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High-dose Epirubicin for Untreated Patients with Advanced Tumours: a Phase I Study

Andrea Martoni, Barbara Melotti, Monica Guaraldi, Maria Adele Pacciarini, Alessandro Riva and Franco Pannuti

In a phase I study, epirubicin was administered as an intravenous bolus at an initial dose of 105 mg/m² in untreated patients with advanced tumours considered resistant to antineoplastic treatment. A 15 mg/m² dose escalation was done every 3 patients if toxicity was below grade 3 or every 6 patients if at least 1 patient had grade 3 toxicity. 18 patients entered the study. The dose was (mg/m²): 105 (3 patients), 120 (3), 135 (3), 150 (6) and 165 (3). The maximally tolerated dose was 165 mg/m². The dose-limiting toxicity was neutropenia. Other side-effects were nausea/vomiting (78%) and alopecia (100%). 4 patients stopped treatment because of a decrease in left ventricular ejection function, without clinical signs of cardiotoxicity. A complete response was observed in a patient with abdominal metastases from unknown origin at 105 mg/m² and a partial response in 2 out of 7 patients with non-operable non-small cell lung cancer, at 135 and 150 mg/m², respectively. The recommended dose for phase II trial is 135–150 mg/m².
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INTRODUCTION

EPIRUBICIN HAS less acute toxicity and cardiotoxicity than its parent drug, doxorubicin, with a similar antitumour activity in a wide spectrum of solid tumours [1, 2]. Two phase I trials, including mostly pretreated patients, have reported a 3 week schedule of epirubicin up to 90 and 100 mg/m², respectively [3–5]. In these studies leukopenia was not dose-dependent and the median white blood cell (WBC) nadirs were 3.9×10^9/l (range 0.8–7.3) and 2.6×10^9/l (1.2–4.1), respectively, suggesting that a further increase of dose was feasible. In addition, in a previous phase II study in our division, myelosuppression was moderate at 90 mg/m² [6]. Our experience was in line with the phase II and III trials in which epirubicin was administered at 50–90 mg/m² every 3 weeks either alone or in combination [2]. In particular, two phase III studies comparing epirubicin with doxorubicin at the same dose (50 mg/m²) in combination with 5-fluorouracil and cyclophosphamide in patients with advanced breast cancer showed better tolerance for epirubicin in terms of acute and cardiac toxicity, with similar activity and survival [7, 8]. Thus we designed this phase I study to define the safety profile of epirubicin given at higher doses than are conventional.

PATIENTS AND METHODS

The eligibility criteria were: patients with non-operable advanced tumours and considered resistant to standard antineoplastic treatments, aged 65 or less, Karnofsky performance status 70% or more, WBC 4×10^9/l or higher and platelets 150×10^9/l or higher, normal cardiac, hepatic and renal functions, no previous chemotherapy or radiotherapy and signed informed consent. Exclusion criteria were liver metastases and cardiovascular disease, including history or presence of congestive heart failure, myocardial infarction, arrhythmia, serious signs of ischaemia, left ventricular ejection fraction (LVEF) by angiocardioscintigraphy 50% or less and hypertension requiring treatment.

The maximally tolerated dose (MTD) was defined as the dose at which WHO grade 3 toxicity (9) occurred in 50% or more of the patients and/or grade 4 toxicity in 20% or more (alopecia excluded).

Epirubicin was administered by an intravenous bolus over 5–7 min. The initial dose was 105 mg/m² and a 15 mg/m² dose escalation was done every 3 patients if no grade 3 toxicities appeared or every 6 patients if a grade 3 toxicity appeared in at least 1 patient. No dose escalation was foreseen in the single patient. Each patient was allowed to continue the treatment at the same initial dose level every 3 weeks. Criteria to stop treatment were: 10% or more absolute decrease of baseline LVEF or decrease below the normal limit of 50%, disease progression and a maximum cumulative dose of 900 mg/m². Dose was reduced by 15 mg/m² in subsequent courses in patients with grade 4 myelotoxicity.

All patients were inpatients. All had ultrasound of the upper abdomen to exclude liver metastases as well as the examinations necessary to define disease extension. Blood count and biochemical tests, including blood urea nitrogen, creatinine, electrolytes, bilirubin, transaminases and alkaline phosphatase were done at entry. Interim blood counts were planned twice a week during treatment. When leukopenia less than 3×10^9/l occurred, blood count was repeated every day until recovery. Angiocardioscintigraphy at rest and electrocardiogram (ECG) were obtained at baseline and before every course. All patients who entered the study were evaluable for toxicitiy.

