

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Table 1 Treatment schedule for dose levels 1–6 (*DLT* dose-limiting toxicity; *5-FU* fluorouracil; *GCSF* granulocyte colony stimulating factor; *HU* hydroxyurea; *IFN* interferon; *XRT* radiotherapy)

	Week 1	Week 2	Week 3	Week 4
Cisplatin[a]	X	(X)	–	–
IFN[a]	5 MU/m² per day	–	–	–
5-FU	–	800 mg/m² per day	–	–
HU	–	500 mg every 12 h × 11	–	–
XRT	200 cGy days 1–5	200 cGy days 1–5	200 cGy days 1–5	–
GCSF[a]	5 μg/kg days 2–6	–	5 μg/kg days 1–7	5 μg/kg days 1–7

[a] Dose escalation. Level 1: 50 mg/m², week 1; level 2: 100 mg/m², week 1 (DLT); level 3: 50 mg/m², week 1; 50 mg/m², week 2; level 4: 50 mg/m², week 1; 100 mg/m², week 2 (DLT); level 5: 50 mg/m², week 1; 100 mg/m², week 2 plus GCSF; level 6: 100 mg/m², week 1; 100 mg/m², week 2 plus GCSF IFN 2.5 MU/m² per day

Introduction

In patients with advanced non-small cell carcinoma (NSCLC) a randomized study comparing radiotherapy alone with radiotherapy and concomitant cisplatin has demonstrated improved survival as a consequence of increased locoregional control; no reduction of distant progression rates was achieved [13, 17, 31]. Induction chemotherapy has also been shown to increase survival rates [8, 19, 21, 22] and in one randomized trial improved survival was demonstrated to occur as a function of increased systemic tumor control [21, 22]. Therefore, concomitant chemoradiotherapy and induction chemotherapy have both resulted in improved survival in NSCLC, albeit as a function of different patterns of increased tumor control. The identification of a treatment regimen incorporating aggressive combination chemotherapy with concomitant radiotherapy might make it possible to achieve increased locoregional *and* systemic tumor control and, thus, might further increase survival rates, as has already been demonstrated in esophageal cancer [14].

Prior phase I or II studies of concomitant chemoradiotherapy to the chest at the University of Chicago have focused on biochemical modulation of fluorouracil (5-FU) and cisplatin as radiation enhancers. We first studied a combination of 5-FU/leucovorin, hydroxyurea (HU) and radiotherapy (FHX) [35, 38]. Subsequently we investigated a combination of cisplatin, interferon alfa-2a (IFN) and radiotherapy (CIX) [40, 41]. All drugs studied in these combinations have been shown to enhance the activity of radiation in vitro and/or in vivo [1, 5, 9, 12, 15, 18, 20, 23–25, 29, 34–36, 39]. In addition, HU can modulate the activity of 5-FU [28], and interferon appears to enhance the activity of cisplatin in some experimental systems and, possibly, in lung cancer [2, 16, 30, 33]. Both regimens were administered over 5 days of every other week on a protracted radiotherapy schedule. Dose-limiting toxicity of FHX was mucositis and that of CIX was cumulative neutropenia. Both regimens had locoregional activity, although systemic activity was low, possibly due to the low single-agent activity of three of the single agents incorporated into these two combinations (5-FU, HU, and IFN) and the low dose intensity of cisplatin as used.

In 1990 Gandara et al reported high systemic activity for cisplatin when it was administered at high doses of 100 mg/m² on days 1 and 8 of a 4-week cycle as a single agent [11]. Similarly, radiation enhancement by cisplatin is felt to be dose- and, possibly, schedule-dependent [23, 36].

Against this background, we designed a phase I study that sought to combine the two previously studied regimens of FHX and CIX into one intensive multidrug chemoradiotherapy regimen with high locoregional activity; in addition, we sought to escalate cisplatin to the dose range studied by Gandara et al. [11] to increase the systemic activity of this combination for future studies in patients with locoregionally advanced chest malignancies being treated with curative intent.

