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Original Paper

High Dose Epirubicin is Effective in Measurable Metastatic Prostate Cancer: a Phase II Study of the EORTC Genitourinary Group

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39 hormone-resistant prostate cancer patients with bidimensionally measurable metastatic lesions were given epirubicin 100 mg/m^2 intravenously every 3 weeks. One patient was ineligible and excluded from analyses. According to WHO criteria, 9 patients (24%) had a partial response, 16 patients (42%) had stable disease (including 3 patients (8%) with a partial response not confirmed 1 month later), 11 patients (29%) had progressive disease, and in 2 patients (5%) response was not evaluated. Toxicity was as expected. Fifty-five per cent of patients had WHO grade 3/4 toxicity for white blood cells, and 3% of patients grade 3 toxicity for platelets. Other toxicities included nausea and vomiting, mucositis and alopecia. 2 patients with pre-existing cardiac disease developed cardiotoxicity (1 grade 2, 1 grade 3). An attempt was made to correlate response with prostate specific antigen (PSA) measurements. A positive trend was seen, but 2 non-responding patients showed a > 50% decrease in value.

Key words: epirubicin, prostate cancer, chemotherapy, hormone resistance, phase II study, prostate specific antigen (PSA)

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INTRODUCTION

THE OVERALL outlook for patients with metastatic prostate cancer who are, or who become, resistant to hormonal therapies is poor, with a median survival of 44 weeks [1]. Survival is considerably shorter for those who develop soft tissue metastases. Unfortunately, chemotherapy has so far proved to be of little value in prostate cancer, and cannot yet be accepted as forming part of the standard management of this disease [2]. No single cytotoxic drug or combination of drugs has been shown to improve survival [2–5].

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The EORTC Genitourinary Cancer Cooperative Group has undertaken a number of phase II chemotherapy studies in the hope of identifying active agents [6–9] and has also been concerned with the need to objectively assess response in phase II studies. A policy of using only bidimensionally measurable soft tissue and visceral lesions has been employed, since the determination of response in (the commoner) bone lesions is currently impossible [10]. In an attempt to identify other useful parameters by which response can be assessed, and to evaluate whether serial values of serum prostate specific antigen (PSA) correlate with objective response, a scientific "side study" was proposed when the study reported here was initiated in 1989.

The rationale for the selection of epirubicin at high dose was based on observations made during a previous study performed by the group (protocol 30841) of low dose epirubicin at the rate of 12 mg/m^2 weekly. Although the overall objective remission rate (complete and partial response: CR + PR) in that study was only 12%, 1 patient achieved a CR and 2 had a PR with marker lesion CR (i.e. the marker lesions vanished, but there was evidence of unmeasurable disease elsewhere). There was good subjective improvement in those patients who responded to this low dose treatment and doubts were raised as to whether or not the intensity of the treatment was too low. It was proposed that

the drug should be tested again at a more conventional dose and schedule. On the basis of the experience of members of the group with epirubicin, at a dose intensity of 100 mg/m^2 every 3 weeks, in treating patients with advanced bladder cancer, this schedule was adopted.

PATIENTS AND METHODS

A phase II study was performed. Only patients with histologically proven carcinoma of the prostate with evidence of disease progression prior to entry into the study were accepted. All patients had to have bidimensionally measurable disease in the form of metastases to lung, superficial lymph nodes, skin and subcutaneous tissues and lymph nodes (if measurable by computed tomography (CT) scan) in the mediastinum, retroperitoneum or pelvis. The initial diameters of such nodes had to be greater than 2.5 cm to allow reliable measurements during follow-up. Liver metastases were also accepted provided they could be measured by either abdominal ultrasound or CT scanning, again with an initial diameter > 2.5 cm. All patients had to have undergone prior hormone manipulation, but additive hormonal therapy which was failing had to be stopped at least 1 day before the protocol therapy was started. For those patients in whom an accelerated relapse was feared when exogenous hormones were to be stopped, the study protocol suggested that the patient should be considered for an orchidectomy. It was also suggested that a reasonable period of time elapsed following hormone withdrawal before the study drug was commenced, in case a further response was seen. Previous cytotoxic drug therapy disqualified the patient, as did the presence of concomitant malignancy, except for basal cell skin cancer. Previous radiotherapy did not disqualify the patient from entry provided there was one unirradiated indicator lesion.

