Cancer Chemother Pharmacol (1992) 29: 178–184

Cancer Chemotherapy and Pharmacology

5-Fluorouracil, leucovorin, hydroxyurea, and escalating doses of continuous-infusion cisplatin with concomitant radiotherapy: a clinical and pharmacologic study*

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Summary. Cisplatin (CDDP), 5-fluorouracil (5-FU), and hydroxyurea (HU) have individually demonstrated activity against several solid tumors, act synergistically with each other in vitro, and may act as radiation sensitizers. Therefore, we designed a phase I study to determine the maximally tolerated dose of cisplatin as given in addition to our previously described combination of 5-FU, HU, and concomitant radiotherapy (XRT). Patients exhibiting advanced solid tumors requiring palliative XRT were eligible. The regimen consisted of 1 g HU given p.o. b.i.d. on days 1–5, 600 mg/m^2 5-FU given i.v. daily by continuous infusion (c.i.) on days 1–5, escalating doses of cisplatin starting at 10 mg/m^2 daily given by c.i. on days 1–5, and involved-field XRT carried out on days 1–5. The cycle was repeated every 14 days until the target XRT dose had been reached. In all, 19 patients were entered at the first dose level, and cumulative grade 3–4 myelosuppression was seen in 16 subjects. As no dose escalation was feasible, the chemotherapy was subsequently altered by using the above regimen for cycles 1, 3, 5, and 7 and substituting the less myelosuppressive regimen of 1 g HU given p.o. b.i.d. on days 1–5, 400 mg/m^2 5-FU given i.v. daily by c.i., and 100 mg leucovorin given p.o. 4 h on days 1–5 for cycles 2, 4, and 6. On this alternating program, 28 patients were treated with escalating doses of CDDP. The dose-limiting toxicity was again myelosuppression, which was prohibitive at a CDDP dose of 20 mg/m^2 daily. In the final phase of the protocol, 30 subjects were treated with the above alternating-cycle regimen at a CDDP dose of 20 mg/m^2 daily and a decreased HU dose of 500 mg p.o. b.i.d. in an attempt to circumvent the myelosuppression associated with this dose of CDDP. Although severe acute toxicity (cycles 1 and 2) was observed less frequently, cumulative toxicity (all cycles) remained pronounced. The other major toxicity encountered was mucositis, which was particularly pronounced in patients receiving radiation to the head and neck and following leucovorin-containing cycles. Plasma concentrations of free platinum did not correlate with the CDDP dose, possibly due to the narrow range of doses given. Pharmacodynamic modeling demonstrated that the CDDP dose and the HU dose were associated with leukopenia. Antitumor activity was demonstrated in a number of solid tumors, particularly non-small-cell lung cancer and head and neck cancer. Due to the high incidence of severe cumulative toxicity, we recommend further use of this regimen only as part of a curative treatment strategy for patients presenting with locoregionally advanced solid tumors.

Introduction

Treatment options for most patients exhibiting locally advanced or metastatic solid tumors remain extremely limited. For a majority of patients, radiotherapy for bulky lesions or chemotherapy for metastatic disease constitute temporary palliative treatment options. Curative therapy is rarely available. At the University of Chicago, we have studied the concomitant administration of combination chemotherapy and radiotherapy to patients presenting with solid tumors in an attempt to increase the local efficacy of radiotherapy through the radioenhancing effects of chemotherapy and to improve systemic tumor control through the early use of chemotherapy [30].

We initially explored the administration of 5-fluorouracil (5-FU) and hydroxyurea (HU) with concomitant radiotherapy every other week in patients exhibiting head and neck cancer [32]. Each of these two drugs has been shown to enhance the efficacy of radiotherapy in vitro [2, 22, 23, 29], and randomized clinical studies have demonstrated

* Supported in part by an American Cancer Society Clinical Oncology Cancer Development Award (to M. J. R.) and by National Cancer Institute grant CA-14599-17

