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Cisplatin-ifosfamide as neoadjuvant chemotherapy in stage IIIB cervical uterine squamous-cell carcinoma*

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Summary. Survival in patients with advanced cervical cancer (stage III B) treated by radical radiotherapy is low. In this study we attempted to assess the efficacy of the *cis*-diamminedichloroplatinum(II) (CDDP)-ifosfamide combination as neoadjuvant chemotherapy in advanced cervical cancer. The treatment schedule was: 20 mg/m^2 CDDP on days 1–5; 1.5 g/m^2 ifosfamide on days 1–5; and 900 mg/m^2 mesna on days 1–5. Courses were given every 28 days. Radiotherapy was given 15 days after the completion of chemotherapy. A total of 26 patients were entered in this trial. Of the 24 patients evaluable for response, 15 (62.5%) achieved at least a 50% reduction in tumor volume, 6 (25%) showed stable disease, and three (12.5%) had progressive disease. At 38 months (mean follow-up) after completion of radiotherapy, 13 of the 24 (54%) evaluable patients were disease-free; 73% of the patients responding to chemotherapy vs 22% of the nonresponders remained free of disease (Fisher's exact test: $P < 0.02$). Major hematologic depression occurred in 2 of the 26 patients evaluable for toxicity. No CNS toxicity was detected. These results are superior to those obtained by radical radiotherapy alone. Future treatment should be directed toward improving response rates as the best way of increasing both local and distant long-term disease control in these patients.

Introduction

Survival in patients with advanced cervical cancer (stage III B) treated by radical radiotherapy is low (5-year survival, 29%–31%) [1, 8]. The large volume of the primary lesion that is not curable by radiotherapy at acceptable doses without normal tissue damage and the significant rate of metastatic disease (27%) [7] are good reasons for these poor results. These two major limitations can be overcome if chemotherapy is given prior to radiotherapy. First, by reducing bulky tumors to minimal/subclinical disease, thereby increasing the probability of local tumor control by radiation therapy, and second, by preventing recurrence outside the radiation fields.

Ifosfamide (IFO) is active against cervical carcinoma, producing response rates of >33% [5]. Toxicity in the form of hemorrhagic cystitis can be prevented by concurrent administration of mesna. IFO/mesna CNS toxicity is uncommon if hepatic function (as indicated by pretreatment serum albumin values) and renal function (as indicated by pretreatment creatinine concentrations) are not impaired [4].

cis-Diamminedichloroplatinum (II) (CDDP) is one of the most active drugs for treatment of cervical carcinoma, resulting in objective response rates of 50% [9]; renal toxicity is rarely observed, provided that this drug is used in patients with creatinine clearance of >50 ml/min and that adequate hydration is given.

IFO displays synergism in animal models with CDDP [3]. Data from phase II studies using combination chemotherapy containing IFO, CDDP, and bleomycin have shown response rates over 70%, and toxicity was easily manageable [6]. Keeping these results in mind, we began this study in an attempt to improve survival in our radiotherapy-treated cervical carcinoma patients by using chemotherapy (IFO-CDDP) in a neoadjuvant setting.

Patients and methods

A total of 26 patients with advanced squamous-cell carcinoma of the cervix were entered in this study. Patient characteristics are shown in Table 1. In all patients, both renal function (serum creatinine concentrations of <1.1 μmol/l, creatinine clearance of >50 ml/min) and hepatic function (serum albumin values of >3.5 g/l) were normal. Bone marrow reserves were adequate, with a total leukocyte count of >3,500/ml, a platelet count of >150,000/ml, and a hemoglobin concentration of >12 g/l.

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Table 1. Patient characteristics and eligibility criteria

Number of patients	26
Age (range)	52 (41–67) years
Mean Karnofsky status (range)	70 (50–100)
Eligibility criteria:	
Stage III B	
Squamous-cell cervical carcinoma	
Serum albumin value	>3.5 g/l
Serum creatinine value	<110 μmol/l
Creatinine clearance	>50 ml/min
Leukocyte count	>3,500/ml
Platelet count	>150,000/ml
Hemoglobin concentration	>12 g/l

Table 2. Treatment schedule

Chemotherapy:		
CDDP	20 mg/m² i. v. (bolus)	Days 1–5
IFO	1.5 g/m² i. v. (bolus)	Days 1–5
Mesna[a]	900 mg/m² i. v. (bolus)	Days 1–5
Saline hydration	>2,000 ml	During treatment
Radiotherapy:		
Whole pelvis 50 Gy/5 weeks		
Reduced fields 20 Gy/5 weeks		

[a] The daily dose of mesna was given in three separate injections at 0, 4, and 8 h after IFO

