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High-dose cisplatin in advanced head and neck cancer*, **

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Summary. In 22 patients with advanced squamous cell carcinoma of the head and neck we evaluated the efficacy and toxicity of 200 mg/m^2 cisplatin administered in 3% NaCl with vigorous hydration. Six patients had previously untreated stage IV disease and 16 patients had recurrent disease, including eight with prior chemotherapy including low-dose cisplatin and carboplatin. Cisplatin was administered as a brief infusion, either 40 mg/m^2/day × 5 or 50 mg/m^2/day × 4, every 28 days. Objective responses were observed in 16 of 22 (73%) patients, including 5 of 6 (83%) previously untreated patients and 11 of 16 (69%) patients with recurrent disease. This included two complete responses, one confirmed pathologically. Fifty-seven courses of drug were administered and toxicity was monitored with serial creatinine clearance determinations, audiograms, and sensorimotor exams. Neuropathy and ototoxicity were dose-limiting and led to the stopping of treatment in 12 of the 16 responders after one to four courses (median three courses). Only two responding patients continued treatment until disease progression occurred at 3 and 4 months after achieving maximum response. Acute, transient nephrotoxicity occurred in four patients; two were retreated. Moderate myelosuppression occurred in all patients but was not treatment-limiting. For most patients the maximally tolerated number of courses was three. The median survival time was 33.5 weeks for recurrent disease patients, 108 weeks for newly diagnosed patients. This regimen is not recommended for the palliation of recurrent disease. However, the very high response rate suggests that high-dose cisplatin may have a useful role in induction or adjuvant chemotherapy regimens.

Introduction

Cisplatin is one of the few cytotoxic agents with well-established activity against head and neck cancer. With standard doses of 80–120 mg/m^2 administered every 3–4 weeks, responses are observed in approximately 33% of recurrent disease patients and 40% of previously untreated patients [7, 13, 14, 16, 17]. In early phase I testing, nephrotoxicity was frequent and dose-limiting [2, 5, 6, 12, 15]. The recommended dose per course was 75–90 mg/m^2. The development of regimens utilizing parenteral hydration and furosemide and mannitol diuresis decreased the incidence of nephrotoxicity and led to a maximum recommended dose for clinical trials of 120 mg/m^2 per course [4, 11]. Recently, investigators have reported the safe administration of up to 200 mg/m^2 in divided doses using 3% saline as the diluting solution [9, 10]. In these trials no significant changes in creatinine clearance were observed in patients with normal renal function and no prior exposure to cisplatin. The patient population in these trials consisted primarily of young males with testicular cancer and women with gynecologic malignancies treated with high-dose cisplatin-containing combination chemotherapy.

In January 1984, we initiated a phase II trial of high-dose cisplatin in patients with advanced head and neck cancer. The objectives were severalfold: (1) to determine the feasibility of administering a course of 200 mg/m^2 cisplatin with hypertonic saline and concomitant hydration to an older population of patients with head and neck cancer; (2) to determine and characterize the dose-limiting toxicities; (3) to determine the maximum number of courses tolerated prior to the development of limiting toxicities; and (4) to determine the complete and partial response rates.

Materials and methods

Patients. Eligible patients had advanced, recurrent carcinoma arising from a primary site in the head and neck or had newly diagnosed stage IV disease. All patients had histologically confirmed squamous cell carcinoma, bidimensionally measurable disease, and had not received radiotherapy or chemotherapy within 4 weeks of study entry. Prior exposure to conventional dosage cisplatin was allowed. Patients were required to have a Karnofsky performance status of at least 60%, a life expectancy of at least 12 weeks, adequate bone marrow reserve (WBC > 3500 cells/μl, platelets > 100000 cells/μl), no evidence of obstructive liver disease (bilirubin < 2.0 mg%), serum creatinine of < 2 mg/dl and 24-h creatinine clearance of > 60 ml/min. There was no age limitation; however, patients over the age of 70 were required to have a perform-

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ance status of at least 70% and creatinine clearance of at least 80 ml/min. Patients with a history of peripheral neuropathy or an abnormal sensorimotor examination were excluded. Adequate auditory function, determined by audiometry, was required. A hearing loss in one ear could not exceed 30 dB at 500, 1000, and 2000 Hz. All patients were able to give meaningful, informed consent. This study was approved by the human investigations review boards at the University of Michigan and Ann Arbor VA Medical Centers.