Patients and methods

The initial objectives of this study were to establish the feasibility of administering the FHX and CIX combinations in direct sequence without interruption by a 1-week break between the two regimens as used previously, and to attempt further escalation of cisplatin and establish its maximal tolerated dose (MTD) and the dose-limiting toxicities. After neutropenia had emerged as an early dose-limiting toxicity, the feasibility of administering GCSF with concurrent chest radiation and IFN to allow further cisplatin dose escalation was studied; finally, we investigated the effects of administering hyperfractionated radiotherapy (XRT) within this combination at the MTD of cisplatin.

Eligible patients had histological or cytological documentation of a malignancy in clinical need of palliative-intent radiotherapy to the chest. All patients had a CALGB performance status of 0–2 and normal bone marrow, kidney and liver function tests, and all had given signed informed consent. There was no limitation on prior chemotherapy.

Treatment schedule

Treatment during week 1 was derived from the previous CIX study [40]. Table 1 outlines the treatment schedule for dose levels 1–6 (single daily fraction of radiotherapy). During dose levels 1–5, the treatment during week 1 consisted of IFN (Roferon A) given s.c. at 5 MU/m² on days 1–5 (Monday to Friday). At dose levels 6–8, IFN was decreased to 2.5 MU/m² in an attempt to decrease renal toxicity (Tables 1, 2). Cisplatin was administered on day 1 at 50–100 mg/m² over 6 h in

Table 2 Treatment schedule for dose levels 7 and 8

	Week 1	Week 2	Week 3	Week 4
Cisplatin	100 mg/m^2 on day 1	100 mg/m^2 on day 1	–	–
IFN[a]	2.5 MU/m^2 per day on days 1–5	–	–	–
5-FU	–	600 mg/m^2 per day on days 1–5	–	–
HU	–	500 mg p.o. every 12 h × 11	–	–
XRT	150 cGy b.i.d. on days 1–5	150 cGy b.i.d. on days 1–5	–	–
GCSF	5 μg/kg on days 2–6	–	5 μg/kg on days 1–7	5 μg/kg on days 1–7

[a] Dose escalation. XRT given in twice-daily hyperfractionated doses in 150 cGy fractions at least 5 h apart. Total cord dose 39 Gy. No IFN given on level 8

1000 ml of D_5NS with 18.5 g mannitol. Fluid orders were adjusted to insure a urine output of greater than 100 ml/h over 4 h before and 12 h after the administration of cisplatin. While the actual time of radiotherapy varied from patient to patient, administration of the daily dose of IFN preceded radiotherapy by 2 h. Radiotherapy was administered at daily fractions of 200 cGy on days 1–5.

Treatment during week 2 was derived from the FHX study [37] and consisted of HU at 500 mg p.o. every 12 h for 6 days (11 doses per cycle), starting on day 0 (Sunday). On days 1–5, a continuous infusion of 5-FU was given at 800 mg/m^2 per day for 5 days, and radiotherapy was administered daily at 200 cGy. During dose levels 3–8, cisplatin was also administered on the evening of day 1 of week 2 at 50–100 mg/m^2. While the actual time of administration of HU and radiotherapy varied from patient to patient, one daily dose of HU preceded radiotherapy at a constant of 2 h.

During week 3, radiotherapy was administered daily for 5 days at 200 cGy. No chemotherapy was administered. Starting with dose level 5, GCSF was added during week 1 on days 2–6 (after cisplatin but with radiotherapy and IFN) and during weeks 3 and 4, in an attempt to decrease the incidence of severe neutropenia. During week 4, no chemoradiotherapy was administered. A second cycle was initiated at the beginning of week 5 in patients requiring radiation doses of more than 3000 cGy. Cycle 2 was delayed by 1 week to allow for attenuation of toxicity to grade ≤ 1.