Table 3. Response to chemotherapy

Evaluable patients	24
Complete response	0/24
Partial response	15/24 (62.5%)
Stable disease	6/24 (25%)
Progressive disease	3/24 (12.5%)
Symptomatic relief	22/24 (92%)

Table 4. Results of treatment

	Responders ($n = 15$)	Nonresponders ($n = 9$)	Total ($n = 24$)
Disease-free	73%	22%	54%
Pelvic disease	20%	56%	33%
Distant metastases and pelvic disease	7%	22%	13%

Fisher's exact test: $P < 0.02$

Table 5. Toxicity

Alopecia (grade 3–4)	42%
Hematologic (grade 3–4)	21%
Nausea and vomiting	90%
Renal impairment	1.4%
CNS toxicity (grade 3–4)	0
Hematuria (grade 3–4)	0

Patients were treated each day with 20 mg/m² CDDP (given as a bolus injection), 1.5 g/m² IFO (given as a bolus injection), and 900 mg/m² mesna (given in three doses at 0, 4, and 8 h after IFO treatment). This regimen was given for 5 days and repeated every 28 days (Table 2). Patients received between 1 and 4 cycles (mean, 2.69 cycles) and were evaluable for response if they completed 2 or more cycles. No dose reductions were carried out. Treatment was delayed for 1 week if patients showed signs of bone marrow or renal toxicity. All patients were referred for pelvic irradiation (whole pelvis, 50 Gy/5 weeks; reduced pelvic volume, 20 Gy/5 weeks) 15 days after chemotherapy.

Results

According to WHO criteria, 15 (62.5%) of 24 patients evaluable for response showed at least a 50% reduction in primary tumor volume; there was no change in disease bulk in 6 cases (25%), and 3 (12.5%) showed progressive disease. Symptomatic relief of pain and hemorrhage was achieved in 22 women (92%) (Table 3).

At 38 months (mean follow-up) after the completion of radiotherapy, 13 of 24 (54%) patients evaluable for response were free of disease. In all, 11 of the 15 patients responding to chemotherapy remained free of disease (73%), 3 (20%) had pelvic disease, and 1 (7%) showed lung metastases with local failure; only two of the nonresponders were free of disease (22%), five (56%) had pelvic disease, and two (22%) developed distant metastases and local failure. There was a statistical advantage in disease-free survival (Fisher's exact test: $P < 0.02$) for responders (Table 4).

All 26 patients were evaluable for toxicity. Neither hemorrhagic cystitis nor grade 3–4 IFO/mesna CNS toxicity was seen. Impairment of renal function (serum creatinine value of >120 μmol/l) occurred in one patient after three courses of chemotherapy. Grade 3–4 alopecia was observed in 11 patients (42%), and transient nausea and vomiting occurred in 63 (90%) of the 70 cycles given. Hematologic toxicity, mainly in the form of leukopenia, led to delayed treatment in 12 courses (17%), and chemotherapy had to be stopped after the 1st cycle in two patients due to severe anemia and leukopenia (4%) (Table 5).

Discussion

According to our results, response to chemotherapy is the rule more than the exception in squamous-cell carcinoma of the uterine cervix. A favorable response rate of 62.5% in advanced cervical carcinoma is comparable with those reported in previous studies [5, 6] using more than two drugs. These regimens have achieved a moderate increase in partial responses, but complete remissions are uncommon.

Disease-free survival in our patients (54% at 3 years) was better than that obtained by radical radiotherapy alone either in our institution or in previous studies [1, 8]. The reduction in tumor size obtained by our cytotoxic neoadju-

vant regimen could explain this therapeutic gain. Thus, the long-term local control of disease achieved after completion of the chemotherapy-radiotherapy schedule is statistically correlated with the response to chemotherapy (73% disease-free responders vs 22% disease-free nonresponders; $P < 0.02$). The relationship between tumor radiocurability and the response of tumor cells to chemotherapy has been described elsewhere [2].

These encouraging results can be obtained without major toxicity. IFO/mesna CNS toxicity (grade 3–4) is easily prevented by careful assessment of pretreatment risks [4], as can be observed in our study. Hematologic toxicity was significant in two patients, but recovery was complete after the cessation of chemotherapy. Renal toxicity is rare (1.4%) if adequate hydration is given.

In conclusion, IFO-CDDP chemotherapy could be useful in the management of advanced cervical cancer. The local and distant disease-free rates achieved in patients responding to chemotherapy compare favorably with those obtained using radical radiotherapy [1, 8]. Long-term follow-up is needed to assess whether neoadjuvant chemotherapy improves survival in these patients or is simply selective for chemo-radiosensitive tumors.

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