

Short Communication

Phase II Study of Weekly 4'-Epidoxorubicin in Patients with Metastatic Adenocarcinoma of the Cervix: an EORTC Gynaecological Cancer Cooperative Group Study

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In this study 22 patients with metastatic adenocarcinoma of the cervix were treated with a weekly bolus injection of 4'-epidoxorubicin at a dose of 12 mg/m². Seventeen patients had received prior radiotherapy, all patients were chemo-naïve. Toxicity was generally absent or very mild. One patient had a complete response and 2 patients had a partial response, one was an unconfirmed partial response, giving a response rate of 14%. Six patients had stable disease. The median progression-free survival and overall survival was 2.8 months and 6.1 months, respectively. In conclusion, 4'-epidoxorubicin used at this dosage and schedule has minimal activity in metastatic adenocarcinoma of the cervix. © 1997 Elsevier Science Ltd.

Eur J Cancer, Vol. 33, No. 9, pp. 1513–1515, 1997

INTRODUCTION

CHEMOTHERAPY IN disseminated cancer of the uterine cervix is still a palliative treatment [1]. Although with combination chemotherapy, higher response rates have been reported, the response duration and survival are generally short.

Doxorubicin as well as 4'-epidoxorubicin as a three-weekly schedule at doses of 50 mg/m² and higher, has shown antitumour activity in carcinoma of the uterine cervix [4–9]. Response rates of 20–48% have been observed, but at the cost of considerable toxicity, especially in those patients who had received prior extensive pelvic radiotherapy [4–6]. Weekly low-dose 4'-epidoxorubicin at a dose of 20 mg total (approximately 12.5 mg/m²) has been suggested to be as effective as three-weekly high dose 4'-epidoxorubicin in patients with breast cancer but is significantly less toxic [10, 11].

We investigated whether an effective palliation with minimal toxicity could be achieved with weekly low-dose 4'-epidoxorubicin in patients with metastatic carcinoma of the

uterine cervix, squamous cell or adenocarcinoma. We previously reported a 4% partial response rate in squamous cell carcinoma of the cervix [12]. The present report is on adenocarcinoma of the cervix.

PATIENTS AND METHODS

Eligibility criteria included histologically confirmed adenocarcinoma of the primary tumour of the cervix; measurable or evaluable disease outside previously irradiated areas with documented progression; life expectancy of at least 2 months; WHO performance score 2; age <80 years; no prior radiotherapy or chemotherapy for at least 4 weeks before entry (mitomycin C, nitrosoureas and extensive radiotherapy for at least 6 weeks) and recovery from toxic effects of prior treatment; no prior therapy with antracyclines; white blood cell count (WBC) > 3 × 10⁹/l, platelet count > 100 × 10⁹/l; normal bilirubin; no active cardiac disease; no clinical signs of brain involvement or leptomeningeal disease; informed consent prior to therapy.

Treatment consisted of a weekly dose of 12.5 mg/m² 4'-epidoxorubicin by intravenous bolus injection. If WBC was 3 × 10⁹/l and/or platelets <75 × 10⁹/l treatment was delayed by 1 week. If after 1 week postponement the WBC was

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Received 8 Nov. 1996; revised 24 Mar. 1997; accepted 1 Apr. 1997.

Table 1. Patient and tumour characteristics at entry

	n	(%)
Patients	22	(100)
Age (years)		
Median (range)	59	(35-70)
WHO performance status		
0	6	(27)
1	9	(41)
2	7	(32)
FIGO stage		
I	10	(45)
II	3	(14)
III	7	(32)
IV	2	(9)
Extent of the disease at entry		
Primary only	2	(9)
Loco-regional recurrent	3	(14)
Metastatic only	11	(50)
Primary not excised and metastatic	3	(14)
Loco-regional recurrent and metastatic	3	(14)
Prior treatment		
Surgery		
None	10	(45)
Curative	10	(45)
Palliative	2	(9)
Prior radiotherapy		
No	5	(23)
Yes	17	(77)
No response	5	(23)
Response	7	(32)
Adjuvant	5	(23)
Site of radiotherapy		
Primary unresected tumour	7	(32)
Postoperative on site of resection	4	(18)
Postoperative on lung and bone metastases	1	(5)
Unknown	5	(23)
Sites of disease		
Lung	10	(45)
Lymph node	7	(32)
Liver	1	(5)
Bone	3	(14)
Locoregional	12	(55)
Skin	1	(5)

between 2.0 and $2.9 \times 10^9/l$ and/or the platelets between 75 and $99 \times 10^9/l$, the dose was reduced by 50%, but if WBC was still $<2.0 \times 10^9/l$ and/or platelets $<75 \times 10^9/l$, treatment was delayed another week for a maximum of 3 weeks.

Response was evaluated by computer tomography (CT) scan, gynaecological and complete physical examination after 6 cycles. Responses were defined according to the WHO response criteria [13]. The sample size calculation was based on the two-stage Gehan's design, aiming to include 14 patients and then adding other patients for each response seen in the first stage [14]. This guarantees that the probability of an active treatment (real response rate $\geq 20\%$) exhibiting no response in the first 14 patients (that is, false-negative result) is 0.05 and allows an estimate of the therapeutic effectiveness with a standard error of 10% [14]. Survival curves and time to progression curves were estimated using the Kaplan-Meier technique [14].

