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Short communication

Carboplatin-based combination chemotherapy for advanced carcinoma of the cervix

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Summary. A combination of carboplatin, vincristine, methotrexate and bleomycin (COMB) was given to 29 patients with locally advanced, metastatic or recurrent cervical carcinoma. A total of 85 cycles of chemotherapy were given, with half of the patients receiving >3 cycles. Both the response rate (32.1%) and the median duration of response (30 weeks) were relatively disappointing. Renal toxicity was minimal, but one-third of our patients experienced severe (WHO grades 3 and 4) nausea and vomiting. This combination showed little advantage over carboplatin used as a single agent.

Introduction

Patients with carcinoma of the cervix who relapse following radical therapy are difficult to treat, as most of them have received prior radiotherapy and only a small minority are suitable for pelvic exenteration. Relapse is usually accompanied by symptoms requiring palliation, such as bleeding, pain from tumour in the pelvic side wall or paraaortic region, or dyspnoea due to pulmonary metastases. This tumour is moderately chemosensitive [10] and chemotherapy may palliate some of the distressing symptoms of the disease.

Cisplatin is presently the most effective single agent used to treat carcinoma of the cervix, producing a response rate of about 40% [8] and median duration of response of 6 months. As well as reducing symptoms, platinum-based chemotherapy may offer a modest survival advantage. In a study comparing combination cisplatin chemotherapy with hydroxurea, the group receiving the cisplatin combination showed a response rate of 57% and a median duration of survival of 11 months as compared with 4 months in either the group that did not receive cisplatin or patients who did not respond to the platinum combination [4]; however, the numbers of patients in this study were small.

The toxicity pattern of cisplatin reduces its usefulness in the palliative treatment of recurrent carcinoma of the cervix. Cisplatin is potentially nephrotoxic and many patients show reduced renal function due to ureteric compression. The incidence of nausea and vomiting is also high. Carboplatin is less nephrotoxic and less emetogenic than Cisplatin and seems to be equally effective in the treatment of ovarian carcinoma [2, 7]. Carboplatin has been used in recurrent carcinoma of the cervix, with single-agent response rates of 15%, 25.5% and 28% being achieved [2, 12, 13], which are similar to those reported in large groups of patients treated with cisplatin [5]. Most regimens are empirical combinations of active agents with differing toxicities; we used a combination of carboplatin with methotrexate, vincristine and bleomycin (COMB). The major toxicities of carboplatin are vomiting and myelotoxicity. The emetic potential of the other three agents is low; moreover, bleomycin and vincristine have little effect on the bone marrow, and the myelotoxicity of methotrexate is moderate and easily modulated by the use of folinic acid. The single-agent response rates are: methotrexate, (16%); vincristine, (23%); bleomycin, (10%) [8].

The aim of the present study was to give COMB to patients with symptomatic carcinoma of the cervix unsuitable for treatment with other modalities so as to assess response rate, duration of response and toxicity. We hoped that this combination would achieve the high response rate associated with cisplatin while producing reduced toxicity.

Patients and methods

A total of 29 patients with locally advanced, recurrent or metastatic carcinoma of the cervix were entered in the study between December 1986 and May 1989. All patients were under 70 years of age, showed a performance status of 0–2 and had measurable or evaluable disease. One subject had an adenosquamous tumour and the rest presented squamous lesions. A full profile of our patients' characteristics is listed in Table 1.

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Table 1. Patients' characteristics

Number of patients		29
Median age (range)		43 (26–70) years
Performance status:		
	0	10 (34.5%)
	1	13 (44.8%)
	2	6 (20.7%)
Stage at entry:		
	III	10 (34.5%)
	IVa	1 (3.5%)
	IVb	18 (62.1%)
Histology:		
	Squamous	28 (96.5%)
	Adenosquamous	1 (3.5%)
Previous radiotherapy:		
	Yes	25 (86.2%)
	No	4 (13.8%)
Site of disease:		
	Pelvic	10 (34.5%)
	Metastatic	7 (24.1%)
	Both	12 (41.4%)

All had a creatinine clearance of >40 ml/min, a WBC count of $>4 \times 10^9$/l and a platelet count of $>100 \times 10^9$/l prior to chemotherapy.

On day 1, previously untreated patients whose creatinine clearance was >60 ml/min were given 400 mg/m^2 carboplatin by infusion, 50 mg/m^2 i.v. methotrexate, 2 mg i.v. vincristine and 30 mg i.m. bleomycin. On day 15, the methotrexate, vincristine and bleomycin doses were repeated. The complete cycle was repeated every 28 days. If the patient had previously received radiotherapy, the carboplatin dose was reduced to 300 mg/m^2 for the first cycle. If the WBC was $>4 \times 10^9$/l and the platelet count was $>120 \times 10^9$/l on day 21, the carboplatin dose was increased to 400 mg/m^2. If creatinine clearance was between 40 and 60 ml/min, the dose of carboplatin and methotrexate was reduced by 25% and 15 mg folinic acid was given every 6 h for 12 doses, starting 24 h after the administration of methotrexate. Toxicity was assessed after each cycle. Response was assessed after two complete cycles using standard UICC (International Union Against Cancer) criteria. Pelvic disease was assessed clinically and by ultrasound examination or computerised tomographic (CT) scanning. Appropriate imaging techniques such as chest radiography or clinical examination were used to measure tumour elsewhere.

Results

A total of 85 cycles of COMB chemotherapy were given; 10 patients received 2 cycles, 6 completed 3 courses, 8 received 4 cycles and 2 were given 6 courses. In 41.4% (12) of the patients, treatment was delayed due to haematological toxicity. The toxicity data on the COMB combination is shown in Table 2. In addition, six patients experienced minor neurological toxicity in the form of paraesthesia and four subjects developed drug-related skin rashes. Among the patients who had undergone prior cisplatin-containing chemotherapy, one of four developed grade 3 WBC toxicity, which was not significantly different from the rate of 32% seen in those who had not previously received chemotherapy.