Objective response was assessed according to WHO criteria. Complete remission (CR) was defined as the complete disappearance of all demonstrable lesions for at least 1 month. Partial remission (PR) was defined as a decrease of 50% or more in the sum of the products of the largest perpendicular diameters of all

Correspondence to A. Martoni.
A. Martoni, B. Melotti, M. Guaraldi and F. Pannuti are at the Division of Oncology, S. Orsola-Malpighi Hospital, 15 Albertoni St, 40138 Bologna; and M. A. Pacciarini and A. Riva are at the Research and Development-Oncology Line, Farmitalia Carlo Erba, Milan, Italy.
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Table 1. Patients' characteristics

M/F	15/3
Median age (range)	57 (39–65)
Median status (Karnofsky)	77 (70–100)
Primary tumour	
Non-small cell lung cancer (NSCLC)	11*
Thyroid†	1
Stomach‡	1
Metastases from unknown origin	5

* Epidermoid 7, large cell 2, adenocarcinoma 2.
† Undifferentiated carcinoma.
‡ Adenocarcinoma.

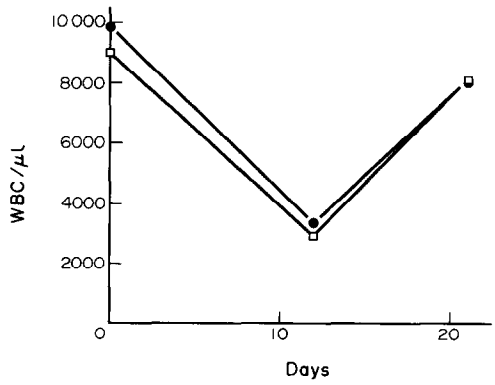

Fig. 1. Myelosuppressive effect after 1st (□—□) and 2nd (●—●) course of high-dose epirubicin in 13 patients. Statistical comparison between 1st and 2nd course (*t* test, mean (S.D.): nadir WBC × 10^9/μl 2.910(1.1) vs. 3.354(1.5), $P = 0.412$ and day, 11.54(3.5) vs. 12.08(2.5), $P = 0.656$ and recovery WBC × 10^9/μl 8.104(2.7) vs. 8.063(4.8), $P = 0.979$, and day 20.54(7.1) vs. 21.38(4.7), $P = 0.725$.

measurable lesions, in the absence of any new lesions and with no progression in any other measurable disease or unquestionable decrease (approximately over 50%) of evaluable but non-measurable lesions. No change (NC) was the condition in which neither a 50% regression in total tumour size nor a 25% increase in the size of one or more measurable lesions could be established. A 25% or more increase in one or more existing lesions and/or the appearance of any new malignant lesion defined the progression of disease (PD).

RESULTS

From January 1987 to December 1988, 18 patients entered the study (Table 1). The number of patients by dose level is shown in Table 2. A total of 48 cycles was administered. Reasons for going off study were: 3 patients completed the study; 5 had disease progression; 4 had a 10% or more absolute decrease of LVEF; 3 had substantial decrease of performance status, and 2 refused to continue the treatment.

Haematological toxicity

Leukopenia was dose-related (Table 2). At 165 mg/m² all patients had grade 3–4 leukopenia. Values of leukopenia after the first and second course in 13 patients who received at least 2 courses of therapy did not show any significant difference (Fig. 1). Grade 4 neutropenia occurred in 1 out of 6 patients treated with 150 mg/m² and in all the 3 patients who received 165 mg/m². The median duration of grade 4 leukopenia was 5 days (range 3–6). After the first course of therapy, recovery from leukopenia occurred on the 21st day in 16 of 18 patients and on the 28th day in the other two.

Out of 2 patients with grade 4 leukopenia after the first cycle, only the 1 who had received 165 mg/m² repeated the treatment with a dose reduction to 150 mg/m². After the third course at 150 mg/m², this patient had severe leukopenia (450/μl), hypotension and fever. He died from septic shock 8 days after the treatment.

Thrombocytopenia was observed in only 2 patients, at 150 (grade 3) and 165 mg/m² (grade 2), respectively. No anaemia occurred.

Table 2. Haematological toxicity

Dose (mg/m²)	Evaluable patients/courses	Leukopenia		Neutropenia (Grade 3/4)
		WBC median nadir (×10^9/l)	Grade 3/4	
First course				
105	3/3	3.74 (2.40–4.30)	0/0	1/0
120	3/3	2.90 (2.14–2.99)	0/0	0/0
135	3/3	2.40 (2.10–4.50)	0/0	0/0
150	6/6	2.58 (0.58–4.20)	2/1	3/1
165	3/3	1.00 (0.91–1.43)	2/1	0/3
All courses				
105	3/12	2.50 (2.40–4.30)	0/0	1/0
120	3/9	1.97 (1.40–2.99)	2/0	1/0
135	3/7	2.10 (1.22–3.70)	1/0	1/0
150	7/17	1.56 (0.45–3.60)	3/2	3/2
165	3/3	1.00 (0.91–1.43)	2/1	0/3

Non-haematological toxicity

All patients had alopecia after the first course (Table 3). Nausea/vomiting occurred in 14 patients (78%), but only 3 had grade 3 vomiting. No preventive anti-emetic therapy was administered. A temperature of 38°C or higher for 2 h 8–10 h after the administration of epirubicin occurred in 5 patients (28%). Grade 2 mucositis was observed in all 3 patients receiving 165 mg/m². 2 patients complained of a chemical phlebitis at 150 mg/m². 1 patient at 165 mg/m² had a herpes zoster episode in the left thoracic wall.

