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Activity of High-dose Epirubicin in Advanced Non-small Cell Lung Cancer

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24 patients with unresectable non-small cell lung cancer (NSCLC) (14 stage IIIB and 10 stage IV) with a performance status of 70% or higher and without liver metastases received 120–165 mg/m² epirubicin as an intravenous bolus every 21–28 days up to the maximum cumulative dose of 900 mg/m². 6 patients (25%) (95% confidence limits 9.8–46.7%) achieved partial remission for a median duration of 7.5 months (range: 3–13+). The median dose actually administered per course was 120 mg/m² in responsive and non-responsive patients. The dose-limiting side-effect was neutropenia. 1 patient receiving the higher dose died of drug-related infection. Other non-dose-related grade 3 side-effects were alopecia (100%) and vomiting (17%). In 4 patients, the treatment was interrupted because of a >10% reduction in the left ventricular ejection fraction as calculated by radionuclide angiocardiography. None of these patients suffered from cardiac symptoms. The median survival was 10 months (range 1–16). These data suggest that epirubicin at 120–135 mg/m² may have higher antitumour activity than standard doses in patients with NSCLC. Further studies are needed to clarify whether or not high-dose epirubicin increases, the risk of cardiotoxicity compared to standard doses.
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INTRODUCTION

EPIRUBICIN is an analogue of doxorubicin that has demonstrated less acute toxicity and less cumulative cardiotoxicity than its parent drug, and, at the same time, a similar antitumour activity in a wide spectrum of solid tumours [1].

However, like doxorubicin, epirubicin has shown poor antitumour activity in the treatment of non-small cell lung cancer (NSCLC) when used at standard doses (≤ 90 mg/m²) [2–4].

Recently, two studies regarding the use of high-dose epirubicin in the treatment of advanced solid tumours have been carried out at our division. The first study was a phase I clinical trial aimed at defining the maximum tolerated dose (MTD) in untreated cancer patients without liver metastases or cardiac disease. Results published elsewhere [5] show that the MTD was 165 mg/m², while the dose suggested for subsequent phase II trials was 135 mg/m². The second study on pharmacokinetics, whose preliminary results have been already published [6], was aimed at verifying the linearity of high-dose epirubicin in similar patients. The majority of patients who entered these two studies suffered from NSCLC. In this study, we analysed the results in relation to the objective response achieved by the patients.

PATIENTS AND METHODS

Patients entered a phase I trial [5] and a pharmacokinetic trial [6] with a histological or cytological diagnosis of unresectable NSCLC. General eligibility criteria were: age ≤ 65 years; performance status ≥ 70% (Karnofsky); absence of liver metastases; WBC ≥ 4000 μl and platelets ≥ 150 000 μl; normal cardiac, hepatic and renal functions; and no previous chemotherapy or radiotherapy.

All patients were staged according to standard protocol [X-rays with tomography and/or computed tomography (CT) of the chest, ultrasound examination of upper abdomen, bronchoscopy, bone scan etc.]. Blood count, biochemical tests and electrocardiogram (ECG) were carried out at entry and before each subsequent course. Interim blood counts were carried out twice a week during the treatment. Radionuclide angiocardiography at rest with evaluation of the left ventricular ejection fraction (LVEF) was obtained at baseline conditions and after every two cycles of therapy. All patients received treatment as inpatients.

24 patients entered this study. They received four dose levels of epirubicin: 120 (10 patients); 135 (4); 150 (7) and 165 mg/m² (3). 9 patients (6 at 120 and 3 at 150 mg/m²) who entered the pharmacokinetic study received the drug at a half-dose once, either in their first or second course.

Epirubicin was administered by intravenous bolus (5–10 min) and repeated every 3 weeks if there was recovery from myelotoxicity (WBC ≥ 4000/μl, platelets ≥ 100 000/μl). If grade 4 myelotoxicity appeared, the subsequent dose was reduced by 15%. No escalation of the initial dose was planned in any case. Treatment was interrupted when a cumulative dose of about 900 mg/m² was reached. The majority of the patients received metoclopramide 0.5 mg/kg 4 h after administration of chemotherapy as antiemetic therapy.

Objective response and toxicity were assessed according to WHO criteria [6]. 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 ≥ 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, in the absence of any new lesions and with no progression in any other measurable disease or unquestionable decrease (approximately > 50%) of evaluable but non-measurable lesons. 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% increase in one or more existing lesions and/or the appearance of any new malignant lesion was necessary in order to define the progression of disease (PD).

An evaluation of the quality of life during the treatment was done by the performance status, symptoms such as pain with scores 0,1,2 according to our scale [8], and body weight.

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Table 1. Patients' characteristics

Patients	
No. of cases	24
M / F	24/0
Median age (range)	60 (36–68)
Median performance status (range)(%)	70% (60–90%)
Histology	
Epidermoid carcinoma	11
Adenocarcinoma	7
Large cell carcinoma	3
Other	3
Stage	
III B	14
IV	10

RESULTS

The main characteristics of the 24 patients who entered this study are reported in Table 1. All were men with a median age of 60 years and a median performance status of 70%. 11 patients had an epidermoid cancer, 7 an adenocarcinoma and 3 a large-cell undifferentiated carcinoma, while in 3 cases the histotype was not classifiable but a small cell cancer was excluded. 14 patients presented stage IIIB and 10 stage IV. 1 patient whose performance status was 60% and a 68-year-old were also included.

A total of 85 cycles were administered and the median number of cycles per patient was two (range 1–8 cycles). The median cumulative dose per patient was 424 mg/m^2 (range 150–900).