The cisplatin dose escalation schedule and the GCSF schedule are summarized in Table 1. There was no cisplatin dose escalation in individual patients. At dose levels 7 and 8 (Table 2), we tested the hypothesis that less esophagitis would be seen if radiotherapy was administered according to a hyperfractionated schedule with a 25% decrease in the 5-FU dose, and that myelosuppression would be reduced in the absence of IFN (level 8). Therefore, high-dose cisplatin, IFN, hydroxyurea, and GCSF were administered as defined for level 6. In week 2, the dose of 5-FU was decreased to 600 mg/m^2 per day. Radiotherapy was administered twice daily during weeks 1 and 2, in 150 cGy fractions at least 5 h apart. No radiotherapy was given during weeks 3 and 4.

Radiation field sizes and total doses were adjusted to each patient's treatment needs. Generally, total doses ranged from 30 Gy, or one cycle (e.g., a patient with systemic metastases and a mass in the chest), to 60 Gy, or two cycles (e.g., a patient with no documented metastases outside of the radiation field). Treatment was given with palliative intent.

Antiemetics were administered at the discretion of the attending physician. A double-lumen venous access device (e.g., Port-a-cath) was recommended prior to initiation of therapy.

Definition of dose-limiting toxicity

Toxicities were assessed following cycle 1 in all patients and cycle 2 in those patients receiving >30 Gy of radiotherapy. Dose-limiting myelosuppression was defined as grade 4 myelosuppression exceeding 4 days in duration or complicated by neutropenic fever during cycle 1. If dose-limiting toxicity (DLT) was observed in 1 of 3 patients, a minimum of 4 and maximum of 6 patients were treated at that dose level. Dose escalation continued until 50% of patients or more (a maximum of 2) treated at a particular dose level developed DLT. Patient accrual at dose level 6 was expanded to allow for better evaluation of the toxicity profile at that dose. For toxicities other than myelosuppression, DLT was defined as grade 3 or 4 toxicity in excess of 7 days in duration.

Dose modifications

Patients who experienced DLT were eligible to continue therapy on protocol after recovery to grade ≤ 1 toxicity, but their doses were reduced in the subsequent cycle.

For dose-limiting grade 3 mucositis, dermatitis, or diarrhea, 5-FU was decreased to 600 mg/m^2 per day. Following grade 4 mucositis, dermatitis, or diarrhea in the previous cycle, 5-FU was decreased to 400 mg/m^2 per day. For grade-3 or -4 mucositis, dermatitis, or other in-field toxicity during radiotherapy or on day 1 of cycle, therapy was delayed until resolution of toxicity to grade ≤ 1.

For a WBC count lower than 1000/ μl or platelet count lower than 25,000/ μl in the previous cycle, HU, cisplatin, and IFN were reduced by 50%. The dose of cisplatin was reduced to 50% for a calculated creatinine clearance of 30–50 ml/min. No cisplatin was administered for a creatinine clearance lower than 30 ml/min. The creatinine clearance was calculated according to the formula of Cockcroft and Gault [6]. Determination of 24 h creatinine clearance by a timed urine specimen was performed if the estimated creatinine clearance was lower than 50 ml/min.

Treatment evaluation

All patients were evaluated for toxicity. Patients who completed at least one cycle of therapy (4 weeks) or had disease progression at any time while on protocol were evaluated for response. Response was evaluated separately within the radiotherapy field and outside the radiotherapy field (when applicable). Standard response criteria were used as previously published [37, 40].

The response rate was expressed as the proportion of patients demonstrating complete response (CR) and/or partial response (PR). Time to progression (TTP) was measured as time from day 1 of therapy until documented disease progression or death from disease. Patients who died of clearly documented other causes after completion of therapy were censored for progression. Survival was measured from the date of registration until last follow-up or death. Actuarial survival and TTP were calculated according to Kaplan and Meyer [7].

