Eur J Cancer, Vol. 29A, No. 1, pp. 147–148, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Phase II Study of Weekly 4′-Epidoxorubicin in Patients with Metastatic Squamous Cell Cancer of the Cervix: An EORTC Gynaecological Cancer Cooperative Group Study

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In this study 24 patients with metastatic cervical cancer were treated with a weekly bolus injection of 4′-epidoxorubicin at a dose of 12.5 mg/m². All patients were followed until disease progression. Toxicity was generally absent or very mild. Only 1 patient (4%) had a partial remission lasting 23 weeks and 9 patients (38%) had stable disease with a median duration of 13 weeks (range 7–36). 4′-Epidoxorubicin at this dose and schedule is not active in metastatic squamous cell carcinoma of the cervix.
Eur J Cancer, Vol. 29A, No. 1, pp. 147–148, 1993.

INTRODUCTION

CHEMOTHERAPY IN disseminated squamous cell cancer of the cervix is still a palliative treatment [1]. Although with combination chemotherapy including cisplatin response rates up to 69% have been reported, the response duration and survival were only 8 and 10 months, respectively, which is achieved at the cost of considerable toxicity [2–7].

Doxorubicin has shown activity in squamous cell carcinoma of the cervix, mainly at doses of at least 50 mg/m² [8–13], which is accompanied by considerable toxicity, especially in those patients who received extensive pelvic radiotherapy [9–11].

Weekly low-dose 4′-epidoxorubicin at a dose of 20 mg total was suggested to be as effective as 3 weekly high dose 4′-epidoxorubicin in patients with breast cancer but is significantly less toxic [14, 15].

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

PATIENTS AND METHODS

Eligibility criteria included histologically confirmed squamous cell cancer of the cervix; measurable or evaluable disease outside previously irradiated areas with documented progression; life expectancy of at least 2 months; performance score WHO ≤ 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 anthracyclines; white blood cells (WBC) $\geq 3 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/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 $< 3 \times 10^9$/l and/or platelets $< 75 \times 10^9$/l treatment was delayed by one week. If after 1 week postponement WBC was between 2.0–2.9 $\times 10^9$/l and/or platelets between 75–99 $\times 10^9$/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 computed tomography (CT)-scan, gynaecological and complete physical examination after 6 cycles. Responses were defined according to the WHO response criteria [16].

RESULTS

27 patients were entered into this phase II study, 24 of these patients were eligible for response. Patients' characteristics are summarised in Table 1. 3 patients were ineligible for the following reasons: 1 patient had a different histology, 1 patient had no measurable disease and 1 patient had a bad general condition.

7 patients received less than 6 cycles, 4 patients because of early death due to malignant disease and 3 patients stopped treatment due to early progression after, respectively 4, 4 and 5 cycles. All other patients received at least 6 cycles. The median number of cycles given was 7, range 1–21.

No complete and only 1 partial response (4%) (95% CI = 0.1–28.7%) has been observed in the 24 evaluable patients. 9 patients (38%) had stable disease. The response was observed in a patient without prior chemotherapy and lasted 23 weeks. Stable disease was observed in 2 patients with prior chemotherapy and 7 chemotherapy naive patients. The time to progression in these patients was median 13 weeks (range 7–36 weeks). 10 patients (42%) had progression and an early death due to malignant disease was observed in 4 patients (17%).

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Revised 29 June 1992; accepted 2 July 1992.

Table 1. Patients' characteristics

No. of patients	24
Age	
Median	53
Range	35–80
Surface area	
Median	1.65
Range	1.2–1.9
Performance status (WHO grade)	
0	6
1	12
2	6
FIGO stage	
I	4
II	11
III	6
IV	3
Prior therapy	
None	0
Radiotherapy	23
Chemotherapy (cisplatin including)	7
Sites of disease	
Lung	11
Lymph node	7
Liver	5
Bone	2
Locoregional	11

Toxicity data were evaluable on a total of 188 cycles; 138 cycles in 17 patients without prior chemotherapy and 50 cycles in 7 patients with prior chemotherapy. In general treatment was well tolerated. Grade 1 nausea and vomiting was observed in 8 (33%) of 24 patients and grade 2 in only 2 patients. 2 patients (8%) had mucositis grade 1, 4 patients (17%) had alopecia; 3 patients (13%) had grade 1 alopecia and 1 patient (4%) had grade 2.

Myelotoxicity was mild. The median WBC count nadir was 5.2×10^9/l (range 1.8–11.3); 2 patients without prior chemotherapy had a grade 1 and grade 3 leukopenia, respectively and 1 patient with prior chemotherapy had a grade 2 leukopenia. The median platelet count nadir was 290×10^9/l (range 94–840).

DISCUSSION

The toxicity from weekly low-dose 4'-epidoxorubicin was mild, the myelotoxicity was especially low for patients who had received extensive prior radiotherapy; only 1 patient had a grade 3 leukopenia. The response rate, however, was far from encouraging. Only 1 of the 17 chemotherapy naive patients had a short lasting response and none of the patients with prior chemotherapy responded. In contrast to the suggested equivalence in efficacy in breast cancer, in cervical cancer the weekly low dose 4-epidoxorubicin administration is less effective than the three times a week administration with doses of 80–120 mg/m^2 [17, 18]. Weekly low dose 4'-epidoxorubicin at a dose of 12.5 mg/m^2 should not be applied in metastatic cervical cancer.

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Acknowledgements—Other contributors to this work were: M. Piccart, Institute Jules Bordet, Brussels; M.S. Aapro, Hospital Cantonal, Geneve; G. Bolis, Clinica Mangiagalli, Milano; N. Natale, Ospedale Sacco, Milano; and W.W. ten Bokkel Huinink, The Netherlands Cancer Institute, Amsterdam.