Acta Oncologica Vol. 34, No. 2, pp. 257–259, 1995

CISPLATIN AND IFOSFAMIDE IN PATIENTS WITH ADVANCED SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX

A phase II trial

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Thirty patients with advanced squamous cell carcinoma of the cervix were included in a phase II study with cisplatin (DDP) and ifosfamide (IF)/mesna. They received a median of 4 courses of chemotherapy and were all evaluable for response and toxicity. Each cycle consisted of 2 500 mg/m² IF i.v. days 1–5; mesna 500 mg/m² i.v. at hours 0 and 2, and 1 000 mg/m² per os at hours 6 and 10, days 1–5; DDP 20 mg/m² i.v., days 1–5. Cycles were repeated every 4 weeks. One patient obtained CR and 14 PR giving an overall response rate of 50%. Mean duration of response was 21 months. Anemia grade 3 developed in 7 patients, leukopenia grade 3 in 9 patients and grade 4 in one patient; thrombopenia grade 3 in 2; creatinine clearance grade 3 in one; CNS grade 3 in one and cystitis grade 3 in one patient. Overall median survival time was about 25+ months (3–63+); after a follow-up of 70 months, 11 patients (37%) are still alive with a median survival of 31+ months. IF plus DDP seems to be a good combination for treatment of advanced cervical cancer, with acceptable tolerance and response rate.

Cisplatin-containing regimens are frequently used in the treatment of cervical cancer (1). Cisplatin and ifosfamide belong to the most active cytotoxic agents yet identified for treatment of this cancer (2–4). Ifosfamide overall objective response rate in advanced cervical cancer with cisplatin combinations varies between 0% and 65% (4). The objective response rate reported with ifosfamide/ cisplatin range depending on patient selection and regimen

chemotherapy and if their primary surgery and/or radiation therapy had failed.

The observations included a complete history and physical examination with base-line laboratory studies. The patients were seen every 2 weeks, with physical examination and repeated laboratory studies for evaluation of response and toxicity.

For admission to the study, the following criteria were used: histological documentation of squamous cell carcinoma, Karnofsky index > 60, signed informed consent of the patient, no less than 2 months elapsed after completion of radiation therapy; normal renal function (serum creatinine < 1.1 μmol/l, creatinine clearance > 60 ml/min), normal hepatic function (serum albumin > 3.5 g/l), WBC $\geqslant 4 \cdot 10^9$/l, platelet count $\geqslant 150 \cdot 10^9$/l and hemo-globin > 12 g/l. Each treatment cycle consisted of 2 500 mg/m^2 ifosfamide in 500 ml saline solution given as a 3-h i.v. infusion on days 1–5, followed by cisplatin 20 mg/m^2 in 500 ml saline solution, given as 1-h i.v. infusion on days 1–5, and 500 mg/m^2 mesna given by i.v. at hours 0 and 2 followed by 1 000 mg/m^2 given orally twice daily on days 1–5. The cycles were repeated every 4 weeks for 6 consecutive cycles, unless definite evidence of disease progression existed. The patients received between 2 and 6 cycles (mean 4) and were examined at 2-week intervals and after the completion of 6 cycles. Treatment was delayed for one week if the patient showed signs of bone marrow or renal toxicity. No dose reductions were used. The patients were assessed by imaging methods whenever possible, including computed tomography, plain x-rays and ultrasound scan. Complete response (CR) was defined as complete disappearance of all known disease as determined by two observations at least 4 weeks apart. Partial response (PR) required a decrease of at least 50% in the total tumour size without appearance of new lesions. No change (NC) or stable disease was defined as $< 50\%$ decrease and $< 25\%$ increase of the total tumour size. Progressive disease (PD) was defined as an increase of $\geqslant 25\%$ in the size of more than one lesion or the appearance of new lesions.

Evaluation of survival was performed according to Kaplan & Meier (14) and Simon & Lee (15).