Patients had to be under the age of 75 years, have an expected survival of more than 60 days and a WHO performance status [11] of 2 or less. The initial full blood count had to show a white blood cell count greater than 4×10^9/l, and platelets $> 100 \times 10^9$/l, unless a depressed count could be proved to be due to tumour invasion of the bone marrow. Adequate renal function as evidenced by a serum creatinine of less than 120 μmol/l was required, as too was adequate liver function with serum bilirubin less than 20 μmol/l.

If there was expected difficulty with follow-up for any reason, or the patient had medical or social conditions preventing the optimal application of the drug, the patient was ineligible for the study. Therefore, since epirubicin has potential cardiotoxic side-effects, this precluded the admission of patients with congestive cardiac failure, significant cardiac arrhythmias, complete bundle branch block, recent myocardial infarction or uncontolled hypertension.

The aim of the study was to determine the objective tumour response rates and duration of response produced by epirubicin when given in a dose of 100 mg/m^2 by bolus intravenous injection with a saline flush-through. The drug was administered every 3 weeks and treatment continued until the development of progressive disease or the stipulated maximum cumulative dose of 1 g/m^2 was achieved. At this dose level, treatment could be continued at the discretion of the investigator, provided that a PR or a good no change (NC) category response was evident and the treatment was being well tolerated by the patient, while recognising the increased risk of cardiotoxicity.

Treatment was withheld if the total white blood cell count was $< 4 \times 10^9$/l, the granulocyte count $< 2 \times 10^9$/l or the platelet count $< 100 \times 10^9$/l. Treatment was postponed for a maximum of 2 weeks if these levels were not reached after which the patient went off study. If the treatment had to be delayed because of a suppressed count, a dose reduction to 75 mg/m^2 was required for the next and subsequent courses of treatment. This dose reduction was also made for individual courses when the nadir total white blood cell count was $< 1 \times 10^9$/l, the granulocyte count $<0.5 \times 10^9$/l or platelet count $<50 \times 10^9$/l. The nadir count was taken as occurring on day 14 of each cycle.

If the serum bilirubin rose to between 30 and 50 μmol/l then the dose was reduced to 50%. Above the upper limit stated the dose was withheld. Any evidence of cardiac or lung toxicity, an allergic reaction or any other toxicity likely to be life-threatening and thought to be due to the investigational drug prompted the patient to go off-study.

At least two courses of the protocol treatment were to be given. Patients not receiving two courses could not be evaluated for response unless they had rapidly progressive disease, when the response was recorded as progressive disease (PD). Patients with an objective response (CR or PR) or NC with a stable performance status were maintained on treatment until objective disease progression or significant toxicity developed. If a CR was achieved, treatment was to continue for at least three more courses if toxicity allowed.

Ancillary treatments, excluding hormones, could be given as medically indicated, but no hepatotoxic drugs were allowed. Radiotherapy could be given concomitantly provided that the treatment did not include the indicator lesion. Treatment could be interrupted or stopped at the discretion of the investigator or at the request of the patient. Patients had to give informed consent according to the rules and regulations of the individual participation institutions. Permission to proceed with the study had to be obtained from the institutional Ethical Committee.

Pretreatment studies included clinical history, physical examination, assessment of performance status, measurement of palpable disease, height, weight, full blood count, biochemical profile, tests of liver and renal function, chest X-ray, ECG (electrocardiogram) and CT scanning and ultrasonography as means of measuring the indicator lesions. Follow-up investigations included the above prior to each dose of epirubicin and an assessment of response was made after every two doses. The WHO criteria for response were used [11]. Tumour size was defined as the product of the two largest perpendicular diameters of the lesions. CR was defined as the complete disappearance of all known disease determined by two observations not less than 4 weeks apart. PR was a 50% or more decrease in total tumour size of the lesion(s) determined by two observations not less than 4 weeks apart. In addition, there could be no new lesions appearing or progression of any lesion. NC was defined as >50% decrease in total tumour size or a > 25% increase in size of one or more of the measurable lesions was demonstrated. PD was defined as a 25% or more increase in the size of any one or more measurable lesions, or the appearance of a new lesion. Early death was defined as death occurring during the first 4 weeks due to tumour progression and early toxic death as death occurring in the first 4 weeks due to drug toxicity.

Extramural review of all the study forms was undertaken by the study coordinator (WGJ), in conjunction with the data manager, statistician and research fellow.