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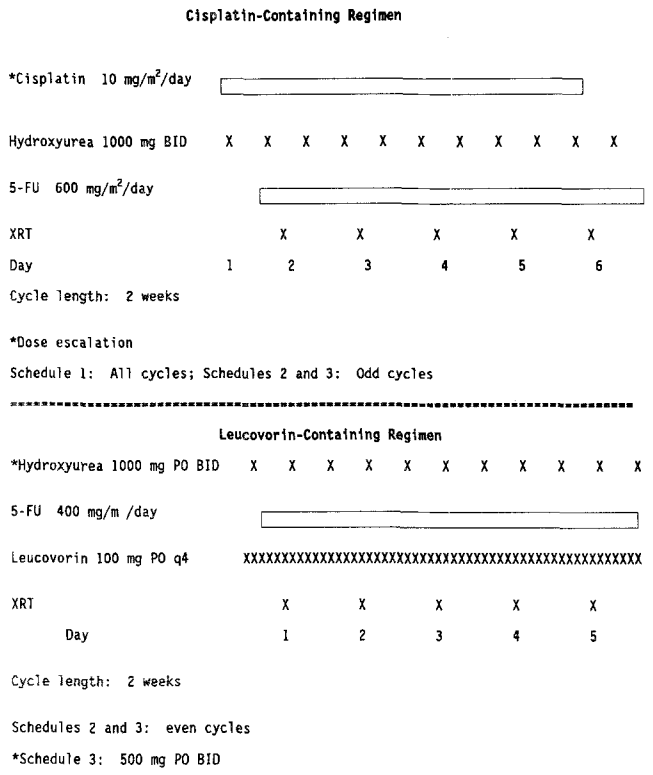

Fig. 1. Schema of the treatment protocol used in the present study

improved survival in patients receiving radiotherapy and concomitant 5-FU (pancreatic, head and neck cancer [17, 18]) or concomitant HU (brain tumors, cervical cancer [12, 16, 20]) as compared with those undergoing radiotherapy alone. In addition, the two drugs may be synergistic, since HU depletes cellular concentrations of deoxyuridine monophosphate (dUMP), thus facilitating binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase (TS) [11, 19]. After identifying the impressive local activity of this combination against head and neck cancer, we wanted to modulate this combination further by adding other drugs.

The choice of cisplatin as the third drug in this regimen was based on four factors. First, it displays high single-agent activity against many solid tumors. Second, cisplatin has been shown to act as a radiation enhancer in experimental systems [5, 8, 30]. Third, it has been shown to be synergistic with 5-FU in vitro, possibly as a consequence of increased intracellular concentrations of reduced folate following the administration of cisplatin, facilitating the formation of a stable ternary complex between 5-FdUMP, TS, and a reduced folate [21]. Thus, cisplatin may modulate 5-FU in a manner similar to that of leucovorin, which acts as a reduced folate and facilitates the formation of the ternary complex. Finally, HU and cisplatin have been postulated to be synergistic, since HU given in high doses may deplete the cell of nucleotides that are necessary for DNA repair following the administration of cisplatin [3, 14, 25, 26, 34]. For this trial, we chose to give cisplatin as a 5-day continuous i. v. infusion because it has been suggested that this schedule results in a higher area under the concentration-time curve (AUC) for non-protein-bound platinum [1, 10], which might lead to higher activity.

Our goal was to use cisplatin at doses that were compatible with high single-agent activity as well as radiation-enhancing effects during each cycle of therapy. Thus, we attempted the administration of total monthly doses of ≥ 100 mg/m^2 [5, 8, 30]. When dose-limiting myelosuppression was encountered early in the course of this study, we decided to give cisplatin on every other treatment cycle and instead to modulate the action of 5-FU in the intervening cycles using high doses of oral leucovorin (LV). We have previously demonstrated that oral administration of LV results in plasma concentrations of reduced folate that are sufficient to produce modulation of 5-FU in vitro [31, 33]. We postulated that modulation of 5-FU by LV in this combination would increase the activity of 5-FU yet induce less myelosuppression, thus enabling further escalation of the cisplatin dose during the alternate cycles.

This report presents the pattern of toxicities encountered, a pharmacologic analysis of ultrafilterable platinum plasma concentrations as measured in selected patients, and the response rate observed according to the tumor types studied. Pharmacodynamic models relating drug doses to observed myelosuppression and mucositis are also described.

Patients and methods

Patients. Eligibility criteria included histologic documentation of neoplastic disease that was not considered to be curable by standard therapy and was located predominately in a site that was amenable to palliative radiotherapy, a performance status of ≤ 3 (Cancer and Leukemia Group B), a normal complete blood count, a 24-h creatinine clearance of ≥ 50 ml/min, and written informed consent of the patients. There was no exclusion based on the extent of prior therapy. Pretreatment patient evaluation included a history and physical examination along with careful documentation of measurable disease when applicable, a complete blood count, serum chemistries, determination of 24-h creatinine clearance, a chest radiograph, and at least one radiographic test (e. g., computerized tomography or magnetic resonance imaging) to document measurable disease.