Results

All 30 patients were evaluable for toxicity and response. All 22 stage III patients and 3 stage IVa patients had previously received radiotherapy as primary treatment. No patients were previously treated with chemotherapy. All patients had metastatic or locally extended disease. In 5 stage IVb patients, not previously operated, the chemotherapy represented the primary treatment. A total of 121 IF/mesna + DDP cycles were given (median, 4 cycles per patient). An objective response was achieved in 15 patients: CR 1 (3.3%) and PR 14 (46.6%) giving an overall objective response rate of 50% (Table 1). The

Table 1

Response to cisplatin and ifosfamide in 30 patients with advanced cervical cancer

Stage	Patients	CR	PR	NC	PD
IIIa	6	–	5	–	1
IIIb	16	1	8	4	3
IVa	3	–	–	1	2
IVb	5	–	1	1	3
Total (%)	30 (100)	1 (3.3)	14 (46.6)	6 (20)	9 (30)

Table 2

Toxicity (grade WHO) after 121 cycles of cisplatin and ifosfamide in 30 patients with advanced cervical cancer

Adverse events	Grade 3		Grade 4	
	n	(%)	n	(%)
Cystitis	1	(3.3)	0	(0)
CNS	1	(3.3)	0	(0)
Vomiting	12	(40.0)	0	(0)
Alopecia	8	(26.6)	6	(20)
Creatinine clr.	1	(3.3)	0	(0)
Leukopenia	9	(30.0)	1	(3.3)
Thrombopenia	2	(6.6)	0	(0)
Anemia	7	(23.3)	0	(0)

FIGO stage III patients responded much better (IIIa, PR 5; IIIb, CR 1, PR 8) than FIGO stage IV patients (PR 1). Mean duration of response was 21 + months. The median number of courses to objective response was two. No obvious relation between response and previous irradiation was found in this study. Thirty-five areas of disease were assessed for response; 14 of 30 lesions (42%) in previously irradiated sites and 1 of 5 lesions in non-irradiated sites showed objective response. One patient stage IVb, treated with chemotherapy, achieved partial response. Six patients (20%) had stable disease and 9 (30%) progressive disease. The overall survival was about 25 + months (range 3–63 +). After a follow-up of 70 months, 11 patients (37%) are still alive with a median survival of 31 + months.

The toxicity is summarized in Table 2 and was graded according to the WHO classification (16).

Of interest is that grade 3 anemia occurred in 7 patients, however without signs of acute or chronic bleeding; blood transfusions were given in these patients. Grade 3 leukopenia was seen in 9 patients and one patient got a grade 4 leukopenia, however without infection. Grade 3 thrombopenia was seen in 2 patients. One patient had moderate transient increase in creatinine clearance. Cystitis grade 3 was observed in one patient; nausea and vomiting grade 3 in 12, alopecia grade 3 in 8, and alopecia grade 4 in 6 patients. One patient experienced hallucinations for 36 h which, however, dissappeared spontaneously. There were no chemotherapy-related deaths.

Discussion

The present study was designed to test the combined activity of ifosfamide/cisplatin in the treatment of stage III–IV cervical cancer. The regimen was fairly well tolerated with a 40% grade III–IV adverse reactions and gave a 50% overall remission rate with improvement of the quality of life. The improvement of quality of life was an important part of the effect and most of the responders could return to their daily activities. Grade 3–4 myelosuppression occurred in 15% and was the most relevant adverse effect. However, no neutropenic infections were observed. Reversible CNS disturbance was registered in one patient. No significant nephrotoxicity was observed. Other studies using lower doses of IF and DDP have reported objective response rates ranging between 27% and 58% (18); the IF dose was in these studies 3.6 g/m^2 to 7.5 g/m^2 and the DDP dose 50–60 mg/m^2 at each course (6, 13, 17, 18). Bolis et al. (12) used IF 3.5 g/m^2 combined with weekly DDP doses and reported a 78% overall response rate. In order to increase the platinum-based effect without increase of the specific toxicity of cisplatin, IF was combined with carboplatin in one study and a 64% objective response rate was seen (19). The use of IF 5 g 24-h continuous infusion plus carboplatin 300 mg/m^2 gave an objective response rate of 59% (20).

The objective results of the present study are very similar to those previously reported by Cervellino et al. (4), after IF/mesna alone, but at higher doses than in the present study. However, the hematologic toxicity was more pronounced with IF/mesna + DDP than with IF/mesna alone. Thus, the combination with DDP does not seem to increase the response rate. However, the duration of response and survival was encouraging. The median response duration was 21 + months (range 8–59) with no obvious difference between patients with or without disease in previously irradiated areas. The survival ranged from 3 to 63 months, with a median of 25 + months.

Ifosfamide/cisplatin given on an outpatient basis is a clearly active regimen in advanced cervical cancer in terms of valuable remissions, often with a duration of more than a year. However, further studies are needed to find suitable chemotherapy regimens for advanced cervical cancer.

ACKNOWLEDGEMENTS

This work was supported by an investigational grant (F-Medic 137) from ASTA Medica AG, Frankfurt. The authors recognize and appreciate the secretarial assistance of Miss Susana Spiegler.

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