Results

This study opened in August 1990, and was closed in March 1993. Follow-up is available through September 1993. The baseline patient characteristics are summarized in Table 3. A total of 49 patients were entered, 37 of whom were male; the age ranged from 30 to 73 years (median 56

Table 3 Patient characteristics

No. entered	49
Male	37
Female	12
Age (years) median	56
Age (years) range	30–73
Performance status	
0	13
1	25
2	11
NSCLC	41
Esophageal	3
Renal	3
Head/neck	1
Neuroendocrine	1
Prior therapy:	
None	28
Surgery	12
Radiotherapy	9
Chemotherapy	6

years). The vast majority of patients had NSCLC; additional patients with esophageal, renal, head and neck, and neuroendocrine cancer located in the chest were also entered on trial. Prior therapy consisted of surgery (12 patients), radiotherapy (9 patients), and/or chemotherapy (6 patients); 28 patients had not received prior therapy.

Toxicity

All 49 patients were evaluated for toxicity. Table 4 details the maximal toxicities observed during cycle 1 in patients treated at dose levels 1 through 8. Dose levels 1–3 did not result in dose-limiting neutropenia, except in 2 patients treated at level 2. However, renal toxicity was encountered in patients treated with 100 mg/m^2 of cisplatin during week 1 and 5 MU/m^2 of IFN (dose level 2). Grade-2 (4 patients) or grade-3 (2 patients) azotemia was observed in 6 of 7 patients treated, reflecting possible synergistic renal toxicity of both agents when given concurrently at these doses. Subsequently, the dose of cisplatin at levels 3–5 was

Table 4 Toxicities in cycle 1, levels 1–8

	Toxicity	WBC	Platelets	Creatinine	Mucositis	Esophagitis	Feeding support[b] (*n*)
Level 1 (50/0)	Grade 0–1/2	1/2	4/0	3/1	0/4	1/1	1
n = 4	3	1	–	–	–	–	
	4	–	–	–	–	2	
	DLT (*n* = 3)	–	–	–	–	–	
Level 2 (100/0)	Grade 0–1/2	1/0	2/0	1/4	3/3	1/0	3
n = 7	3	5	5	2	1	6	
	4	1	–	–	–	–	
	DLT (*n* = 0)	2	–	2	–	1	
Level 3* (50/50)	Grade 0–1/2	3/1	4/0	5/0	3/0	1/0	4
n = 6	3	1	1	–	1	3	
Phase II	4	–	–	–	1	1	
	DLT (*n* = 1)	–	–	–	–	1	
Level 4 (50/100)	Grade 0–1/2	0/1	0/3	4/2	2/4	2/3	3
n = 6	3	2	2	–	–	1	
	4	3	1	–	–	–	
	DLT (*n* = 3)	2	–	–	–	1	
Level 5 (50/100)	Grade 0–1/2	1/2	2/0	5/0	2/3	1/0	1
n = 5 (GCSF)	3	2	3	–	–	3	
Phase II	4	–	–	–	–	1	
	DLT (*n* = 0)	–	–	–	–	–	
Level 6[a] (100/100)	Grade 0–1/2	2/2	1/3	12/0	6/4	5/3	4
n = 13 (GCSF) ↓ IFN	3	4	2	–	0	3	
	4	4	6	–	2	1	
	DLT (*n* = 5)	3	3	–	2	1	
Level 7[a] (100/100)	Grade 0–1/2	0	0	3/1	4/0	1/3	3
n = 5 (GCSF) ↓ IFN	3	2	0	0	0	0	
BID-XRT	4	2	4	0	0	0	
	DLT (*n* = 2)	0	2	0	0	0	
Level 8 (100/100)	Grade 0–1/2	2/0	0	3/0	1/1	2/0	1
n = 3 (GCSF) no IFN	3	0	1	–	–	1	
BID-XRT	4	1	2	–	1	–	
	DLT (*n* = 2)	1	2	–	1	–	