Treatment plan. Patients were treated with a total dose of 200 mg/m^2 cisplatin repeated every 28 days. The dose was divided over 5 days (40 mg/m^2) or 4 days (50 mg/m^2) in an attempt to shorten hospitalization time. Prior to treatment, patients received overnight hydration with normal saline plus 20 mEq KCl/l at 125 cc/h. Four hours prior to drug administration the hydration was increased to 250 cc/h and this was maintained for 4 h after treatment. The pretreatment hydration rate was then resumed and the sequence repeated for each daily treatment. The cisplatin dose was mixed in 250 cc of 3% NaCl and infused over 30–45 min. Twenty milligrams of furosemide was administered intravenously at the start of the cisplatin infusion. Total intake and output were carefully monitored.

Prior to each course of cisplatin, patients underwent a complete physical examination which included sensorimotor testing, an audiogram, and assessment of measurable disease parameters. Laboratory studies included 24-h creatinine clearance, serum electrolytes, BUN, creatinine, CBC, and platelet count. During treatment, patients were monitored with daily serum electrolytes, BUN, and creatinine determinations. CBC, platelet count, and serum magnesium were determined on days 1 and 5. Monitoring between treatments consisted of weekly CBC and differential count, platelet count, serum electrolytes, creatinine, and Mg^{2+}.

Subsequent cycles were attenuated to 75% of the dose of the preceding cycle if the nadir WBC was less than 1500 cells/μl or the nadir platelet count less than 50000 cells/μl. On day 28, if the WBC was less than 3500 cells/μl or platelets were less than 100000 cells/μl treatment was held until recovery. Treatment was otherwise continued until the development of progressive disease or the occurrence of other nonhematologic toxicity. Toxicity requiring study termination included neuropathy of at least grade 2 (defined as absent deep tendon reflexes, motor weakness, and peripheral nerve pain), symptomatic high-frequency hearing loss (3000–8000 Hz range) or any hearing loss in the speaking range (350–2000 Hz),or a drop in creatinine clearance to less than 60 ml/min. All patients with an asymptomatic high-frequency hearing loss were informed and consent was obtained to continue therapy. An adequate trial consisted of 4 weeks of treatment and toxicity monitoring.

Complete response (CR) was defined as disappearance of all evidence of tumor, including normalization of X-rays and biochemical tests, for a minimum of 4 weeks; partial response (PR) as a 50% or greater decrease in the sum of the products of the greatest perpendicular diameters of all lesions for a minimum of 4 weeks without the appearance of any new lesions; stable disease as a measurable response less than that required for PR or a less than 25% increase in the sum of the products of the greatest perpendicular diameters for a minimum of 4 weeks; and progression as unequivocal increase of at least 25% in the size of any measurable lesion or the appearance of new lesions.

Results

Twenty-two patients were treated and all were evaluable for response and toxicity. The first 11 patients entered into the trial were treated on the 5-day schedule. Patient characteristics are detailed in Table 1. Six patients with stage IV disease were previously untreated. Three of these patients had bulky, unresectable disease, one had pulmonary metastases, and two were potentialy resectable ($T_2N_2M_0$ tonsil, $T_2N_3M_0$ hypopharynx). Two of the eight patients previously treated with chemotherapy had received cisplatin-containing adjuvant chemotherapy only. Two patients had prior exposure to cisplatin in low dosage (80 mg/m^2 every 4 weeks) for treatment of recurrent disease and two patients had prior exposure to carboplatin.

