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European Journal of Cancer 37 (2001) 1624–1628

European Journal of Cancer

www.ejconline.com

Phase II study of mitomycin-C and cisplatin in disseminated, squamous cell carcinoma of the uterine cervix. A European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group study

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Received 20 March 2001; accepted 3 April 2001

Abstract

The aim of this study was to investigate the tumour response rate and toxicity of a combination chemotherapy consisting of mitomycin-C and cisplatin in patients with disseminated squamous-cell carcinoma of the uterine cervix. Chemotherapy consisted of mitomycin, 6 mg/m^2 intravenously (i.v.), and cisplatin, 50 mg/m^2 given i.v., both administered on day 1 of each cycle. The regimen was repeated at 4-weekly intervals. Mitomycin-C/cisplatin were used to treat 33 evaluable patients aged 29–67 years (median: 50 years). All patients except 1 had previously been treated with either surgery, radiation or both. At the initiation of chemotherapy, 8 patients had loco-regional and disseminated disease and 25 women had only distant metastases. The overall response rate was 42% (95% confidence interval (CI): 26–61%). Five complete and nine partial responses were observed with a median duration of response of 7.9 months (95% CI: 3.7–23.5 months). 9 patients had stable disease and 10 developed progressive disease during mitomycin-C/cisplatin-treatment. World Health Organization (WHO) grade III/IV side-effects were documented in 15 women, of whom 10 had gastro-intestinal toxicity, 3 had haematological toxicity, 1 had alopecia and 1 developed an allergic reaction to cisplatin. There were neither drug-related deaths nor severe or irreversible renal or hepatic dysfunction or peripheral neuropathy. The median progression-free survival was 5.0 months (95% CI: 3.6–6.2 months) for all patients and 10.5 months (95% CI: 6.2–15.2 months) for the responders. The median overall survival was 11.2 months (95% CI: 6.5–18.4 months).The mitomycin-C/cisplatin combination showed antitumour activity in the treatment of advanced or recurrent squamous-cell carcinoma of the uterine cervix. The regimen was well tolerated and could be administered on an outpatient basis.

Keywords: Mitomycin-C; Cisplatin; Phase II study; Cervical cancer

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0959-8049/01/$ - see front matter
PII: S0959-8049(01)00178-2

1. Introduction

Chemotherapy has a palliative role in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IVb or recurrent cervical carcinoma after failure following surgery or radiotherapy. Cisplatin is considered the single most active cytotoxic agent in carcinoma of the uterine cervix [1–3].

The Gynecological Cancer Group (GCG) of the European Organization for Research and Treatment of Cancer (EORTC) had demonstrated activity of the four-drug regimen (vincristine/bleomycin/mitomycin-C/cisplatin) in patients with disseminated squamous-cell carcinoma of the uterine cervix [4]. To improve tolerance and reduce the accompanying toxicity, the present mitomycin-C/cisplatin-regimen was studied on an outpatient schedule of administration using the same dosages of mitomycin-C and cisplatin as in our previous trial.

2. Patients and methods

2.1. Eligibilty criteria

Patients included in the study needed to have disseminated, histologically-confirmed squamous-cell carcinoma of the uterine cervix and should have no prior chemotherapy exposure. The index lesions needed to be measurable or evaluable and outside previously irradiated areas. Patients should be 70 years old or younger, and should have a good performance status (World Health Organization (WHO) grade $\leqslant 2$). Adequate renal (creatinine clearance $\geqslant 1$ ml/s/1.73 m^2) and liver (bilirubin $\geqslant 25$ μmol/l) function, and normal white blood cell ($>4.0\times10^9$/l) and platelet ($>130\times10^9$/l) counts were required. All patients were informed of the mitomycin-C/cisplatin treatment and the involved risks and gave consent.

2.2. Treatment schedule

Patients were treated with mitomycin-C/cisplatin-combination chemotherapy using the following dosage and schedule of administration: mitomycin, 6 mg/m^2 i.v., and cisplatin, 50 mg/m^2 intravenously (i.v.), both administered on day 1 of a 4-week regimen.

