Eur J Cancer, Vol. 27, No. 7, pp. 864–866, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Epirubicin in Advanced Endometrial Adenocarcinoma: a Phase II Study of the Grupo Ginecologico Español para el Tratamiento Oncologico (GGETO)

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27 patients with FIGO stage III–IV endometrial adenocarcinoma were entered in a phase II trial evaluating activity and safety of epirubicin given at 80 mg/m² intravenously every 3 weeks. 2 complete remissions (including a pathological one) and 5 partial responses were observed for a response rate of 26% (95% confidence interval 11–46). The median time to progression and median survival for all treated patients was 6 and 9.5 months, respectively. Treatment was well tolerated. Haematological toxicity was mild. The median total cumulative dose of epirubicin was 480 mg/m² (160–880) and cardiac toxicity was not observed. Further studies with higher doses of epirubicin in combination with other active drugs are indicated.
Eur J Cancer, Vol. 27, No. 7, pp. 864–866, 1991

INTRODUCTION

DURING THE initial evaluation of the doxorubicin analogue, 4'-epirubicin, the EORTC clinical screening group found some activity in a small group of patients with advanced endometrial carcinoma [1]. Thus it was decided to assess the possible role of this new drug in this carcinoma.

PATIENTS AND METHODS

Patients with histological diagnosis of endometrial adenocarcinoma with FIGO stage IV or III were considered suitable for the study. Inclusion criteria were: no previous treatment with chemotherapy, Karnofsky index of 50 or more, leucocytes greater than 4000/μl and platelets greater than 100 000/μl at entry, serum bilirubin lower than 1.5 mg/dl and creatinine below 2.0 mg/dl. Patients with brain metastasis, presence of second malignancy (excluding localised basal skin carcinoma) or previous history of cardiac disease were excluded. The study was approved by the ethics committee of each centre participating in the study and consent was required from all patients according to institutional requirements.

Pretreatment staging consisted of physical examination, haemogram and biochemistry, abdominopelvic computed tomography (CT) scan, lung radiograms and bone scintigraphy. Epirubicin was administered at a dose of 80 mg/m² intravenous bolus every 3 weeks on an outpatient basis. Standard doses of methoclopramide or alizapride were used as antiemetic at the investigator's discretion. Cardiac function during therapy was assesed by means of physical examination and electrocardiogram (ECG) performed every two cycles. WHO criteria [2] were used to evaluate response and toxicity. The first evaluation was made after the second cycle of epirubicin. In the absence of progressive disease, or grade 4 or clinical cardiac toxicity, the maximal total cumulative dose of epirubicin allowed was 880 mg/m².

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Revised 28 Feb. 1991; accepted 9 Apr. 1991.

RESULTS

From January 1986 to December 1988, 27 patients entered this study. Their characteristics are shown in Table 1.

Activity

All entered cases are evaluable for efficacy. 2 patients, both with vaginal disease, reached complete remission (CR), 1 of them confirmed pathologically, for a duration of 2+ and 10 months, respectively. A partial response (PR) was observed in 5 patients for a duration of 5, 5, 6+, 7+ and 12 months. An additional case with massive ascites had complete resolution of her disease after the second cycle of epirubicin: she was treated with ten courses of chemotherapy, maintaining a disease-free status during 12 months, but relapsed and died 13 months after entry into the study. As this patient had non-measurable disease she was not included in the responding group. 14 patients had no change and 5 presented progressive disease (PD) at the first evaluation. The characteristics of patients with CR or PR are depicted in Table 2. Vaginal, pelvic and lung were the most responsive sites. A minor response was detected in 1 out of 3 patients with liver involvement, while no activity was observed in bone and lymph-node lessions. The median time to progression and median survival for all treated patients was 6 months (range: 1–18) and 9.5 months (range: 2–19+), respectively.