Treatment plan. The treatment protocol during the first phase of this study (schedule 1) called for administration of a 5-day continuous infusion of cisplatin along with continuous-infusion 5-FU and oral HU together with concomitant radiotherapy every other week. (Fig. 1). Following initial hydration with 500 cc normal saline (NS) over 3 h, half of the daily cisplatin dose was given in 1,000 cc 5% dextrose in NS (D_5NS) over 12 h for a total of 10 doses starting at 7:00 p. m. on day 1 of each cycle. The dose of cisplatin on this initial schedule was 10 mg/m^2 daily. The dose of 5-FU was 600 mg/m^2 per day, with the total daily dose being delivered in 1,000 cc 5% dextrose in water (D_5W) over 24 h starting at 7:00 a. m. on day 2. The HU dose was 1 g given p. o. every 12 h for a total of 11 doses starting at 7:00 p. m. on day 1, with 1 daily dose preceding radiotherapy by 2 h. Radiotherapy was carried out on days 2–6 at daily fractions of 180–200 cGy. Total radiotherapy doses depended on the tumor type and location and on the extent of prior radiation treatment. On completion of the cisplatin infusion on day 6, 500 cc NS along with 20 mEq KCl was infused over 2 h, after which 500 cc D_5W together with 4 g magnesium sulfate was given over 2 h. No therapy was undertaken on days 7–14.

When cumulative dose-limiting toxicity was seen at this dose level, the regimen was changed (schedule 2) in that cisplatin was given only during odd cycles (1, 3, 5, and 7) and LV was substituted for cisplatin

Table 1. Patients' characteristics

	Number	Percent
Patients entered	77	100
Schedule 1	19	25
Schedule 2	28	36
Schedule 3	30	39
Age (years):		
Median 60		
Range 24–80		
Men	46	64
Women	31	36
Performance status:		
0	3	4
1	42	55
2	25	32
3	7	9
Prior therapy:		
None	28	36
Surgery	32	42
Radiation	24	31
Chemotherapy	19	25
Tumor origin:		
Lung	26	34
Head and neck (all histologies)	26	29
Breast	9	12
Colorectal	4	5
Other	12	21

during even cycles (2, 4, and 6; Fig. 1). The LV was given orally at a dose of 100 mg every 4 h from 7:00 p.m. on day 1 until completion of the 5-FU infusion on day 6. During LV-containing cycles, the 5-FU dose was decreased to 400 mg/m^2 daily. In the second phase of this study, the dose of cisplatin ranged from 10 to 20 mg/m^2 per day in four dose levels (10, 13, 16, and 20 mg/m^2 daily). Dose escalation was performed after a minimum of three patients had been evaluated for a minimum of two cycles at the preceding dose level. There was no escalation of the cisplatin dose in individual subjects. The maximally tolerated dose (MTD) of cisplatin was defined as the dose at which >50% of the patients developed acute (cycles 1 or 2) grade 3 or 4 toxicity; if grade 3 or 4 toxicity was seen in 1–2 of the first 3 patients at a given dose level, a minimum of 6 subjects were treated. In the third and final phase of the study (schedule 3), the dose of HU was decreased to 500 mg given twice daily, whereas the doses of and schedules for cisplatin, 5-FU, and LV remained as defined for the second phase (Fig. 1).

Hematologic toxicities and mucositis were assessed at least once weekly during protocol therapy. In the presence of a WBC of <2,500/μl or a platelet count of <100,000/μl, the dose of cisplatin was decreased to 75% of the calculated dose (if applicable) and that of HU was reduced to 50% of the planned level. Following a WBC of ≤2,000/μl or a platelet count of ≤75,000/μl, 50% of the planned dose of cisplatin and 500 mg HU daily were given. The cycle was postponed for 1 week in the presence of a WBC <1,000/μl or a platelet count of <50,000/μl. These dose adjustments were based on hematologic parameters obtained during days 1–3 of a cycle. For myelosuppression encountered on days 4 and 5, no adjustments were made. In addition, the dose of cisplatin was decreased by 50% in the presence of a creatinine clearance of 30–50 cm^3/h (calculated according to Cockcroft and Gault [4] and this drug was withheld when the creatinine clearance reached <30 cm^3/h. The 5-FU dose was adjusted when mucositis or dermatitis had been observed in the preceding cycle of the same regimen. In the presence of grade 3 mucositis or dermatitis, the dose was decreased by 33%, and following grade 4 mucositis it was reduced by 50%. When persistent mucositis or dermatitis graded ≥3 was encountered on day 14, the next cycle was delayed for 1 week.