Pre-hydration with 1 l of normal saline over 1 h, and i.v. infusion of furosemide preceded the administration of the chemotherapeutic agents. Mitomycin-C was given by i.v. push, immediately followed by i.v. push of mannitol, and i.v. infusion of cisplatin diluted in 500 ml of normal saline over 30 minutes. Posthydration consisted of 1 l of normal saline administered over 1 h. Diuresis was monitored closely during the 2.5-h infusion time ($\geqslant 200$ ml over the first half-hour, $\geqslant 150$ ml over the next 2 h). In the absence of disease progression or major side-effects, the desired minimum of nine cycles was administered.

2.3. Dose modifications

Dose modifications were determined by the severest toxicity. In the event of mild/moderate myelosuppression (white blood cell count): $2.6–3.9\times10^9$/l, or platelet count (PLT): $76–129\times10^9$/l), the dose of mitomycin-C was reduced by 50%. In the event of more severe haematological toxicity (white blood cells $\leqslant 2.5\times10^9$/l, or platelets $\leqslant 75\times10^9$/l), mitomycin-C was postponed for a maximum of 2 weeks. Persisting myelosuppression required withdrawal of mitomycin-C for that particular cycle, and a 25% reduction of mitomycin-C for the next cycle. In the event of hepatic toxicity based on elevated bilirubin levels (25–50 μmol/l or >50 μmol/l), the dose of mitomycin-C was reduced by 50 or 75% of the initial dose, respectively. In the event of renal impairment (creatinine clearance $\leqslant 0.67$ ml/s), the chemotherapy regimen had to be stopped.

2.4. Criteria for response and evaluability

Patients were considered clinically assessable for response if they had received at least two mitomycin-C/cisplatin cycles. Selected indicator lesions were measurable or evaluable. Tumour masses were measured bidimensionally with the same instrumental test (computed tomography (CT), ultrasound (US) or X-ray) as used at baseline. Treatment response and toxicity were assessed according to WHO criteria [6].

2.5. Statistical considerations

The main endpoint was response to treatment. Duration of response, survival, and side-effects were also described. The sample size calculation was based on the two-stage Gehan's design [7] aiming to include 6 patients at first, and then including additional patients according to the number of responses observed in the first stage. This guaranteed that the probability of an active treatment (real response rate $\geqslant 40\%$) exhibiting no responses in the first 6 patients (that is, false negative result) was less than 5% and allowed the effectiveness of the treatment regimen to be estimated with a standard error of 10%.

3. Results

48 patients were entered into this phase II trial. 13 were considered ineligible due to age older than 70 years ($n=6$), no evaluable lesions ($n=3$), inadequate blood counts ($n=2$) and adenocarcinoma of the cervix ($n=2$).

Table 1
Response by various factors for 33 patients with disseminated, squamous-cell carcinoma of the uterine cervix treated with mitomycin-C/cisplatin

	n	CR	PR	Response rate (95% CI)
Extent of disease				
Distant metastases only	25	5	7	48 (28–69)
Loco-regional and distant metastases	8	–	2	25 (3–65)
Site				
Loco-regional	8	–	1	13 (0–53)
Lymph nodes	22	4	6	46 (24–68)
Lung	11	1	1	18 (2–52)
Other[a]	7	3	2	71 (29–96)
Age (years)				
<50	16	1	5	38 (15–65)
$\geqslant 50$	17	4	4	47 (23–72)
Performance status at entry				
0	19	4	6	53 (29–76)
1	10	1	3	40 (12–74)
2	4	–	–	– –
Histological subtype				
Keratinising	11	3	4	64 (31–89)
LCNK	8	–	2	25 (3–65)
SCNK	3	–	–	– –
Not specified	11	2	3	46 (17–77)

CI, confidence interval; CR, complete response; LCNK, large-cell non-keratinising; *n*, number of patients; PR, partial response; SCNK, small-cell non-keratinising

[a] Bone, vagina, liver and cutaneous metastases.

33 patients received the required minimum of two mitomycin-C/cisplatin-courses for response evaluation, and 34 patients were assessable for toxicity.

