Cancer Chemother Pharmacol (1990) 26 (Suppl): S 33–S 35

Cancer Chemotherapy and Pharmacology

Phase II study of carboplatin/ifosfamide in untreated advanced cervical cancer*

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Summary. A total of 32 patients with advanced squamous-cell carcinoma of the cervix were treated with 300 mg/m^2 i.v. carboplatin and 5 g/m^2 ifosfamide as a 24-h i.v. infusion, both given on day 1 every 4 weeks. In all, 3 (9%) complete responses (CRs) and 19 (59%) objective responses (CR+PR) were achieved in 32 patients. Myelosuppression with leukopenia and/or thrombocytopenia of WHO grade 4 in 28% and 13% of patients, respectively, was the main toxicity. The results of our study suggest that carboplatin/ifosfamide is active as neoadjuvant treatment in advanced cervical cancer.

Introduction

The prognosis of patients with inoperable cervical cancer is poor despite improved radiotherapeutic techniques. Patients with International Federation of Gynecology and Obstetrics (FIGO) stage III disease show a 5-year survival of approximately 30%, and stage IV patients show that of <10% [6]. The use of chemotherapy to reduce bulky tumors to minimal disease to increase the efficacy of subsequent radiotherapy seems to be of therapeutic interest.

At the present time, cisplatin-containing regimens are more frequently used in the neoadjuvant treatment of cervical cancer. In randomized multicenter studies, cisplatin and carboplatin have shown comparable antineoplastic activity in advanced cervical cancer that had mostly been pretreated with radiation [8, 9, 13, 14]. In three randomized studies with a total of 360 patients, carboplatin induced statistically significantly less nephro-, oto-, and neurotoxicity as well as nausea/vomiting than did cisplatin [12].

In randomized multicenter studies in cervical cancer that had mostly been pretreated with radiation, remissions [8, 9] were achieved with carboplatin in 18% of patients. In nonrandomized phase II studies, remissions were obtained with ifosfamide in 31% of patients [3, 5, 10]. Apart from cisplatin, both drugs belong to the few agents that induce a complete response (CR) rate of $\geq 5\%$ in mainly radiotherapeutically pretreated patients [1, 3, 5, 7–10, 14]. Based on these data, a phase II study with carboplatin/ifosfamide was carried out in untreated, advanced squamous-cell carcinoma of the cervix.

Patients and methods

Untreated patients with inoperable, histologically confirmed squamous-cell carcinoma of the cervix entered the study. Eligibility criteria included: WHO performance status of ≤ 2; age of ≤ 75 years; no brain metastases; normal bone marrow, renal, and hepatic functions; and the informed consent of the subject. The size of neoplastic lesions was determined before the start of treatment, prior to each cycle, and 4 weeks after the last cycle. A complete hemogram, hepatic and renal function tests, and serum electrolyte values were controlled before the start of treatment, before each cycle, and 4 weeks after the last cycle. During chemotherapy, complete blood counts were monitored weekly. Tumor response and toxicity were evaluated using WHO criteria [11].

Treatment. Chemotherapy consisted of 300 mg/m^2 i.v. carboplatin on day 1 and 5 g/m^2 i.v. ifosfamide on day 1. Carboplatin was given as an i.v. infusion over 30 min, and ifosfamide was given as a 24-h i.v. infusion; starting immediately prior to the ifosfamide infusion, 9.2 g mesna was given i.v. over 36 h.

Treatment was repeated every 4 weeks if leukocytes and thrombocytes had recovered to $\geq 3{,}000/\text{mm}^3$ and $\geq 1{,}000{,}000/\text{mm}^3$, respectively, and if creatinine clearance was ≥ 60 ml/min. If these values had not been reached, treatment was delayed by a maximum of 2 weeks.

Results

A total of 34 patients were admitted into the study; 2 were excluded from evaluation because of incorrect histology. In all, 32 patients received at least one cycle of chemotherapy and were evaluable for response and toxicity; their

* Presented at the Satellite Symposium "Ifosfamide in Gynecological Tumors" of the 5th European Conference on Clinical Oncology and Cancer Nursing, London, September 3–7, 1989

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Table 1. Patients' characteristics

Patients (*n*)	32	
Median age (years)	51	(range, 31–70)
Median WHO performance status	1	(range, 0–2)
FIGO stage:		
IIb	2	
IIIa	2	
IIIb	15	
IVa	5	
IVb	8	

Table 2. Results obtained in 32 patients

	Total CRs	Total CRs+PRs	Total NCs	Total PDs
Patients (*n*)	3 (9%)	19 (59%)	8 (25%)	5 (16%)
95% confidence limits	0–19%	42%@–76%		10%–40%

Table 3. Results according to stage of disease in 32 patients

Stage	Patients	CRs	CRs+PRs	NCs	PDs
IIb	2	0	2	0	0
IIIa	2	0	0	2	0
IIIb	15	2	10	2	3
IVa	5	1	2	3	0
IVb	8	0	5	1	2

Table 4. Hematologic toxicities according to WHO scale in 32 patients

Toxicity	WHO grade:				
	0	1	2	3	4
Leukopenia	0	1 (3%)	12 (38%)	10 (31%)	9 (28%)
Thrombocytopenia	17 (53%)	2 (6%)	4 (13%)	5 (16%)	4 (13%)
Anemia	9 (28%)	14 (44%)	8 (25%)	0	1 (3%)