Performance status deteriorated in 3 patients such that treatment was stopped: 1 patient after the first course of 150 mg/m² and 2 patients at 165 mg/m². All these patients had grade 4 neutropenia. No patient had congestive heart failure.

4 patients stopped treatment because of a fall in LVEF (Table 4). 3 patients had an absolute decrease in LVEF of 14, 20 and 25% at the cumulative doses of 240, 300 and 315 mg/m² respectively. The fourth patient stopped treatment because LVEF fell below the normal limit of 50% after the first dose of 150 mg/m². In the first and fourth patients shown in Table 4, angiocardioscintigraphy was repeated after 2 months: LVEF was slightly increased (from 52 to 54% and from 46 to 47%

*Table 3. Non-haematological toxicity**

Dose (mg/m²)	Alopecia	Fever	Mucositis	Diarrhoea	Infection	Phlebitis
105 ($n = 3$)	0/3	0/0	0/0	0/0	0/0	0/0
120 ($n = 3$)	0/3	0/0	0/0	1/0	0/0	0/0
135 ($n = 3$)	0/3	0/0	0/0	0/0	0/0	0/0
150 ($n = 6$)	0/6	3/0	0/0	0/0	0/1	1/1
165 ($n = 3$)	0/3	2/0	3/0	0/0	1/0	0/0
Total ($n = 18$)	0/18	5/0	3/0	1/0	1/1	1/1

*Grades 1 and 2/3 and 4.

Table 4. Treatment suspension because of possible cardiac toxicity

Primary tumour	Dose (mg/m²)		LVEF*		Cardiac symptoms	Status
	Single	Cumulative	Baseline	After		
Unknown	105	315	77	52	No	Dead (16 mo)
NSCLC	120	240	65	51	No	Dead (9 mo)
NSCLC	150	300	62	42	No	Dead (4 mo)
Unknown	150	150	52	46	No	Alive (>16 mo)

* Normal = 50% or more.

respectively). None of these patients presented clinical signs of cardiotoxicity. 3 died from tumour progression and the fourth is alive.

Non-specific ECG changes (sporadic supraventricular premature beats and ventricular repolarisation alterations) were seen during treatment in 3 patients.

Response

12 patients out of 18 were evaluable for response after at least 2 cycles of therapy. Of the other 6, 4 received 1 course only, 1 was lost to follow-up after the second course and 1 did not have evaluable lesions. 1 patient with abdominal metastases from unknown origin at 105 mg/m² had a CR of 19 months' duration. PR was observed in 2 out of 7 patients with NSCLC (one epidermoid and one large cell) at 135 and 150 mg/m² and the duration of response was 4 and 8 months, respectively. NC was reported in 5 patients and 4 had PD.

DISCUSSION

Doses of epirubicin higher than those initially recommended in responsive tumours (i.e. 50 mg/m² in combination and 60–90 mg/m² as single agent) have been explored, with the aim of defining a higher dose that could be safely given and might lead to greater efficacy in solid tumours.

Feld *et al.* [10] studied 33 previously untreated patients with NSCLC. A MTD of 165 mg/m² daily every 3 weeks was reached, at which level 4 of 7 patients had febrile neutropenia with a median nadir WBC of 1.3×10^9/l and a median nadir platelet count of 76×10^9/l. 7 out of 33 patients (21%) had PR. An MTD of 165 mg/m² was found with a recommended dose of 150 mg/m² in another study of 12 patients with NSCLC [11]. Response rate was 17%. Walde *et al.* [12] and Karp *et al.* [13] did phase I studies in various tumours. They reported MTDs of 180 mg/m² and 150 mg/m², respectively, and recommended a dose between 135 and 150 mg/m² for phase II studies. In all these trials the dose-limiting toxicity was granulocytopenia whereas mucositis was dose-limiting only one study [12] in which the highest dose of epirubicin had been reached (180 mg/m²).

The feasibility of using high-dose epirubicin has also been investigated in pretreated patients. Blackstein *et al.* [14] studied pretreated patients with advanced breast cancer and found an MTD of 150 mg/m², suggesting 135 mg/m² as the phase II dose.