Toxicity

All cases were included in the safety analysis. The median values for leucocytes and haemoglobin evaluated on day 1 of the cycle was 4700/μl (range: 1700–10300) and 11g/dl (range: 6.9–14), respectively. Thrombocytopenia was not detected. No patient needed admitting or supportive treatment due to therapy. Grade 4

Table 1. Patients' characteristics

Parameter	*n*
Mean age (range)	56 (37–69)
Histological grade at diagnosis	
G1	10
G2	8
G3	5
GX	4
Previous treatment	
Surgery	
Radical	18
Palliative	9
Radiotherapy	
Only external (Co60)	3
Only intracavitary	3
Both	14
Hormonotherapy	
MPA	4
TAM+MPA	1
Median time from diagnosis to advanced disease (months)	10 (0–84)
Median Karnofsky index at entry	90 (50–100)
FIGO stage at entry	
III	11
IV	16
Site of disease	
Vagina	11
Lung	9
Pelvis	6
Ascites*	3
Bone	3
Liver	3
Lymph-nodes	2

TAM = tamoxifen, MPA = medroxiprogesterone acetate.
* All with positive peritoneal cytology.

Table 2. Characteristics of responding patients

Age	KI	Previous RT: Intr.	Previous RT: Ext.	Previous HT	Grade	Site/ response	Duration of response*	Surv.*
64	90	N	Y	N	G1	Vagina/CR	10	10+
63	100	Y	Y	N	G2	Vagina/CR	2+	2+
66	70	Y	Y	N	G3	Lung/PR	12	15+
64	100	Y	Y	N	G1	Pelvis+ vagina/PR	7+	7+
63	100	Y	Y	N	G2	Pelvis+ vagina/PR	5	7+
55	100	Y	Y	Y	G2	Vagina/PR	5	9+
63	100	Y	Y	Y	G1	Lung/PR	6+	8+

KI = Karnofsky index at entry, RT = radiotherapy, HT = hormone therapy, Intr. = intracavitary, Ext. = external, Surv. = survival.
*months.

toxicity was not observed. Only 1 case had grade 3 leukopenia. 12 patients had anaemia but none needed blood supply. The median grade of epirubicin induced emesis was 1 with 5 cases presenting grade 3 vomiting. 4 patients had mucositis, but the incidence of diarrhoea was minimal. Treatment-related fever was detected in 3 patients. Complete or partial alopecia was observed in 22 cases. The median epirubicin cumulative dose was 480 mg/m^2 (range: 160–880); 13 patients reached an epirubicin cumulative dose higher than 550 mg/m^2. Cardiac toxicity was not observed.

DISCUSSION

This study has demonstrated that epirubicin at a dose of 80 mg/m^2, intravenously every 3 weeks, is able to induce responses in patients with endometrial adenocarcinoma. The parent drug, doxorubicin, was evaluated in endometrial cancer during the 1970s. In one study [3] 21 patients with advanced endometrial adenocarcinoma in relapse or progressing after progestin therapy were treated with doxorubicin 50 mg/m^2 intravenously every 3 weeks. 1 complete and 3 partial responses were observed for a 19% response rate (95% CI = 5–42%). Doxorubicin produced 3 and 2 instances of severe and life-threatening haematological toxicities; the median overall survival was 9.3 months. In the second trial [4], 43 patients with advanced or recurrent endometrial carcinoma no longer amenable to surgery or radiotherapy were treated with doxorubicin 60 mg/m^2 intraveously every weeks: 16 out of 43 cases achieved complete or partial remission, a 44% response rate (95% CI = 29–60%), with an impressive frequency of complete remissions, 11 of 43 (25%) (95% CI = 13.5–41%). The median overall survival was 6.8 months. Most patients suffered from haematological toxicity: 6 and 2 patients demonstrated grade 3 and 4 leukopenia, respectively, and 1 case had grade 4 thrombocytopenia. In addition, congestive heart failure was noted in 3 cases and in 1 of them was lethal. In the present study, 27 patients with advanced endometrial carcinoma received epirubicin 80 mg/m^2 intravenously every 3 weeks. 7 patients reached complete or partial response for a response rate equal to 26% (95% CI = 11–46%) 2 cases—7% (95% CI = 1–24%)—achieved complete response and the median overall survival, 9.6 months, is similar to those reported in patients treated with combination chemotherapy regimens [5]. Toxicity analysis demonstrates that this dose level produces mild haematological toxicity, with only 1 patient presenting grade 3 leukopenia. The median epirubicin total cumulative dose was 480 mg/m^2 (160–880) but 13 cases reached cumulative doses higher than 550 mg/m^2. However, no patient had cardiac toxicity.