Standard response criteria defined a complete response (CR) as representing the complete disappearance of 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 (indicator lesion), a lack of growth of other existing lesions, and the absence of new lesions for at least 28 consecutive days. Stable disease defined was defined as either no change or a decrease of <50% in the size of an indicator lesion, and progressive disease was defined as an increase of ≥25% in the product of perpendicular diameters of the indicator lesion or the appearance of new metastatic lesions.

Statistical analysis. Associations between the severity of mucositis and both the type of schedule (cisplatin versus cisplatin/leucovorin) and the site of cancer (head and neck vs all other sites) were analyzed using the chi-square test [24]. Statistical significance was set at a P value of 0.05. Least-squares regression and Pearson's correlation coefficient [9] were used to measure the strength of linear association between the plasma concentration and the dose of cisplatin.

Multivariate linear regression to investigate pharmacodynamic models was performed by forward stepwise regression [6]. Hematologic toxicities as measured by the natural log of the WBC or platelet nadir were used as dependent variables. Comparison of such models was assessed by the F test and overall correlation. Individual variables were maintained in the model for statistical significance of $P \leq 0.15$. Stepwise logistic regression was carried out to identify factors associated with an increased risk for severe mucositis. The dependent variable was a bivariate measure (grade 0–1 vs grade 2–4). Significance was assessed using the chi-square test. The dose intensity of cisplatin, 5-FU, and HU was calculated by dividing the total dose of each drug per square meter of body surface area that was given to a patient by the total duration of treatment in weeks.

Pharmacologic studies. To assess the concentration of total filterable platinum in plasma, 7–10 cc blood was collected into a heparinized Vacutainer tube on days 3 and 5 of chemotherapy. Immediately after collection, plasma was separated by centrifugation, transferred into a presoaked Amicon (Danvers, Mass) membrane cone, and then centrifuged at 300 g for 30 min. The ultrafiltrate was transferred into a cryogenic tube and stored at –70° C until analysis.

For analysis of platinum concentration in the samples, the plasma ultra-filtrates were evaporated to dryness under nitrogen and reconstituted in one-tenth of the initial volume, and the platinum content was assessed by flameless atomic absorption spectrometry using a Perkin Elmer 1100 atomic absorption spectrometer (Perkin Elmer Corp., Norwalk, Conn.) fitted with an HGA 400 furnace controller and an AS40 autosampler. Platinum concentrations were calculated from a concomitantly performed standard curve for platinum absorbance.

Results

From December 1987 to February 1989, 77 patients were entered on this protocol. The pretreatment characteristics of the subjects are listed in Table 1. The median age was 60 years, and the majority of patients showed a performance status of 1 or 2. Subjects presenting with a variety of solid tumors were treated on the protocol, but most had been diagnosed as having either squamous-cell head and neck cancer (22 patients), non-small-cell lung cancer (26 subjects), or breast cancer (9 cases). Most patients had received prior therapy with surgery, radiotherapy, and/or chemotherapy. All subjects were treated with palliative intent. In all, 19 patients were treated on the first schedule; 28, at the 4 cisplatin dose levels of the second schedule; and 30, on the third schedule.