"Phase II" denotes dose levels that might be tested in phase II studies

[a] 1 patient unevaluable

[b] Patients with nasogastric or gastric feeding device

Table 5 Toxicities, cycle 2, Levels 1–8

Level/cisplatin dose/*N*	Toxicity grade	WBC	Platelets	Creatinine	Mucositis	Esophagitis	Dose reduction				Patients with cycle delay (*n*)
							Cisplatin	5-FU	HU	IFN	
Level 1 (50/0)	0–2	3	3	3	3	2	0	0	0	0	3
n = 3	3	–	–	–	–	1	–	–	–	–	–
	4	–	–	–	–	–	–	–	–	–	–
Level 2 (100/0)	0–2	3	3	6	6	6	3	0	1	0	1
n = 6	3	3	1	–	–	–	–	–	–	–	–
	4	–	2	–	–	–	–	–	–	–	–
Level 3 (50/50)	0–2	2	2	3	3	–	0	2	0	0	2
n = 3	3	1	1	–	–	3	–	–	–	–	–
	4	–	–	–	–	–	–	–	–	–	–
Level 4 (50/100)	0–2	1	3	4	4	3	2	1	0	0	2
n = 4	3	2	–	–	–	–	–	–	–	–	–
	4	1	–	–	–	–	–	–	–	–	–
	Unknown	–	–	–	–	1	–	–	–	–	–
Level 5 (50/100)	0–2	1	1	3/0	3	3	0	0	0	0	0
n = 3 (GCSF)	3	2	1	–	–	–	–	–	–	–	–
	4	–	1	–	–	–	–	–	–	–	–
Level 6 (100/100)	0–2	4	6	10	9	6	4	3	1	0	4
n = 10 (GCSF) ↓ IFN	3	4	1	–	–	2	–	–	–	–	–
	4	1	3	–	1	–	–	–	–	–	–
	Unknown	1	–	–	–	2	1	1	1	1	–
Level 7 (100/100)	0–2	3	0	4	4	2	3	0	2	2	1
n = 4 (GCSF) ↓ IFN	3	0	2	–	–	1	–	–	–	–	–
BID-XRT	4	1	2	–	–	1	–	–	–	–	–
Level 8 (100/100)	0–2	1	–	1	1	1	1	0	0	1	1
n = 1 (GCSF) No IFN	3	–	1	–	–	–	–	–	–	–	–
BID-XRT	4	–	–	–	–	–	–	–	–	–	–

decreased to 50 mg/m^2 in week 1, and cisplatin was escalated during week 2. At levels 6–8, the cisplatin dose during week 1 was again increased to 100 mg/m^2; however, the dose of IFN was reduced to 50% to ameliorate this renal toxicity. No severe or life-threatening renal toxicity was observed at any of the subsequent dose levels, indicating that this toxic renal interaction may be dependent on cisplatin and IFN doses.

Level 4 (cisplatin dose of 50 and 100 mg/m^2 in weeks 1 and 2) was dose-limiting. Of 2 patients with dose-limiting neutropenia, 1 died of pneumonia while neutropenic, and the other of a cardiopulmonary arrest. To determine whether further cisplatin intensification was feasible with growth factor support, GCSF was added to the regimen during weeks 1, 3, and 4. No grade 4 neutropenia was observed in patients treated at dose level 5 with the same cisplatin dose as on level 4 but with GCSF support. Increased thrombocytopenia was not observed. At dose level 6, 13 patients received the targeted cisplatin dose of 100 mg/m^2 in weeks 1 and 2. One patient died of a bleeding gastric ulcer on day 4 of cycle 1 and was not evaluated for other toxicities. DLT was documented in 5 patients and consisted predominantly of myelosuppression. A total of 6 patients developed grade 4 thrombocytopenia, and 8 patients had grade-3 or -4 neutropenia. Thus, considerable toxicity was observed at this dose level, although DLT as defined for this study was observed in only 5 of 13 patients.