The lack of severe haematological toxicity of epirubicin, 80 mg/m^2 every 3 weeks, suggests that higher doses can be given. The clinical use of epirubicin employing doses above 90 mg/m^2 is under active development: a broad phase II study using doses from 100 to 120 mg/m^2 every 3 weeks has shown that this drug can be safely administered in patients with solid tumours, mucositis being the major toxicity [6]. Escalating doses of epirubicin, 60–120 mg/m^2 every 4 weeks, have been tested in patients with advanced cervical cancer, achieving a high response rate with acceptable toxicity; this trial has also demonstrated that maintenance therapy with 120 mg/m^2 every 4 weeks is feasible [7]. Another study with epirubicin 120 mg/m^2 every 3 weeks in breast cancer has reported encouraging results, with mild haematological toxicity and no patient requiring hospitalisation for treatment related sepsis [8]. One recent trial [9], evaluating single agent epirubicin in small cell lung cancer, has shown activity, confirming that doses ranging between 100 to 120 mg/m^2 every 4 weeks can be safely administered in patients with no prior chemotherapy. Dose intensity analysis applied to endometrial cancer demonstrates that a linear correlation between major response and average dose intensity exists for doxorubicin and cisplatin [10]. The use of higher doses of epirubicin in combination with cisplatin might provide an attractive approach to the treatment of patients with advanced endometrial carcinoma.

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Acknowledgement—We thank Mrs Conchita Florián for her contribution to the preparation of this manuscript.

Eur J Cancer, Vol. 27, No. 7, pp. 866–870, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Effective New Low Toxicity Chemotherapy with Carboplatin, Vinblastine and Methotrexate for Small Cell Lung Cancer: a Randomised Trial against Doxorubicin, Cyclophosphamide and Etoposide

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Carboplatin has been incorporated into a new low toxicity combination chemotherapy regimen with methotrexate and vinblastine (CVM) against small cell lung cancer (SCLC). We have compared CVM (carboplatin 300 mg/m², vinblastine 6 mg/m², methotrexate 30 mg/m², all intravenously every 4 weeks) with ACE (doxorubicin 40 mg/m², cyclophosphamide 600 mg/m², etoposide 100 mg/m² all intravenously day 1–3, every 3 weeks) in a randomised trial. 36/54 evaluable patients treated with CVM achieved an objective response (67%) (95% confidence limits [CL] 54–79%) compared with 44/50 treated with ACE (88%) (95% CL 80–97%, $P = 0.06$). For patients with limited disease treated with CVM, 14/17 (83%) (95% CL 64–100%) had an objective response compared with 14/15 (93%) (95% CL 81–100%) treated with ACE (not significant). Overall median survival was 8 months for CVM and 7 months for ACE. Haematological toxicity was significantly lower for CVM than ACE and consequently dose reduction/delay and infection were less with CVM. Subjective toxicity was low and alopecia was significantly less for CVM than ACE. CVM is an active, well tolerated new chemotherapy regimen for SCLC.
Eur J Cancer, Vol. 27, No. 7, pp. 866–870, 1991

INTRODUCTION

COMBINATION CHEMOTHERAPY for small cell lung cancer (SCLC) achieves useful palliation for the majority of patients and has been shown in several randomised studies to prolong median survival [1, 2]. However, long-term survival and cure is rare, occurring in only 5–10% of patients [3]. Intensive chemotherapy regimens and high-dose chemotherapy with or without autologous bone marrow rescue have resulted in higher response rates but have failed to achieve any significant improvement in overall survival and are often associated with considerable treatment-related morbidity [4–6]. In this context an intensive carboplatin-based regimen given in combination with ifosfamide and etoposide was recently shown by our unit to achieve a high response rate but only marginal survival benefit, at the expense of considerable toxicity [7].

An important aim should therefore be to design palliative regimens of low subjective toxicity appropriate for treating the majority of patients with SCLC. As part of this aim, we wished to develop a treatment regimen that did not cause alopecia. Carboplatin, an active agent at conventional dose in SCLC [8], was a suitable candidate in this respect, but it proved difficult to identify others. Initially we piloted a regimen using carboplatin with methotrexate and vincristine which both have useful single agent activity in SCLC [9, 10]. This achieved an overall response rate of 70% in the first 17 patients: 5 complete response (CR) and 7 partial response (PR) but toxicity was high for a palliative therapy, including significant alopecia, neuropathy and constipation. Vinblastine was therefore substituted for vincristine on the

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Revised 28 Mar. 1991; accepted 8 Apr. 1991.