Table 2. Hematologic toxicities

	Number of patients	Median WBC nadir (range)	Median platelet nadir (range)	% WBC Grade			% Platelet Grade			Number of Neutropenic episodes	Fatal episodes
				2	3	4	2	3	4		
Schedule 1:											
Acute	19	2.3 (0.3–5.4)	139 (12–260)	26	26	11	11	11	16	5	Sepsis (1 patient)
Cumulative	18	1.1 (0.3–2.7)	44 (12–180)	17	44	44	6	38	33		Pulmonary embolus (1 patient)
Schedule 2: Level 1											
Acute	4	2.4 (1.5–4.6)	158 (23–237)	50	25	0	0	0	25	0	
Cumulative	4	1.2 (0.8–2.9)	60 (15–223)	25	25	50	0	25	50		
Level 2											
Acute	6	2.5 (1–5.3)	133 (45–193)	33	33	0	17	17	0	0	
Cumulative	6	1.8 (1–4.7)	73 (16–243)	0	67	0	33	33	17		
Level 3											
Acute	9	1.9 (0.7–6.8)	113 (42–576)	11	33	22	0	33	0	0	Bowel perforation)
Cumulative	6	1.7 (0.7–3)	76 (15–157)	17	50	17	0	50	0		(1 patient
Level 4											
Acute	8	1.8 (0.8–2.8)	61 (5–204)	38	38	25	13	38	25	0	
Cumulative	6	1 (0.8–2.1)	29 (24–49)	17	33	50	0	83	17		
Schedule 3:											
Acute	30	2.9 (0.1–15.1)	114 (9–443)	27	23	10	3	27	10	4	Sepsis (1 patient)
Cumulative	24	1.7 (0.1–7.9)	84 (8–443)	21	50	21	21	33	29		

Toxicities

The occurrence of hematologic toxicities by schedule and dose level is summarized in Table 2. Acute toxicities (cycles 1 and 2 only) and cumulative toxicities (all cycles in patients receiving >2 cycles) are presented separately.

For the 19 patients treated on schedule 1, the 2-week cycle duration did not enable complete recovery from toxicity for a given cycle, thus resulting in pronounced dose-limiting cumulative toxicity. In all, 7 of 19 patients (37%) developed grade 3 or 4 myelosuppression during cycles 1 or 2, whereas 16 of 18 (88%) did so when all treatment cycles were evaluated. Thus, cumulative myelosuppression precluded escalation of the cisplatin dose on this schedule.

A total of 28 patients were treated on schedule 2, and escalation of the cisplatin dose from 10 to 20 mg/m^2 daily was carried out in 4 dose levels. As shown in Table 2, hematologic toxicity was encountered at all dose levels of schedule 2. Acute toxicities were more pronounced on levels 3 and 4, at which an increased incidence of grade 4 neutropenia was observed. In all, 5 of 9 patients (55%) on dose level 3 developed grade 3–4 acute myelosuppression. Because this lasted only 1 day in 1 of these subjects, it was decided to proceed to level 4, on which 63% of the patients developed myelosuppression graded >2. Cumulative toxicities were also pronounced on level 4, with 83% of our patients developing grade 3 or 4 neutropenia and 100% exhibiting grade 3 or 4 thrombocytopenia. The latter was particularly evident in the range of nadir platelet counts observed in patients who were treated on level 4 ($24–49 \times 10^3/\mu l$).

Finally, on schedule three, the dose of cisplatin was fixed at the target dose of 20 mg/m^2 given every other cycle, and the HU dose was decreased to 500 mg given twice daily on all cycles in a further attempt to ameliorate myelosuppression. As shown in Table 2, this resulted in a lower incidence of severe acute toxicity; however, cumulative toxicity remained pronounced.

To determine whether the lower HU dose on schedule 3 would enable the administration of more cisplatin, we calculated the dose intensity of cisplatin, 5-FU, and HU at all dose levels used in the study. Table 3 presents the mean dose of each drug as given in milligrams per square meter of body surface area for each week of therapy as well as the percentage of the intended weekly dose that this mean reflected. As demonstrated, schedule 3 enabled the delivery of total doses of cisplatin similar to those used on

Table 3. Dose intensity

	Number of cycles	CDDP		5-FU		HU	
		mg	% of intended dose	mg	% of intended dose	mg	% of intended dose
Schedule 1	106	19.6	78	1365	91	4457	89
Schedule 2:							
Level 1	19	12.6	84	1134	88	4000	80
Level 2	35	16.8	88	1224	94	4488	90
Level 3	36	19.8	92	1190	94	4335	87
Level 4	30	21.4	79	1045	82	3376	67
Schedule 3	147	23.1	85	1148	90	2157	86

Data are expressed in mg/m^2 per week

Table 4. Schedule and site dependence of mucositis

	Head and neck cancer		Schedule (all patients)		Schedule (head and neck cancer patients)	
Mucositis	No	Yes	1	2,3	1	2,3
Grade 0–1	85%	52%	95%	65%	89%	31%
Grade 2–4	15%	48%	5%	35%	11%	69%
	$P = 0.003$		$P = 0.01$		$P = 0.011$	

level 4 of schedule 2, whereby the incidence of severe or life-threatening toxicity was lower. However, this was achieved by substantially lowering the HU dose.