RESULTS

Twenty-three patients were entered into this phase II study, 22 of whom were eligible; 1 patient was excluded because all measurable lesions had been previously irradiated. The patient and tumour characteristics for all eligible patients are summarized in Table 1. None of the patients received prior chemotherapy. The median interval between diagnosis and start of chemotherapy was 18 months (range 0-81 months), the median treatment-free interval was 13 months (range 0-69 months). The median number of administered cycles was six (range 1-46). Eight patients received less than six cycles because of early progression (6 patients), early death (1 patient), and another patient was lost to follow-up after 2 cycles.

In general, treatment was well tolerated. Nausea and vomiting WHO grade 1 was observed in 8 patients (36%), grade 2 in 1 patient (5%) and grade 3 in 2 patients (9%). One patient (5%) had mucositis grade 1, 4 patients (18%) had alopecia grade 1 and 2 patients (9%) had grade 2. Myelotoxicity was mild. The median WBC nadir was $6.0 \times 10^9/l$ (range 2.1-14.5). The median platelet count nadir was $240 \times 10^9/l$ (range 60-575). Treatment delay was reported in 8 patients, in whom 2 were drug related: severe vomiting in one and thrombocytopenia in the other.

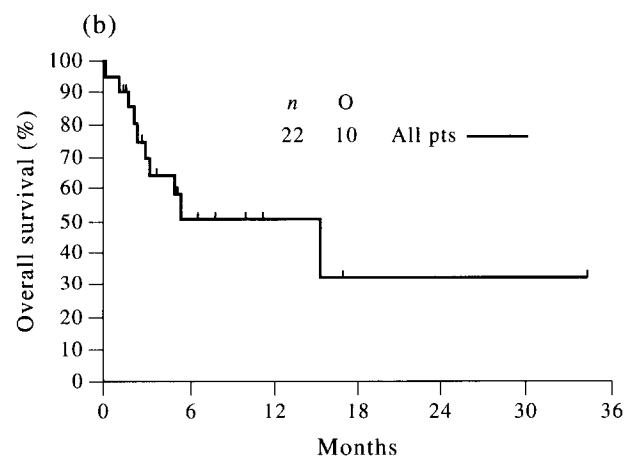
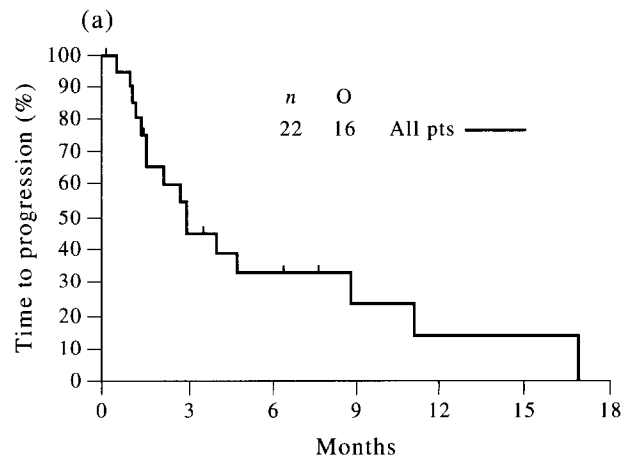


Figure 1. Time to progression (a) and overall survival (b).

Four patients were not evaluable for response: 1 patient had an early death not treatment or tumour related; 1 patient refused treatment after the first cycle; 1 patient was lost to follow-up after two cycles; and no CT scan was performed for the fourth patient after three cycles as the clinical condition worsened.

One complete and two partial responses, one not confirmed, was observed in the 22 eligible patients, giving a response rate of 14% (95% exact confidence interval: 3–35%). Complete response was observed in a patient with a lymph node metastasis outside the irradiated area; the treatment-free interval was only 1 month; she received a total of 10 cycles. The response lasted for 16 months, and she was still alive after a follow-up of 34 months. The patient with the partial response developed lung metastases 18 months after radiotherapy to the primary tumour, she received 26 cycles. The response lasted more than 4 months. One other patient had a partial response of the primary tumour after 6 cycles, but the patient refused further treatment; she was irradiated to the indicator lesion before response confirmation. Six patients (27%) had a stable disease and 9 patients (41%) had progression. The median progression-free survival of the 22 eligible patients was 2.8 months and the median duration of survival was 6.1 months (Figure 1).

DISCUSSION

The haematological and non-haematological toxicity from weekly low-dose 4'-epidoxorubicin was mild, especially myelotoxicity. Only in 1 patient did thrombocytopenia exceed grade one toxicity. The response rate (14%) was somewhat higher than those observed in epithelial cervical cancer (4%) [12]. However, the median progression-free survival and overall survival were only 2.8 months and 6.1 months, respectively.

The response rate of 4'-epidoxorubicin in this trial is disappointing in view of its activity in other tumours. This may be partially explained by the relatively low dose chosen for this trial. Despite this low dose, some activity was observed (14% based on all eligible patients and 17% if based on the 18 patients who were evaluable for response). Therefore, further investigation of the drug with higher doses, especially in view of the mild toxicity, may be recommended. Another possibility could be using 4'-epidoxorubicin in combination with other drugs. Cisplatin might be a reasonable choice as the combination of cisplatin and doxorubicin proved active in adenocarcinoma of the endometrium [16].

In conclusion, weekly low dose 4'-epidoxorubicin as single agent at a dose of 12.5 mg/m² has low activity and should not be used in metastatic adenocarcinoma of the cervix.

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Acknowledgements—This publication was supported by grant numbers 2U10-CA11488-14–5U10-CA11488-26 from the National Cancer Institute (Bethesda, Maryland, U.S.A.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.