RESULTS

The study was initiated on 28 April 1989 and closed on 26 February 1992. 39 patients were entered. They have all now gone off-study and the study forms have been evaluated by the

Table 1. Best overall response—38 eligible patients

Response	No. of patients	Percentage
Partial response	9	24
No change*	16	42
Progressive disease	11	29
Not evaluated	2	5
Total no. of patients	38	100
Overall response rate (all patients)		24% (11.4–40.2)†
Overall response rate (evaluable patients)		25% (12.1–42.2)†

* Including 3 patients in partial response, not confirmed by a second measurement. † Figures in parentheses = 95% confidence interval.

Table 2. Response by type of marker lesion

Measurable lesion	Response CR	PR	NC	PD	Non-evaluable	Total
Lymph nodes	12	10	9	8	3	42
Lung	0	0	3	3	1	7
Liver	3	8	8	1	2	22
Skin	0	0	0	1	0	1
Subcutaneous	0	1	1	1	0	3

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

study coordinator. One patient was ineligible by virtue of not having a bidimensionally measurable marker lesion. He has been excluded from analyses, leaving 38 patients fully evaluable for response, time to progression and toxicity analyses. All the patients had objective evidence of progression at the start of the study and met the inclusion criteria as detailed above. These patients came from 14 institutions in Europe. The mean age of the patients was 63 years (range 45–75). 27 of the patients had undergone an orchidectomy at some time prior to study entry and the other 11 had received additive hormone treatment. 15 patients had received prior radiotherapy treatment.

Table 3. Haematological toxicity (nadir values)—38 eligible patients

	% Toxicity WHO grade 0	1	2	3	4	% Grade 1–4	% Grade 3–4
White blood cells	2	3	12	19	2	95	55
Neutrophils*	9	2	6	6	6	69	41
Platelets	34	3	0	1	0	11	3
Haemoglobin	12	12	8	6	0	68	16

* Nine missing values.

Table 4. Distribution of nadirs (day 14)

Blood parameter	Median value	Limits	Measure
White blood cells	1.9	0.60–4.80	10^9/l
Neutrophils	1.09	0.05–5.20	10^9/l
Platelets	187	37–413	10^9/l
Haemoglobin	6.15	4.30–8.60	mmol/l

Table 5. Non-haematological side-effects—38 patients evaluable for toxicity

	Toxicity (worst) by WHO grade 0	1	2	3	4	% Grade 3–4
Nausea/vomiting	9	13	9	5	2	18
Diarrhoea	31	6	1	0	0	0
Mucositis	29	5	2	2	0	5
Phlebitis	36	0	1	1	0	3
Cutaneous reaction	36	1	1	0	0	0
Allergy	38	0	0	0	0	0
Liver toxicity*	32	0	1	0	0	0
Renal toxicity†	36	0	0	0	0	0
Pulmonary toxicity‡	36	0	1	0	0	0
Cardiotoxicity§	33	0	1	2	0	6
Neurotoxicity	32	4	2	0	0	0
Alopecia	9	7	9	12	1	34
Drug fever‖	30	3	4	0	0	0
Hypotension†	36	0	0	0	0	0
Infection	34	2	1	1	0	3
Haemorrhage	36	2	0	0	0	0
Ototoxicity¶	37	0	0	0	0	0

* Five missing values. † Two missing values. ‡ One patient had pre-existing pulmonary insufficiency. § Two patients had pre-existing cardiac disease. ‖ One patient had a pre-existing fever. ¶ One missing value.

Response

The overall response rates are shown in Table 1. 9 patients (24%) achieved a PR, among whom 1 patient had an unexplained dose reduction during part of the treatment. Another 3 patients (8%) were categorised as having NC since the PR was not confirmed 4 weeks after first documentation. 2 patients were excluded from the evaluation of response because of the following reasons: a different method of imaging was used to measure objectively the indicator lesion from the original (ultrasound/CT), and this was not allowed by the study protocol; the response was never assessed after the second course. The response by marker lesion is shown in Table 2 (patients often had more than one marker lesion). Fifteen CRs were evaluated in marker lesions, but since these patients also had other lesions which did not completely respond, the overall response rate had to be classified as PR. The median duration of response (PR) was computed by an actuarial method (Kaplan–Meier) and found to be 28 weeks (range 20–90).

