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SINGLE AGENT EPIRUBICIN IN SQUAMOUS CELL CERVICAL CANCER

A phase II trial

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Abstract

Thirty consecutive patients with FIGO stage III-IV, squamous cell uterine cervix cancer were entered in a phase II trial evaluating activity and safety of epirubicin when given at a dose of 80 mg/m^2 i.v., every 3 weeks. Two complete responses (including a pathological complete remission) plus 3 partial responses were observed among 27 evaluable patients with a response rate of 18.5% (95% confidence limits = 7.6%–36.4%). The median time to progression and median survival for all treated patients were 3 and 8 months respectively. Treatment was well tolerated. Haematological toxicity was mild. WHO grade 4 toxicity was not observed. The median total cumulative dose of epirubicin was 360 mg/m^2 (80–840 mg/m^2). Congestive heart failure was not noted. Further studies in cervical cancer with higher doses of epirubicin as single agent or in combination with other non-myelotoxic drugs are indicated.

Key words: Cervical cancer, epirubicin, phase II trial.

During the initial evaluation of the doxorubicin analog 4-epirubicin, the EORTC clinical screening group found one partial response among 6 cases with advanced cervical cancer (1). At this time there was no standard chemotherapy for patients with locally advanced or metastatic cervical cancer (2), and it was thus decided to assess activity and side-effects of epirubicin as single agent in patients with advanced uterine cervix cancer.

Material and Methods

The 30 patients with histological diagnosis of squamous cell cervical cancer who entered the study had received the following primary treatment: one patient surgery alone, 22 patients surgery plus pelvic radiotherapy, and 7 patients with advanced cancer no previous treatment. All patients with FIGO stage III or IV, relapsed after primary treatment and primary advanced cervical cancer, were considered suitable for the study. Inclusion criteria were: no previous treatment with anthracyclines, Karnofsky index $\geqslant 50$, more than 4 000 leukocytes/mm^3 and more than 100 000 platelets/mm^3, serum bilirubin < 15 mg/l and creatinine < 20 mg/l. Patients with brain metastasis, presence of second malignancy (excluding localized basal cell skin carcinoma) or previous history of cardiac disease were excluded. Informed consent was required from all patients.

Pretreatment staging consisted of physical examination, hemogram and biochemistry, abdominopelvic CT scan, lung radiograms and bone scintigraphy. Epirubicin was administered at a dose of 80 mg/m^2 i.v. bolus, every 3 weeks. Standard doses of methoclopramide or alizapride were used as antiemetic according to choice by the investigator. Cardiac function during therapy was assessed by physical examination and electrocardiogram performed at every second cycle. WHO criteria (3) were used to evaluate response and toxicity. The first evaluation was made after the third cycle of epirubicin. In the absence of progressive disease, grade 4 or continued grade 3 toxicity or clinical cardiac toxicity the maximal total cumulative dose of epirubicin allowed was 880 mg/m^2.

From January 1986 to December 1987, 30 consecutive

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Table 1

Epirubicin in cervical squamous cell cancer. Patients characteristics

Parameters	n
Number entered	30
Median age (range) 59 (38–77) years	
Squamous cell carcinoma	30
Histological grade	
G1	10
G2	10
G3	5
GX	5
Initial treatment	
Surgery	1
Surgery + pelvic radiotherapy	22
No previous treatment	7
Previous chemotherapy (cisplatin-based) of recurrence	2
Median disease-free interval after initial treatment (range) 19 (0–108) months	
FIGO stage at entry in trial	
Stage III	14
Stage IV	16
Median Karnofsky index at entry 80% (50–100)	
Site of disease	
Vagina	16
Pelvis	12
Lymph nodes	7
Lung	5
Bone	4
Peritoneum	1
Liver	1

patients were entered into the study. Their characteristics are shown in Table 1. The median age was 59 years (38–77), the median Karnofsky index at entry was 80 (50–100). Ten and 5 out of 25 cases in which grading was available had histological grade 2 and 3 at diagnosis respectively. Twenty-two cases had previously received radiotherapy and 2 cisplatin-based chemotherapy. There were 14 and 16 patients with stage III and IV respectively. The median time from diagnosis to evidence of advanced disease was 19 months. Seven patients had visceral involvement: 1 peritoneum, 1 liver and 5 lung.

Results

Activity. Among the 30 entered patients, one was lost to follow-up after the first cycle and 2 died, having received 1 and 2 courses of epirubicin respectively before evaluation: 27 cases were evaluable for activity. Two complete and 3 partial responses were observed: response durations were 10 and 14 months for the complete and 2, 3 and 6 months for the partial responders. Eleven cases had no change and 11 presented progressive disease at the first evaluation. The characteristics of patients with complete or partial response are reported in Table 2. Three out of six patients not previously exposed to radiotherapy responded; in contrast only 2 cases among the evaluable patients previously treated with radiotherapy reached major response ($p = 0.01$). Table 3 summarizes response related to the site involved showing that the most responsive sites were vaginal and nodal disease. The median time to progression and median survival for all treated patients were 3 months (1–14) and 8 months (1–14+) respectively.