The present analysis is based on 33 fully evaluable patients who started the protocol treatment. At entry, age varied between 29 and 67 years with a median of 50 years. The WHO performance status was 0 for 19 patients, 1 for 10 patients and 2 for 4 patients. Primary loco-regional treatment consisted of surgery in 4 patients, radiotherapy outside the current index lesions in 16 patients, a combination of surgery and radiotherapy in 12 women, and 1 woman was not previously treated. At entry into the mitomycin-C/cisplatin-study, 8 patients had loco-regional disease plus distant metastases and 25 women had only distant metastases.

The overall response rate was 42% (95% confidence interval (CI): 26-61%), 5 women had a complete (CR) and 9 had a partial response (PR). Furthermore, 9 patients had stable disease and 10 were progressive from the start of mitomycin-C/cisplatin-treatment. The median duration of response was 7.9 months (95% CI: 3.7–23.5 months). Table 1 shows the response rates by various predictive factors.

At a median follow-up of 12.6 months (range: 1.4–30.2 months) from the start of mitomycin-C/cisplatin-chemotherapy, 15 patients were alive and 18 patients had died due to malignant disease. Only 1 patient was alive with no evidence of disease after 13 months. The median progression-free survival was 5.0 months for all patients (95% CI: 3.6–6.2 months), and 10.5 months (95% CI: 6.2–15.2 months) for the responders. The overall median survival was 11.2 months (95% CI: 6.5–18.4 months).

Side-effects due to the mitomycin-C/cisplatin-regimen were documented using WHO toxicity criteria (Table 2). Although the mitomycin-C/cisplatin-regimen did not result in grade III/IV renal or hepatic side-effects or

Table 2
Side-effects due to treatment (worst value of World Health Organization (WHO) grading)

Side-effects $n=34$	0	1	2	3	4	Grade 3/4 (%)
White blood cells	12	15	5	2	0	6
Platelets	29	4	1	0	0	0
Haemoglobin	9	17	7	1	0	3
Nausea/Vomiting	0	7	18	6	3	26
Diarrhoea	27	4	1	2	0	6
Mucositis	31	2	1	0	0	0
Bilirubin	33	1	0	0	0	0
Serum creatinine	32	1	1	0	0	0
Pulmonary toxicity	32	1	1	0	0	0
Fever with drug	27	4	3	0	0	0
Allergy	32	1	0	0	1	3
Cutaneous reaction	32	2	0	0	0	0
Alopecia	23	6	4	1	0	3
Infection	32	2	0	0	0	0
Neurotoxicity, peripheral	33	1	0	0	0	0

peripheral neurotoxicity, severe gastrointestinal toxicity was observed in 1/3 of the patients. Furthermore, a 54-year-old woman developed a generalised allergic reaction during the ninth infusion of cisplatin. She went off the study having a clinical CR to the mitomycin-C/cisplatin-regimen.

The median white blood cell count nadir was 3.5×10^9/l (range: 1.7–7.4), the median platelet count nadir was 154×10^9/l (range: 59–370) and the median haemoglobin nadir was 6.4 mmol/l (range: 4.4–7.2). Grade III myelotoxicity was reported in 3 patients. 2 of them had low blood cell counts approaching cycle 9 requiring treatment delay in both and a blood transfusion in 1 of them because of severe anaemia. However, the third patient developed severe leucopenia (nadir white blood cells: 1.8×10^9/l) and mild anaemia during the first mitomycin-C/cisplatin-cycle. She was treated with blood transfusions, needed treatment delay and a 50% reduction of the dose of mitomycin-C. After the third cycle, chemotherapy was stopped because of haematological toxicity and grade II renal side-effects while she had a PR to mitomycin-C/cisplatin. 5 months after the start of mitomycin-C/cisplatin she died due to disease.

4. Discussion

The literature concerning the use of chemotherapy in disseminated cervical carcinoma consists mainly of regimens containing platinum-compounds. In a PubMed search of published trials between 1966 and 1999, 13 phase II/III trials testing the activity of four different mitomycin-C/cisplatin-based chemotherapeutic regimens in patients with squamous-cell carcinoma of the uterine cervix were identified (Table 3) [2,4,8–18].