A significantly higher incidence of grade 2–4 mucositis was seen in patients receiving radiation to the head and neck and in subjects who were treated with the LV-containing regimen on schedules 2 and 3 (Table 4). The latter was particularly pronounced in patients receiving head and neck radiation. Mucositis graded ≥ 2 was seen almost exclusively in that group of subjects, indicating that toxicity to the mucosa by 5-FU was increased in the presence of LV and radiation, despite a 33% reduction in the dose of 5-FU as compared with that used in the cycles containing cisplatin. Other extra-medullary toxicities, including renal toxicity, were generally mild to moderate in degree and were not dose-limiting on any of the schedules tested.

Pharmacologic studies

Concentrations of ultrafilterable platinum in plasma were measured in 23 patients treated on this protocol. Samples were obtained on days 3 and 5 of each cisplatin-containing cycle from every patient evaluated, except for one in whom drug levels were measured only during the first three cycles of therapy. For this analysis, we included all samples taken from patients who received the full dose of cisplatin for 5 days of a given cycle. A total of 50 cycles were thus analyzed. The median platinum plasma levels and ranges are outlined in Table 5. As noted, the measured plasma concentrations of ultrafilterable platinum were highly variable within each group of patients, indicating substantial interpatient pharmacokinetic variability.

Table 5. Plasma concentrations of ultrafilterable platinum as a function of cisplatin dose[a]

Cisplatin dose	Day 3		Day 5	
	Cycles	Median (range)	Cycles	Median (range)
10 mg/m^2/daily	26	9 (1.1–21)	29	10.5 (1.5–51)
13 mg/m^2/daily	7	14.3 (9.8–17.3)	8	17.5 (1.5–24)
16 mg/m^2/daily	2	6 (6)	1	7.5
20 mg/m^2/daily	15	11.3 (3.8–27.8)	12	17.5 (2.3–54.8)

[a] For patients who received 100% of the dose for 5 days
Data are expressed in ng/ml

Table 6. Multivariate models of hematologic and nonhematologic toxicity: linear model of Ln[a] and logistic model of the risk of severe mucositis

Variable	Beta coefficient	*P* value
Ln (WBC nadir)		
Ln (WBC pretreatment)	0.27	0.11
HU dose (cycle 1)	–0.09	0.02
Cisplatin dose (cycle 1)	–0.01	0.02
Risk of severe mucositis:		
Head and neck primary[b]	2.22	0.0009
Cisplatin schedule[c]	2.30	0.011

[a] WBC nadir
[b] Head and neck primary: 0, no; 1, yes
[c] Cisplatin schedule: 0 = all cisplatin; 1 = alternating cisplatin/LV cycles

Linear regression analysis disclosed no correlation between the plasma concentrations of ultrafilterable platinum measured on day 5 and the dose of cisplatin delivered ($r^2 = 0.05$) and revealed no correlation between the plasma concentration of ultrafilterable platinum measured on day 3 (obtained approximately 36 h after the start of the drug infusion) and the cisplatin dose ($r^2 = 0.02$).

Pharmacodynamic models

Multivariate linear regression was employed to investigate pharmacodynamic models relating hematologic toxicity (natural log of both, WBC nadir and platelet nadir) to doses of the three drugs used in this regimen. As described above, on schedules 2 and 3, LV replaced cisplatin on even cycles (2, 4, and 6), and the HU dose was decreased to 500 mg b.i.d. on schedule 3. The pharmacologic variables tested were the total dose on cycle 1 and on cycle 2 separately (cisplatin, HU, 5-FU) and the schedule type (1 vs 2 and 3). The demographic variables tested included age, sex, pretreatment creatinine clearance, WBC and platelet count, and the site of cancer (head and neck vs all others).

The best model for WBC nadirs comprised three variables (Table 6). A lower WBC nadir was associated with a higher cisplatin dose on cycle 1, a higher HU dose on cycle 1, and a lower pretreatment WBC (three-variable model; $r^2 = 0.12$, $P = 0.044$). An adequate model for platelet nadirs could not be constructed from these data, although the HU dose was found to show a marginal correlation with this parameter.