Toxicity

All 38 patients were evaluable for toxicity. Haematological toxicity was as expected with approximately 50% of patients suffering grade III/IV WHO toxicity for white blood cells and neutrophils as can be seen in Table 3. Nadir values are shown in Table 4. Non-haematological side-effects reported during treatment are shown in Table 5. These were much as expected with 18% grade III/VI nausea and vomiting and 34% alopecia grade III/IV. 2 patients with pre-existing cardiovascular disease developed cardiotoxicity. One patient developed myocardial ischaemia during his fourth and last cycle, and a second patient developed angina pectoris with decreasing ejection fraction

Table 6. Comparison of objective tumour response and prostate specific antigen (PSA) response (25 eligible patients with at least two PSA measurements during treatment)

PSA response	Objective tumour response					Range of PSA changes	Total
	PR	NC*	NC	PD	Non-evaluable	% of initial value	
⩾ 50% decrease	5	1	1	1	0	0.3–44	8
< 50% decrease	1	3	0	2	1	59–93	7
Increase	0	0	4	5	1	108–670	10
Total	6	4	5	8	2	—	25

* Partial remission without confirmation of the response at or after 8 weeks.

during the second cycle with an overall response of NC. On the whole, treatment was well tolerated although 4 patients went off-study due to toxicity for the following reasons: (a) sudden deterioration in general condition with progressive pain and general malaise after five cycles, having achieved a PR remission; (b) nausea and vomiting grade IV after a total of three cycles in PR; (c) reduced blood counts, phlebitis, diarrhoea, nausea and vomiting, the patient going off-study after five cycles with a NC category of response; (d) cardiotoxicity with a decreasing ejection fraction on echocardiography after two cycles (NC response) in the face of pre-existing heart disease.

2 patients refused to continue treatment and 2 patients went off-study after reaching the maximum cumulative dose (1 g/m^2).

Correlation of response with PSA estimations

25 of the eligible patients had at least two serum PSA investigations performed during the study period. The PSA response in terms of a ⩾ 50% decrease, a < 50% decrease or an increased value was compared with the objective tumour responses observed and is shown in Table 6. From this it can be seen that there is a general trend towards a positive correlation, although it must be pointed out that 2 patients with NC or PD responses had a > 50% decrease in PSA estimations. It is generally felt that on the basis of the data available, no further comment can be made except that this phenomenon needs to be validated in the next study performed by the group.

DISCUSSION

This phase II study of epirubicin (given at a dose of 100 mg/m^2 every 3 weeks) reveals that this agent has good antitumour activity when used at this dose in patients with progressive measurable metastatic disease from prostate cancer. It is recognised that this highly selected patient population with soft tissue/visceral metastases is not typical of the great majority of prostatic cancer patients with metastatic disease. However, in those patients in which a response was observed, there was generally a decrease in symptoms and an improvement in performance status. Twenty-four per cent of patients had a confirmed PR, 3 further patients had a PR which was not confirmed 1 month later. The median duration of PR was 28 weeks (range 20–90). Patients in the NC category had a mean duration of response of approximately half this duration (15 weeks). This response rate is much improved to that reported by us in 1987 [8], when a low dose weekly regime had been used, but the dose intensity is almost three times greater. Toxicity was as expected but manageable. 2 patients of the 38 evaluable developed cardiac problems (1 fatal) despite the exclusion of patients with prior cardiac conditions at study entry. The response rate and manageable toxicity suggest that this treatment is a useful addition to the pitifully small list of active agents in the treatment of this disease.

In an attempt to validate the suggestion that PSA may become a useful way of monitoring response in patients undergoing phase II chemotherapy studies in prostate cancer, a trend was seen to support this suggestion, although further work is necessary in order to validate this. PSA has become a very useful tool for the clinician managing prostate cancer [12], though the reliability of PSA and serum acid phosphatase (SAP) measurements to monitor response in patients with bidimensionally measurable hormone refractory prostatic carcinoma remains to be proved [13]. It may be that the natural biology of prostate cancer is such that the expression of PSA might be switched off in patients developing soft tissue metastatic disease. Soft tissue metastases are usually detected in only approximately 10–15% of patients with metastases in any case. Therefore, these patients may not be representative of the metastatic prostate cancer patient population with bone metastases predominating. This leads us back to the original question as to whether or not such indicator lesions as soft tissue lesions can be used to assess response in this patient population. The EORTC Genitourinary Group will attempt to assess response in subsequent studies using a variety of objective, biochemical and subjective criteria including quality of life instruments. The role of PSA as a potential measure of response will be investigated further.

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