Severe or life-threatening esophagitis was observed frequently at dose levels 1–6 of this study, reflecting the severe in-field toxicity of this chemoradiotherapy program. Although we attempted to palliate this toxicity by offering nutritional support devices to patients (nasogastric or gastric feeding tubes), a reduction in the severity of esophagitis was desirable. We postulated that esophagitis could be reduced by limiting radiotherapy to weeks 1 and 2, thus allowing for repopulation of normal mucosal cells in the esophagus during weeks 3 and 4. Therefore, at dose levels 7 and 8 the radiation schedule was altered to 150 cGy twice daily during weeks 1 and 2, to give an identical cycle dose of 3,000 cGy. As shown in Table 4, this did indeed result in a low incidence of esophagitis more severe than grade 2 during cycle 1. However, 6 of 7 patients treated had grade-4 thrombocytopenia, which was dose-limiting in 4. Therefore, thrombocytopenia seemed to be further increased by the use of twice-daily radiotherapy to the chest. Furthermore, during evaluation of the toxicities encountered during cycle 2 (Table 5), severe esophagitis was seen in 2 of 5 patients, although at a later time point, when it was less likely to interfere with the completion of therapy. The omission of IFN at dose level 8 did not seem to have any major effect on myelosuppression and was not pursued further.

Table 5 indicates that during a second cycle of this therapy myelosuppression and esophagitis remained the

Table 6 Responses (*CR* complete response; *PD* progressive disease; *PR* partial response; *SD* stable disease; *UE* unevaluated)

	n	CR	PR	SD	PD	UE
In field						
NSCLC	41	1	16	10	1	13
Renal	3	–	1	1	–	1
Head/neck	1	1	–	–	–	–
Esophagus	3	–	3	–	–	–
Neuroendocrine	1	–	1	–	–	–
Out of field						
NSCLC	18	1	–	2	5	10
Renal	2	–	–	–	–	2
Head/neck	1	–	1	–	–	–
Esophagus	1	–	1	–	–	–

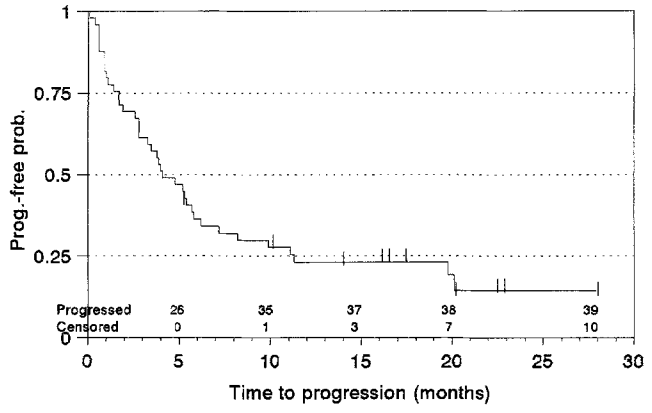

Fig. 1 Time to progression (TTP) for all patients

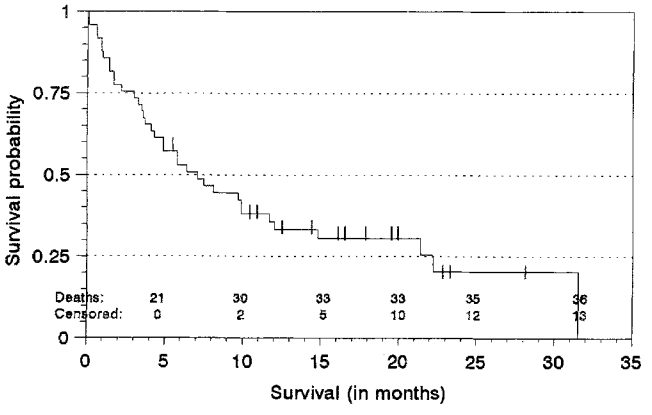

Fig. 2 Overall survivial for all patients

most significant toxicities. Dose reductions and the frequency of a delay of cycle 2 are also indicated.