Toxicity. Toxicity was evaluated in 28 patients. The median values for leukocytes, platelets and haemoglobin evaluated on day 21 were 5 900/mm^3 (1 600–15 800), 296 000/mm^3 (160 000–650 000) and 105 g/l (72–146). No patient needed hospitalization or supportive treatment. Table 4 shows haematological and non-heamatological toxicity, concerning the worst grade observed in each patient during epirubicin therapy. Grade 4 toxicity was not observed. No leukopenia was observed in 25/28 patients; nor was thrombocytopenia seen. Treatment-related anemia was observed in 13 patients but none needed blood supply. The median grade of epirubicin-induced emesis was 2, with 5 cases presenting grade 3 vomiting. Seven cases presented grade 1 mucositis. The incidence of diarrhea was minimal. Complete or partial alopecia was observed in 21 cases. The median epirubicin cumulative dose was 360 mg/m^2 (80–840); 8 cases reached an epirubicin-cumulative dose higher than 500 mg/m^2. Three cases treated with epirubicin-cumulative doses of 450, 810 and 840 mg/m^2 had grade 1 cardiac toxicity with transient ECG changes without clinical cardiac symtoms. No patient developed congestive heart failure.

Table 2

Characteristics of responding patients

Patient code	Age y.	Grade	KI at entry	Previous		Site–response	Overall response	Duration of response (months)	Survival (months)
				RT	CT				
5 C	64	G2	90	+	–	Lung-PR	PR	2	10
20 C	57	GX	50	+	–	Lymph nodes-PR	PR	3	9
22 C	51	G3	100	–	–	Vaginal-PR	PR	6	6+
9 C	70	GX	80	–	–	Pelvis-CR Vaginal-CR	CR	10	10+
11 C	73	G3	90	–	+	Vaginal-CR*	CR	14	14+

*Pathologically complete response.
KI = Karnofsky index; RT = radiotherapy; CT = chemotherapy.

Table 3

Epirubicin in cervical cancer. Site of disease and response

Site of disease	Number/total	CR	PR	NC	PD
Vaginal	15/16	2	1	6	6
Pelvic mass	9/12	1	–	5	3
Lymph nodes	7/7	1	1	3	2
Lung	4/5	–	1	1	2
Bone	3/4	–	–	1	2
Peritoneum	1/1	–	–	–	1
Liver	1/1	–	–	–	1

Table 4

Epirubicin in cervical cancer. WHO toxicity highest grade registered in each patient

Type	Grade				
	0	1	2	3	4
Leukopenia	25	2	–	1	–
Thrombocytopenia	28	–	–	–	–
Anemia	15	9	3	1	–
Nausea + vomiting	3	5	15	5	–
Mucositis	21	7	–	–	–
Diarrhea	25	1	1	1	–
Fever	27	1	–	–	–
Alopecia	7	2	7	12	–
Cardiac	25	3	–	–	–

Discussion

The present study has demonstrated that epirubicin at a dose of 80 mg/m^2 is able to induce major responses in patients with squamous cell uterine cervix cancer; 2 complete responses, including a pathological complete response, and 3 partial remissions occurred among 27 evaluable cases. The response rate was 18.5% (95% confidence limits 7.6–36.4%). Most patients in our study were chemotherapy naïve. Only two patients had previously received cisplatin-based chemotherapy and one of them achieved a partial response. Among the 22 patients who previously had received radiotherapy the response rate was low, similarly to what has been observed in phase II trials with other active drugs (4). The parent drug, doxorubicin, has been evaluated in cervical cancer during the last decade with response rates ranging from 6.6% to 21% (5–7). The absence of severe myelotoxicity of epirubicin indicates that higher doses of epirubicin can be given. The clinical use of epirubicin, employing doses above 90 mg/m^2 every 3–4 weeks is under investigation. An extensive phase II study using epirubicin doses from 100 to 120 mg/m^2 every 3 weeks has shown that epirubicin can be safely administered to patients with solid tumours, with mucositis as the major toxicity (8). Escalating doses of epirubicin, 60 to 120 mg/m^2 every 4 weeks, have been recently tested in patients with advanced cervical cancer: 8 complete and 10 partial responses were observed in 38 evaluable patients with acceptable toxicity. This trial also demonstrated that maintenance therapy with epirubicin 120 mg/m^2 is feasible (9). Future trials with epirubicin in cervical cancer should address the optimal dose of this anthracycline analog as single agent or in combination with other active non-myelotoxic drugs.

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