The response rate according to prior treatment is shown in Table 2. Among the 22 patients there were two CR and 14 PR (73% CR + PR). One CR in a previously untreated patient was confirmed pathologically after surgical resection. Three of the four patients who had received prior cisplatin in lower doses responded. These patients consisted of one prior responder to a cisplatin-containing

Table 1. Patient characteristics

No. of patients	22
Median age (range)	53 (24–65)
Median performance status (range)	70 (50–90)
Males/females	19/3
Prior treatment	
No treatment	6
Surgery	12
Radiation therapy	15
Chemotherapy	8
Cisplatin – 4	
Carboplatin – 2	
Primary site	
Oral cavity	4
Oropharynx	9
Pyriform sinus	3
Larynx	1
Nasopharynx	2
Hypopharynx	2
Unknown primary	1
Sites of measurable disease	
Local-regional	17
Local-regional + distant	3
Distant only	2

Table 2. Results

Response	Total	No prior treatment	Recurrent disease
Complete (CR)	2	1	1
Partial (PR)	14	4	10
Stable	1	0	1
Progression	5	1	4
CR + PR/no. of pts	16/22 (73%)	5/6 (83%)	11/16 (69%)

adjuvant chemotherapy regimen and two recurrent disease patients, one refractory to low-dose cisplatin and one initial nonresponder. Both carboplatin-treated patients entered into the trial were nonresponders to carboplatin. One of these responded to high-dose cisplatin.

A total of 57 courses of high-dose cisplatin were administered, 30 to patients on the 5-day treatment schedule and 27 to those on the 4-day schedule. Hematologic toxicity affecting all three blood elements was observed in all patients (Table 3). There was a trend for a delay in recovery with successive doses; however, count nadirs did not vary appreciably after one or five courses. Nine patients had treatment delays for prolonged recovery from myelosuppression. However, only four patients required a 25% dose reduction. There was one admission for a febrile episode in a granulocytopenic patient who was blood-culture negative. There was no difference in hematologic toxicity between the 5-day course and the 4-day course.

Neuropathy and ototoxicity were the most common nonhematologic toxicities observed (Table 4). Six patients developed a grade 2 peripheral neuropathy while on study. One of these patients, removed from study for ototoxicity after three courses, had further increase in his peripheral neuropathy off treatment, eventually becoming bedridden (grade 3). The time course for the development of symptoms of neuropathy was variable, ranging from 2 to 5 months from the start of cisplatin. No improvement was observed after stopping treatment, perhaps due to the brief survival time of most patients. A complete set of serial audiograms was not obtained in five patients. Of the 17 sets evaluable, 14 showed a high-frequency hearing loss, including patients who also demonstrated a loss in the speaking range. Repeat audiograms at intervals for up to 6 months after stopping treatment showed no reversibility in ototoxicity.

Other observed toxicities were nausea and vomiting, grade 1–2 in 16 patients and grade 3 requiring hydration in one. All patients were treated with metochlopramide containing antiemetic regimens. Diarrhea, not clearly drug-related, occurred in four, and mild alopecia was noted in six patients. Transient nephrotoxicity occurred in four patients, with maximum creatinine levels of 6.0, 3.9, 2.7, and 2.1 mg/dl. Two were retreated without recurrence of creatinine elevation above 2 mg/dl. The other two patients were taken off study, one because of progressive disease and the other because of ototoxicity. In four patients nephrotoxicity was monitored by measuring daily excretion of the tubular enzymes alanine aminopeptidase and *N*-acetyl-β-D-glucosaminidase. Enzyme and total protein excretion did not vary significantly from determinations made in patients receiving a single 100 mg/m^2 dose [15]. None of these four patients experienced increases in serum creatinine.

The primary reason for stopping cisplatin treatment in the majority of responding patients (12 of 16) was the development of toxicity (Table 5). Six patients had progressive disease after one or two courses of cisplatin. Two patients who had brief PR lasting 4 and 5 months respectively had concurrent neurotoxicity and ototoxicity warranting removal from study. In 12 other responding patients, treatment was stopped because of the development of either ototoxicity (nine patients) or neuropathy (three patients). One responding patient refused to travel to our center and was taken off study. One patient with bulky unresectable disease achieved maximum response (PR) after three courses and was taken off study to receive full-course radiotherapy. No patient was removed from study because of nephrotoxicity. Disease progression was noted within 2 months of stopping cisplatin in all patients. The median survival time of the 16 recurrent disease patients was 33.5 weeks (range 18–66 weeks). The median survival time of the six newly diagnosed patients was 108 weeks (range 21–121+ weeks).