Table 5. Nonhematologic toxicities according to WHO scale in 32 patients

Toxicity	WHO grade:				
	0	1	2	3	4
Serum creatinine	30 (94%)	2 (6%)	0	0	0
Serum bilirubin	32 (100%)	0	0	0	
SGOT	31 (97%)	1 (3%)	0	0	0
SGPT	30 (94%)	2 (6%)	0	0	0
Nausea/vomiting	2 (6%)	6 (19%)	22 (69%)	2 (6%)	0
Alopecia	6 (19%)	1 (3%)	9 (28%)	16 (60%)	0
Diarrhea	31 (97%)	0	1 (1%)	0	0
Infections	31 (97%)	0	1 (3%)	0	0
Bleeding	31 (97%)	0	1 (3%)	0	0
Neurologic (central)	29 (91%)	2 (6%)	1 (3%)	0	0

clinical characteristics are shown in Table 1. A total of 88 cycles were given (median, 2 per patient). Among these 32 patients, 19 (59%) remissions, including 3 (9%) CRs were achieved (Table 2). The 95% confidence limits for a CR was 0–19%; that for an objective response (CR+PR) was 42%–76%. Responses according to the stage of disease are given in Table 3.

Toxicity

Myelosuppression was the main toxicity (Table 4). Leukopenia and thrombocytopenia of WHO grade 4 were seen in 28% and 13% of the patients, respectively; grade 4 anemia was observed in one patient. The occurrence of these toxicities did not lead to premature withdrawal from treatment. Nonhematologic toxicities are shown in Table 5. Except alopecia (60%) and nausea/vomiting (6%), nonhematologic toxicities above grade 2 did not occur.

Discussion

The results of our study suggest that the combination of carboplatin/ifosfamide induces higher overall response rates in cervical cancer than does either drug given as a single agent. The remission rate of carboplatin/ifosfamide in a neoadjuvant setting was 59%, including 9% CRs.

These data suggest that the antineoplastic activity of carboplatin/ifosfamide in cervical cancer is comparable with that of cisplatin-containing regimens [2, 4]. However, comparison of response rates in cervical cancer is difficult because noninvasive tumor measurements are less precise than surgical evaluations. Regardless of these limitations, carboplatin/ifosfamide made conditions for subsequent radiotherapy or surgery more favorable in almost two-thirds of the patients.

References

1. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ (1985) Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3: 1079
2. Buxton EJ, Meanwell CA, Hilton C, Mould JJ, Spooner D, Chetiyawardana A, Latief T, Paterson M, Redmann CW, Luesley DM, Blackledge GR (1989) Combination bleomycin, ifosfamide and cisplatin chemotherapy in cervical cancer. J Natl Cancer Inst 81: 359
3. Coleman RE, Harper PG, Gallagher C, Osborne R, Rankin EM, Silverstone AC, Slevin ML, Souhami RL, Tobias JS, Trask CW, Wiltshaw E (1986) A phase-II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 18: 280
4. Coleman RE, Clarke J, Slevin ML, Wiltshaw E, Harper PG (1988) Ifosfamide (I) and ifosfamide + cisplatin (P) chemotherapy for advanced cervical carcinoma. Br J Cancer 58: 273
5. Dinh TV, Dillard EA, Doherty MG (1989) Ifosfamide in cervical cancer: early phase-II results in patients with advanced or recurrent disease (Abstr. 617). Proc Am Soc Clin Oncol 8: 158
6. FIGO (1988) Report on the results of treatment in gynecological cancer, vol 20, FIGO

7. Forastiere AA, Schnur GA (1984) Cervical cancer: role of chemotherapy. In: Forastiere AA (ed) Gynecologic cancer. Churchill Livingstone, New York Edinburgh London Melbourne, p 93
8. Lira-Puerto V, Silva A, Groshen S, Martinez R, Morris M, Morales-Canfield F, Tenoric F, Muggia F (1989) Carboplatin (CBDCA) or CHIP: final report of the 3rd phase-II NCI-PAHO study in advanced cervical cancer. Proc Am Soc Clin Oncol 8: A622
9. McGuire WP, Arseneau JC, Blessing JA, Given FT, Hatch KD, Creasman WT, DiSaia PJ, Teng NN (1988) Randomized comparison of carboplatin (CP) and iproplatin (IP) in advanced squamous carcinoma of the uterine cervix (SCUC): a Gynecologic Oncology Group (GOG) study. Proc Am Soc Clin Oncol 7: A521
10. Meanwell CA, Mould JJ, Blackledge G, Lawton FG, Stuart NSA, Kavanagh J, Latief TN, Spooner D, Chetiyawardana AD (1986) Phase II study of ifosfamide in cervical cancer. Cancer Treat Rep 70: 727
11. Miller AB (1981) Reporting results of cancer treatment. Cancer 47: 207
12. Rozenzcweig M, Martin A, Beltangady M, Goodlow J, Bragmann K, Wiltshaw E, Mangioni C, Adams M, Canetta R (1989) Comparison of carboplatin and cisplatin given as first line single agent chemotherapy for stage III/IV ovarian cancer: a metaanalysis of three randomized trials. In: Proceedings, Carboplatin Workshop Program and Abstracts, San Francisco
13. Symonds RP, Burnett RA, Habeshaw T, Kaye SB, Snee MP, Watson ER (1989) The prognostic value of a response to chemotherapy given before radiotherapy in advanced cancer of cervix. Br J Cancer 59: 473
14. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr, Hatch KD (1989) A randomized comparison of a rapid versus prolonged (24 h) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 32: 198