The present mitomycin-C/cisplatin-regimen is active in patients with disseminated cervical cancer. The response rate and the observation of complete responses restricted to extra-pelvic disease corroborates the previous EORTC study testing vincristine/bleomycin/mitomycin-C/cisplatin [4].

This outpatient mitomycin-C/cisplatin-regimen was generally well tolerated and did not result in severe renal or hepatic side-effects or peripheral neurotoxicity. Nausea/vomiting was the most frequent severe adverse effect. However, the usual antiemetic treatment with dexamethasone and 5HT3-antagonists was not applied at that time. Haematological toxicity was dose-related and included mainly leucopenia and anaemia.

Since the mid-1970s, at least 40 cytotoxic agents, alone, and in combination have been evaluated. Several tested agents have shown some activity including four which are of particular interest because of their relatively high response rates in carefully conducted trials: cisplatin, ifosfamide, mitolactol (dibromodulcitol) and paclitaxel [18–23].

The EORTC/GCG reported the results of a phase III trial comparing bleomycin/vindesine (eldisine)/mitomycin-C/cisplatin versus single agent cisplatin in 287 patients with disseminated squamous cell carcinoma of the uterine cervix. Although bleomycin/vindesine (eldisine)/mitomycin-C/cisplatin showed a significantly higher response rate, the four-drug regimen resulted in more (non)haematological side-effects, and failed to show a survival benefit [18].

The Gynecologic Oncology Group (GOG) recently published the results of a randomised trial comparing cisplatin versus cisplatin/mitolactol versus cisplatin/ifosfamide in 438 eligible patients. Their results showed a significantly higher response rate and longer progression-free survival for cisplatin/ifosfamide compared with single agent cisplatin, but at the cost of greater toxicity and with no improvement in survival [22]. Furthermore, the GOG recently performed a phase II study of paclitaxel and cisplatin as first-line therapy [23]. Since the results suggested enhanced therapeutic benefit, a phase III trial comparing the paclitaxel/cisplatin combination with cisplatin alone has been conducted. The preliminary results again did not show any survival benefit for the combined regimen [24].

In conclusion, the development of effective combination chemotherapy should be based on the use of logically-designed combinations of active drugs in large

Table 3
Mitomycin-C/cisplatin-containing regimens in disseminated squamous-cell carcinoma of the cervix

Author (Ref.)	Chemotherapy	*n*	CR	PR	Response rate (%)
Present study	MP	33	5	9	42
Senapad [8]	MP	15	6	3	60
Smith [9]	BMP	10[a]	1	2	30
		44[b]	3	4	16
Hoffman [10]	BMP	25	–	6	24
Picozzi [11]	BMP	28	2	4	21
Chambers [12]	BOMP	18	4	4	44
Lahousen [13]	BOMP	17[a]	3	7	59
		22[b]	3	7	45
Vermorken [4]	VBMP	50	8	12	40
Belinson [14]	BOMP	14	1	2	21
Alberts [15]	BOMP	14	4	2	43
Shimizu [16]	BOMP	19	6	9	79
Chauvergne [17]	BE′MP	34[a]	2	23	74
		26[b]	1	9	38
Alberts [2][c]	P	9	1	2	33
	MP	51	2	11	25
	BOMP	54	4	8	22
Vermorken [18]	P	144	28		19
	BEMP	143	44		31

B, bleomycin; CR, complete response; E, vindesine (eldisine); E′, etoposide; M, mitomycin-C; *n*, number of patients; O, vincristine (=oncovin); P, cisplatin; PR, partial response.

[a] No prior treatment.

[b] Previously treated with radiotherapy and/or surgery.

[c] Randomised phase II trial.

phase III trials with single-agent cisplatin as the control. Although the results of this mitomycin-C/cisplatin combination indicated antitumour activity, the presently available data from the literature do not suggest that this regimen will be superior to cisplatin alone in terms of survival.

Acknowledgements

The authors would like to thank Mrs A. Thomson for her useful corrections to the manuscript.

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