Response

The in-field response by type of malignancy is described in Table 6. A majority of evaluable patients with NSCLC responded (17 of 28). Some patients who presented with

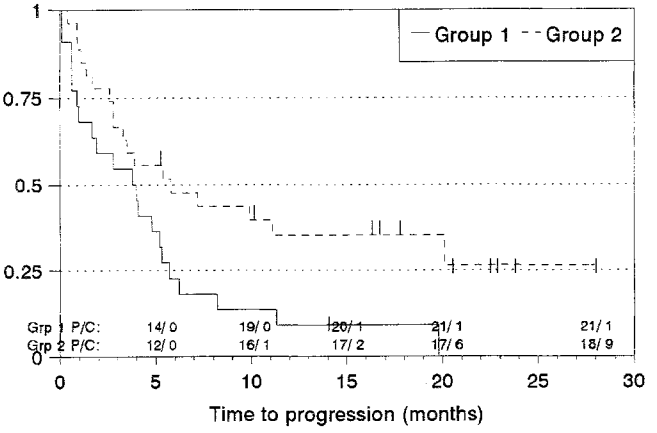

Fig. 3 TTP according to treatment group

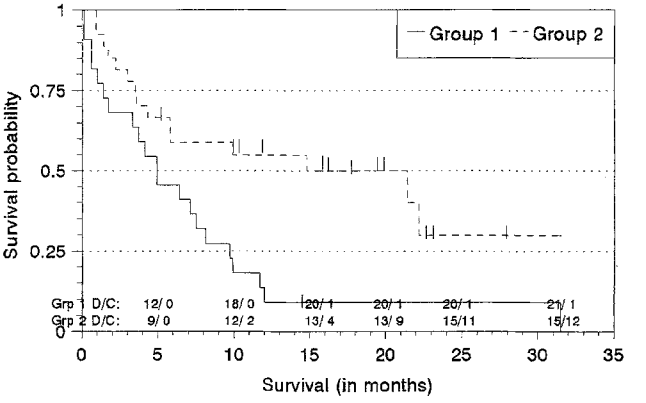

Fig. 4 Overall survival according to treatment group

"out-of-field" metastatic disease at the start of treatment were also evaluated for response at those sites. Activity included a CR in 1 patient with NSCLC, and 2 PRs in patients with metastatic head and neck and esophageal cancer, respectively. Five patients had progression of their disease. Twelve of these patients were not re-evaluated for disease status at distant sites.

TTP and survival

TTP and overall survival for the entire study group are outlined in Figs. 1 and 2. At a median follow-up of 17 months for surviving patients, the median time to progression was 4.0 months, and the median survival was 6.4 months. Currently, 10 patients remain progression-free and 13 are alive. For further analysis of this concomitant chemoradiotherapy regimen, we divided our patient population into two groups. Group 1 included 22 patients, who presented with metastatic disease that was not included in the radiotherapy field. Group 2 included 27 patients in whom all known disease was included in one contiguous radiotherapy field. We expected patients in group 2 to have more durable responses and to be a more representative group of patients for future studies of this regimen in

patients with locoregionally advanced solid tumors of the chest. The median TTPs for patients in groups 1 and 2 were 4 months and 6 months, respectively (Fig. 3). Overall, 10 patients in group 2 remain progression-free. The median survival is 5 months for patients in group 1 and 15 months for those in group 2 (Fig. 4). Overall, 12 patients remain alive in group 2, while only 1 patient in group 1 is still alive. The 2-year survival rate for group 2 patients with NSCLC is 30%.

Finally, we evaluated the site of first disease progression. The vast majority of patients progressed outside of the radiation field. Seventeen patients with NSCLC progressed outside the chest, 5 progressed within the radiotherapy field, and 1 patient progressed both within and outside of the radiation field. Eight NSCLC patients had no documented progression.

Discussion

The goal of this phase I study was to define a chemoradiotherapy regimen that would result in enhanced locoregional therapy while also having systemic activity. We conclude that high-dose cisplatin at 100 mg/m^2 on days 1 and 8 can be administered with 5-FU, HU, IFN and concomitant radiotherapy, and recommended dose level 5 for phase II testing. However, toxicity is substantial and maximal supportive care, including GCSF and nutritional support, is required. DLTs are myelosuppression and esophagitis. The use of twice-daily radiotherapy (level 7) appears to decrease the severity of early esophagitis; however, severe thrombocytopenia is prohibitive.