One patient died of septicaemia while neutropaenic after the first cycle of COMB, before response could be assessed. Of the remaining 28 subjects, 3 achieved a

Table 2. Toxicity of COMB[a]

	WHO grade					Total patients (*n*)
	0	1	2	3	4	
Haemoglobin	37.5%	25%	25%	12.5%	0	8
Leucocytes	25%	3.6%	28.6%	32.1%	10.7%	28
Platelets	67.9%	7.1%	10.7%	7.1%	7.1%	28
Nausea/vomiting	6.9%	24.1%	34.5%	24.1%	10.3%	29
Alopecia	64.3%	21.4%	14.3%	0	0	28
Oral	63%	3.7%	25.9%	7.4%	0	27
Diarrhoea	78.6%	14.3%	3.6%	3.6%	0	28
Renal	96.4%	3.6%	0	0	0	28
Pulmonary	96.3%	0	3.7%	0	0	27

[a] Worst toxicity observed over the number of courses received

complete response (CR), 6 showed a partial response (PR), 8 remained stable and 11 had progressive disease, for an overall response rate of 32.1% (95% confidence interval, 16%–52%). The median duration of response was 30 weeks (95% confidence interval 17–71 weeks). Of the four patients who had received previous chemotherapy (including two responders to prior treatment with cisplatin), none responded to the COMB regimen. In the chemotherapy-naive group the objective response rate was 37.5% (three CRs and six PRs;) 95% confidence interval, 20–61%). The response rates were evaluated according to site of disease. In the ten patients with pelvic disease alone there was a 30% (one CR and two PRs) response rate; five subjects remained stable and two had progressive disease. Women with metastatic disease alone showed a response rate of 28.5% (2/7), comprising 1 CR and 1 PR; the remaining 5 subjects presented progressive disease. In patients with both metastatic and pelvic disease, a 36.3% (4/11) response rate was obtained (1 CR, 3 PRs, 3 remained stable, 4 progressed).

Of the four patients who had received neither prior chemotherapy nor radiotherapy, one with pelvic and nodal disease achieved a CR lasting for 92 days. Of the other complete responders, one had a supraclavicular nodal mass and remained in CR for 47 days and the other had a pelvic mass that resolved completely. The latter then proceeded to pelvic exenteration. This case represented a clinical and radiological CR, but the pathological specimen revealed microscopic tumour within the cervix. However, this patient remains free of disease at 703 days. Of the six subjects who achieved a PR, two had local pelvic disease alone, three had pelvic disease with metastasis and the other had liver and lung metastasis but showed no evidence of recurrent pelvic disease. All had previously undergone radiotherapy.

Discussion

The COMB regimen produced a moderate response rate associated with more toxicity than was expected. The incidence of WHO grade 2–4 nausea and vomiting was 69% despite combinations of metoclopramide, dexamethasone and lorazempam, indicating that carboplatin was not markedly less emetogenic than cisplatin in the present study.

Of the 85 cycles of chemotherapy, 15 were delayed due to haematological toxicity, with 42% of patients having a leucocyte count of $<2 \times 10^9$/l. There was one death due to septicaemia early in the study. However, we were surprised by the low incidence of thrombocytopenia. As hoped, there was no renal toxicity and virtually no hair loss. It has been suggested that the response rate differs for various sites of metastatic disease, lung metastasis being particularly responsive. In one study using cisplatin there was a 73% overall response rate, with a 53% CR rate being observed for lung metastasis. However, there were no CRs within previously irradiated pelvic fields and a PR rate of only 21% was achieved [15].

The relative ineffectiveness of chemotherapy against pelvic disease has been ascribed to poor drug penetration into previously irradiated tissue and to the development of drug resistance [1]. In agreement with results obtained in other studies [9, 17], the response observed in our patients did not appear to be affected by the site of metastasis or previous radiotherapy. In the present study the only long-term survivor underwent pelvic exenteration following a clinical CR, suggesting that radical surgery should be considered in metastasis-free patients with localised pelvic disease that shrinks in response to chemotherapy.

The response rate for our version of COMB (32%) was similar to that reported by Rustin and Newlands (26%), and the conclusions of these authors [16] may be correct in that cisplatin is more effective than carboplatin in recurrent carcinoma of the cervix. However, the small numbers of patients in that study and the present investigation make it difficult to draw definitive conclusions. Two of four patients in our study had previously responded to neoadjuvant cisplatin but none of these subsequently responded to COMB. In another study in which 22 patients whose disease had progressed on single-agent carboplatin were given cisplatin, 4 responses were achieved, 2 which involved CRS, suggesting a lack of total cross-resistance between cisplatin and carboplatin [13]. Again, the numbers of patients in our study were too small to enable conclusions to be drawn about cross-resistance.

A recent report showing that cisplatin, ifosfamide and bleomycin produced an objective response in 49 patients (69%) is encouraging, but as there was no improvement in the median duration of survival (10.2 months) as compared with that obtained in other studies, the toxicity was unacceptably high [6]. It is noteworthy that the Roswell Park Memorial Institute initially reported 71% response rates using weekly administration of cisplatin [14], but a later report showed that the response rate fell to 27% after greater numbers of patients had been accrued into the study [11]. In the present study, combination carboplatin chemotherapy showed no advantage over the administration of carboplatin alone. Further studies aimed at identifying other new agents for the treatment of advanced cervical cancer remains a high priority.

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