Finally, a logistic model was used to identify variables associated with an increased risk of severe (grade 2–4) mucositis (Table 6) as observed in 19 of our patients. Two variables were found to be associated with a higher risk: the inclusion of LV in the regimen and cancer of the head and neck (two-variable model; $\chi^2 = 20.61$, $P < 0.0001$).

Response

A total of 55 patients were assessed for response, including 26 presenting with non-small-cell lung cancer; among the latter, 9 had stage IIIB disease, 13 had stage IV disease, and 4 had recurrent disease. Of 19 evaluable patients, 1 achieved a CR, 8 showed a PR, and 10 exhibited no response. Of 10 patients with metastatic disease, 3 responded in nonirradiated sites of disease, indicating the activity of this combination of drugs in the absence of radiation.

A total of 22 patients presenting with squamous-cell or salivary-gland cancer of the head and neck were treated on this protocol; 9 had recurrent disease, 6 exhibited metastatic disease, 2 had primary unresectable disease, and 5 displayed residual microscopic disease following initial surgery. In all, 15 subjects were assessed for response; 7 achieved a CR, 4 showed a PR, and 4 exhibited no response (3 within the radiation field and 1 outside the field).

Nine patients with metastatic breast cancer were treated on this protocol. Six of these were evaluated for response; four responded, two completely and two partially. Additional responses were seen in three patients presenting with colorectal cancer; in one of two subjects each who exhibited gastric, anaplastic thyroid, or prostate cancer; and in one patient afflicted with esophageal cancer. Two subjects presenting with metastatic sarcoma and one patient each who exhibited pancreatic cancer, melanoma, or mesothelioma failed to respond. Most of the observed responses were of short duration, reflecting the advanced nature of the diseases treated.

Discussion

We studied the interaction of cisplatin, 5-FU (± LV), HU, and concomitant radiotherapy on an alternating-week schedule. Escalation of the cisplatin dose as initially planned proved to be infeasible and a different regimen was conceived, resulting in cisplatin administration only during every other cycle. Systemic toxicity consisting of acute and cumulative myelosuppression was dose-limiting, and cisplatin doses exceeding 100 mg/m^2 monthly could not be given in this regimen on any schedule. Myelosuppression was particularly pronounced at the higher cisplatin doses given on levels 3 and 4 of schedule 2. The substitution of LV for cisplatin during even-numbered cycles enabled escalation of the cisplatin dose during cisplatin-containing cycles, albeit not beyond the total dose originally delivered on schedule 1 (i.e., 100 mg/m^2 every 4 weeks). At the same time, LV-containing cycles resulted in a higher incidence of severe mucositis, particularly in patients receiving head and neck radiation. This was observed despite a reduction in the dose of 5-FU during LV-containing treatment cycles.

The lack of correlation between the cisplatin dose and the plasma concentrations of free platinum in this study was unexpected. It may be attributable to the narrow range of cisplatin doses used and to the high interpatient variability of plasma concentrations observed at each cisplatin dose level. The results of pharmacodynamic modeling, however, are consistent with our clinical observation in that a higher cisplatin dose was associated with leukopenia. Likewise, HU produces myelosuppression as its major side effect, usually in the form of leukopenia [7].

The rationale for choosing a 5-day infusion schedule for cisplatin in this study was based on the higher AUC value for non-protein-bound platinum that has been suggested by some [1, 10] but not all investigators [28] for that schedule. It was also felt that the infusion circumvented the need for definition of a precise interval between the administration of cisplatin and the delivery of radiotherapy. Animal studies [13, 15, 27] demonstrated the highest degree of enhancement when cisplatin was given on a divided daily schedule prior to radiation. Moreover, on that schedule, lower degrees of normal tissue toxicity were also observed. No comparative trial in humans has studied the timing of cisplatin administration in relation to concomitant radiation in terms of toxicity or efficacy. Considering the observation of myelosuppression as the dose-limiting toxicity in this study and a previous trial [10], a different cisplatin schedule might be preferable for this combination if it resulted in less myelosuppression.

The activity seen for this regimen in some patients exhibiting advanced solid tumors suggests that further clinical exploration of this combination may be warranted. Current trials at our institution aim at decreasing the toxicity of this regimen through the use of a different cisplatin schedule and the addition of a colony-stimulating factor in patients presenting with head and neck cancer.

Acknowledgements. We wish to thank Drs. M. F. Kozloff, R. Desser, C. Shapiro, and R. Jacobs for treating their patients in this study and Ms. S. Jarman for preparing the manuscript.

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