The inclusion of IFN in this study was based on laboratory data indicating enhancement of radiotherapy and cisplatin [2, 5, 9, 12, 15, 16, 18, 20, 24, 25, 28–30, 33, 34]. In addition, the feasibility of combining IFN with cisplatin and radiotherapy had been demonstrated in our previous phase I study [40]. Of interest was an apparent synergistic renal toxicity between cisplatin and IFN, as observed at dose level 2. We are not aware of previous reports of this toxic interaction. Additional studies are currently in progress for more careful definition of the role of IFN as a modulator of cisplatin and radiation.

The use of GCSF in this study was not initially planned. Only after dose-limiting neutropenia had been observed at dose level 4 was GCSF added; it was administered with radiotherapy (and IFN) in weeks 1 and 3. Its administration during week 2 was avoided, since increased toxicity had been reported when cell-cycle-specific drugs were administered concurrently with GCSF [4, 26, 32].

Recent studies have also indicated that administration of GCSF with radiotherapy may result in increased toxicity. Bunn et al. [3] studied the role of GM-CSF chemoradiotherapy in 213 patients with limited stage small-cell lung cancer. Patients were treated with VP-16 and cisplatin on days 1–3, and chest radiotherapy, which was also started on day 1. Patients were randomized to receive or not to receive GM-CSF on days 4–14 of all six planned chemotherapy cycles. An interim analysis demonstrated a statistically significant increase in severe thrombocytopenia and in the number of severe infections in the GM-CSF arm. Overall tumor response rates were significantly lower in the GM-CSF arm (63% vs 80%). Momin et al. [27] also reported lower median nadir platelet counts in a group of patients with NSCLC receiving chemoradiotherapy with GCSF.

On the other hand, Fushiki and Abe randomized 52 patients undergoing radiotherapy to receive GCSF or placebo concurrently with the radiation for 14 days [10]. The group receiving GCSF had no febrile episodes, and their requirements for antibiotics were lower. WBC count was also significantly higher in the group receiving GCSF.

The phase I design and the small cohort size in our study do not allow for firm conclusions on the role of GCSF with concurrent radiotherapy (and IFN). We note, however, that thrombocytopenia was not higher at dose level 5 than at level 4 and that neutropenia was ameliorated. These two dose levels differed only in that patients at dose level 5 received GCSF after dose-limiting neutropenia had been observed at level 4. Thus, in patients treated with once-daily radiotherapy, GCSF may be of benefit. On the other hand, patients receiving twice-daily radiotherapy had a high incidence of severe thrombocytopenia.

The activity of this regimen, when measured as in-field response or TTP, is encouraging, particularly in patients with all known disease included in the radiation port (group 2). The activity against clinically detectable metastatic disease appeared to be similar to that of other currently available cisplatin-based regimens. The high toxicity profile suggests that further investigations of this regimen be limited to a curative-intent treatment setting. For NSCLC, it would be of interest if this or a similar intensive concomitant chemoradiotherapy combination can result in higher survival rates than reported for a less toxic approach utilizing cisplatin and vinblastine as induction chemotherapy [8, 19]. The latter has been shown to result in median survival of 14 months and a 26% 2-year survival rate in unresectable stage III disease [8]. When patients were retrospectively assigned to stage IIIA or IIIB, median survival rates in that study were 17 months and 12 months, respectively [19]. Our regimen might also be of interest in esophageal cancer; a phase II study in that disease has been initiated at our institution.

In conclusion, two feasible dose levels (with and without GCSF) were identified for possible phase II trials. Dose levels 5 and 6 allowed for safe administration of this regimen with GCSF and single-daily-fraction radiotherapy. Since we were able to retreat more patients at level 5 during cycle 2 with the same dose, this is our recommended phase II dose level. If it was intended that the administration of GCSF be avoided, the dose level recommended would be dose level 3, although then the dose intensity of cisplatin would not be superior to that of other currently used regimens. While the use of hyperfractionated radiotherapy resulted in a lower incidence of severe esophagitis during cycle 1, more thrombocytopenia was also seen. In view of this significant myelosuppression, level 7 would be feasible only with maximal supportive

care, including platelet transfusions, and is not recommended.

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