Table 3. Hematologic toxicity

	Median nadir (range)	Median day of nadir (range)	Median day of recovery (range)
WBC	2600 (700–5800)	21 (15–34)	30 (22–77)
Granulocytes	984 (119–2540)	21 (10–69)	30 (21–77)
Platelets	116 000 (9000–206 000)	16 (11–41)	22 (18–55)
Hb decrease	>2.0 g – 15 patients		

Table 4. Nonhematologic toxicity

Toxicity ototoxicity[a]	Median loss (range)	No. of patients
3000–8000 Hz	45 dB (15–60)	14
1000–2000 Hz	20 dB (10–40)	2
Neuropathy grade		
1		4
2		5
3		1
Nausea/vomiting		17
Diarrhea		4
Alopecia (mild)		6
Nephrotoxicity	(*Cr* >2.0 mg/dl)	4

[a] Seventeen evaluable patients

Table 5. High-dose cisplatin: reasons for study termination

	No. of patients	Courses completed
Progressive disease	8	5[a], 4[a], 2, 2, 2, 1, 1, 1
Ototoxicity	9	3, 3, 3, 3, 3, 3, 2, 2, 1
Neuropathy	3	4, 4, 2
Refused treatment	1	2
Maximum response	1	3
Total	22	

[a] Concurrent neuropathy and ototoxicity

Discussion

The armamentarium of useful drugs to treat head and neck malignancies is very limited. Cisplatin is one of the few agents that have been studied closely enough to establish the response rate and limiting toxicities in conventional dosage regimens. This trial demonstrated the feasibility of administering a 200-mg/m^2 divided dose to head and neck

cancer patients. The method of hydration was less vigorous than that used by other investigators [1, 9]. The incidence of acute, reversible, nephrotoxicity was 18%. In all four patients, serum creatinine elevation occurred after the first cycle and returned to normal. Litterst has postulated that administration of cisplatin in hypertonic saline lowers binding to plasma proteins and tissue binding sites with resultant decrease in nephrotoxicity [8]. The smaller daily dose and vigorous hydration, including the diuretic effects of 3% NaCl, may play a significant role in this protective renal effect. Clearly this mechanism does not protect against other toxicities. Ototoxicity and neuropathy were the major toxicities observed, resulting in the early withdrawal of 12 responding patients after a median of three courses (range one to four courses). Of note is the fact that three of the four patients who tolerated four or five courses before the development of limiting toxicity underwent dose reductions to 150 mg/m^2. Myelosuppression was manageable and also not treatment-limiting.

Of great importance was the response rate observed in this trial. The 73% CR + PR rate was nearly double the expected 30%–40% reported in similar patients treated with standard doses of cisplatin. Further, the activity observed in patients who were unresponsive or refractory to lower doses supports a dose-response effect for cisplatin in this disease. No differences in response rate or toxicity were evident between the 4-day and 5-day schedules, although patient numbers are small.

The response duration could be assessed in only two patients who continued on treatment until progressive disease was documented at 3 and 4 months after achieving PR and CR status. Disease recurred in all other responders with recurrent disease within 2 months of stopping cisplatin. The lack of a higher CR rate in these patients was disappointing. This may in part be due to the characteristics of the patient population, large tumor bulk, and extensive prior treatment. It is interesting that the one pathologically confirmed CR was in a previously untreated patient.

Based on these results the maximum number of tolerable courses is limited to three, and we would therefore see no role for high-dose cisplatin in the palliative treatment of head and neck cancer. An appropriate role for high-dose cisplatin may be in the adjuvant treatment of potentially curable patients.

In summary, high-dose cisplatin with hypertonic saline results in a high response rate in both recurrent disease and newly diagnosed patients. Administration of cisplatin with 3% NaCl, hydration, and in divided doses ameliorates nephrotoxicity but affords no protection against other toxicities. Neuropathy and ototoxicity are dose-limiting. Further evaluation of its role in a combined modality approach seems warranted.

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