Our study is in line with these experiences and confirmed that epirubicin could be administered in higher doses than those indicated in the initial phase I trials [3–5]. In fact, we found an MTD of 165 mg/m², dose-limiting toxicity being neutropenia. As for haematological toxicity, the WBC nadir occurred in most patients between days 12 and 14 after administration and recovery values were reached by the 21st day. The worst haematological toxicity was observed in all the patients treated at the highest dose level (165 mg/m²). 2 of these patients could not continue the treatment, even at reduced dose, because of a performance status deterioration, while the third patient died from septic shock after 2 other courses at the reduced dose of 150 mg/m². Mucositis was observed only at 165 mg/m² and was moderate in all the patients affected. 3 patients had a decrease of 14–25% in LVEF at a cumulative dose between 240 and 315 mg/m² without clinical signs of cardiotoxicity. One of the advantages of epirubicin over doxorubicin is decreased cardiotoxicity. In fact the median cumulative dose of laboratory cardiotoxicity was reported to be 892 mg/m² for epirubicin compared with 360 mg/m² for doxorubicin [15]. Our data suggest that the use of high-dose epirubicin is more favourable as regards cardiotoxicity. In addition, the use of high-dose epirubicin was not associated with higher cardiotoxicity when compared with a standard dose [16].

We saw 2 PR out of 7 NSCLC patients, in line with earlier observations [10,11]. Because of our findings, we feel that other well-designed phase II studies in this type of tumour are advised to explore the therapeutic efficacy of high-dose epirubicin in NSCLC.

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Phase II Study of High-dose Epirubicin in Non-small Cell Lung Cancer

J. Wils, I. Utama, L. Sala, J. Smeets and A. Riva

24 patients with measurable advanced non-small cell lung cancer (NSCLC) were treated with epirubicin 135–150 mg/m² every 3 weeks. There were 6 partial responses. Randomised studies should reveal whether and how incorporation of epirubicin into combination chemotherapy can enhance outcome in advanced NSCLC.
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INTRODUCTION

EVEN THOUGH chemotherapy is widely used in the treatment of non-small cell lung cancer (NSCLC), the choice of the most effective regimen is controversial. A few single agents lead to 15–20% survival rates. These agents, with limited activity, include cisplatin, vinca alkaloids, ifosfamide and mitomycin. Cisplatin may be synergistic with vindesine or etoposide, and many investigators consider both combinations as standard treatment. However, there is a need for new drugs to be incorporated into combination chemotherapy.

Epirubicin is a doxorubicin analogue with a similar spectrum of activity but with less acute toxicity when given in doses between 60 and 90 mg/m². Since higher drug doses might result in better response rates, the assessment of epirubicin in higher than conventional doses is of interest. Phase I–II studies suggested that epirubicin can be administered in doses up to 150 mg/m² without a steep increase in myelosuppression [1–4]. One of these studies was done in patients with NSCLC and 6 responses were observed among 31 patients [2]. Because we have reported a high response rate in patients with stage III–IV NSCLC with a combination of cisplatin, etoposide and epirubicin, although any additive role of epirubicin was not evident [5], we have assessed high-dose epirubicin as a single agent in patients with advanced NSCLC. We selected stage IV patients because of their very short survival, making the role of the more commonly used but more toxic cisplatin-based regimens questionable.

Correspondence to J. Wils.
J. Wils is at the Department of Internal Medicine and I. Utama and L. Sala are at the Department of Pulmonary Diseases, Laurentius Hospital, 6043 CV Roermond, The Netherlands; J. Smeets is at Farmitalia Carlo Erba Benelux, Nivelles, Belgium; and A. Riva is at Farmitalia Carlo Erba, Oncology Line, Milan, Italy.

PATIENTS AND METHODS

Eligibility criteria included histologically proven NSCLC, performance status 2 or under, age 75 years or less, no previous chemotherapy or radiotherapy, adequate organ function and measurable lesions. Preferably, stage IV patients were included but stage III patients with more adverse prognostic signs, such as performance status 2 and significant weight loss, could also be entered.

The starting dose of epirubicin was 135 mg/m² as an intravenous bolus every 3 weeks. If white blood cell (WBC) nadir was $\geq 2.0 \times 10^9$/l, platelet nadir was $\geq 70 \times 10^9$/l and/or mucositis was grade 1 or less the dose of epirubicin was escalated to 150 mg/m². If WBC fell below 1.0×10^9/l, platelets fell below 40×10^9/l and/or mucositis was over grade 2, the dose had to be decreased to 120 mg/m². The same criteria were applied for a decrease to 135 mg/m² after a primary dose increase. In all other cases the dose had to remain the same.

Pretreatment evaluation included physical examination, measurement of indicator lesions, cardiac function by Scintiscan ejection fraction and laboratory values for kidney, liver and bone marrow function.

Response was evaluated by WHO criteria after two cycles. Physical examination, scoring of toxicity, ejection fraction and