Response

The analysis of the response is reported in Table 2. No CR was observed. 6 patients (25%) achieved PR, 8 (33%) NC while 10 presented PD (42%). 1 patient, classified as NC, showed a 35% objective reduction in the tumour lesion. Objective remission was observed in 3/11 epidermoid cancer, 1/7 adenocarcinoma, and 2/3 large cell undifferentiated carcinoma. Response by stage was 3/14 stage IIIB and 3/10 stage IV. Analysis of objective response by initial dose level was 3/10 120 mg/m^2, 1/4 135 mg/m^2, 2/7 150 mg/m^2 and 0/3 165 mg/m^2. There was no difference between responders and non-responders in regard to the median dose intensity administered per course (120 mg/m^2). The median response duration was 7.5 months (range 3–13+) and the median progression-free survival was 3.5 months (range 1–13+).

During the treatment most of the patients presented no significant variations in the parameters considered for a quality of life evaluation. However, objectively responsive patients experienced a pain reduction in 2/2, a performance status improvement in 3/6 and a body weight increase (+2 kg) in 4/6. 3 patients (1 at the dose of 150 mg/m^2 and 2 at 165 mg/m^2) presented a deterioration in their performance status after the first course, and treatment was consequently stopped.

Table 2. Objective response

	n	%
CR	0	0
PR	6	25
NC	8	33
PD	10	42
Total	24	100

CR = complete remission, PR = partial remission, NC = no change, PD = progressive disease.

Table 3. Toxicity

Side-effects (WHO grade)	Dose (mg/m^2) 120 (*n* = 10)	135 (*n* = 4)	150 (*n* = 7)	165 (*n* = 3)	Total (*n* = 24)
Neutropenia					
1	1	0	1	0	2
2	5	2	1	0	8
3	3	1	2	0	6
4	1	1	3	3	8
Total	10	4	7	3	24(100%)
Thrombocytopenia					
2	1	0	0	1	2
3	0	0	1	0	1
Total	1	0	1	1	3(12.5%)
Nausea/vomiting					
1	3	1	0	0	4
2	2	3	5	1	11
3	2	0	1	1	4
Total	7	4	6	2	19(79%)
Mucositis					
2	0	0	0	3	3(12.5%)
Alopecia					
3	10	4	7	3	24(100%)
Infections					
1	0	0	0	1	1
4	0	0	0	1	1
Total	0	0	0	2	2(8%)
Fever					
1	0	0	2	0	2(8%)
Phlebitis					
2	1	0	0	0	1(4%)

The median survival was 10 months (range 1–16). At the moment 9 patients are still alive after a median follow-up of 8 months (range 3–13) since beginning treatment.

Toxicity

Table 3 reports the incidence and intensity of the side-effects. Myelosuppression was the most important toxic side-effect. All patients had dose-related neutropenia. Grade 4 neutropenia in particular was observed in 8 patients (33%) and in all 3 patients who received the higher dose level. After the first course, the median neutrophils nadir was 677/μl (range 144–1470) on day 12 (range 8–20) and the median time of recovery was day 19 (range 14–27). Grade 3 thrombocytopenia was only recorded in 1 patient.

All patients presented alopecia either following the first or the second course. Nausea/vomiting occurred in 19 (79%) patients, but only 4 (17%) experienced grade 3 vomiting. Grade 2 mucositis was only observed in the 3 patients who received the 165 mg/m^2 dose.

1 of the 3 patients who received the 165 mg/m^2 dose continued the treatment at the reduced dose of 150 mg/m^2. After the third course, this patient presented severe leukopenia (WBC 450/μl),

Table 4. Epirubicin in advanced NSCLC

Ref.	Dose (mg/m² every 21–28 days)	No. of patients	Response (CR+PR)(%)
At standard doses (≤ 90 mg/m²)			
Kalman [2]	65–85	34	1 (3)
Martoni [9]	90	17	1 (6)
Joss [3]	90	75	4 (5)
Meyers [4]	75	64	4 (6)
Total (95% confidence limits)		190	10 (5) (2.5–9.5)
At high doses (≥ 120 mg/m²)			
Feld [10]	35–60 daily × 3 days	33	7 (21)
Holdener [11]	120–90	12	2 (17)
Henss [12]	150	18	4 (22)
Wils [13]	135–150	24	6 (25)
Present series	120–165	24	6 (25)
Total (95% confidence limits)		111	25 (23) (13.5–31.6)

hypotension and fever. He died 8 days after the epirubicin dose, maybe as a result of a septic shock.

In 4 patients the treatment was stopped owing to a 14, 20, 25 and 31% absolute decrease in LVEF at the cumulative doses of 240 (120), 560 (120), 300 (150) and 516 mg/m² (150), respectively. In 2, the drop was under the level of 45%. None of these patients presented any clinical signs of cardiotoxicity either at that time or subsequently.

DISCUSSION

The phase II studies that had initially assessed epirubicin in NSCLC using single doses ≤ 90 mg/m² reported very disappointing results with response rates < 6% (95% confidence limits 2.5–9.5%) (Table 4).

We have studied the results, particularly the objective response, obtained at our division in patients with unresectable NSCLC treated with high-dose epirubicin (120–165 mg/m²) in two phase I and pharmacokinetic clinical studies. The prognosis of the patient population was highly favourable owing to the young age, good performance status, no previous antitumour treatment and more than half of the patients having stage IIIB disease. Overall, we observed an objective remission rate of 25% (95% confidence limits 9.8–46.7) for a median duration of 7.5 months. Responses were observed at all dose levels with the exception of the highest (165 mg/m²). The median dose actually administered in responsive and non-responsive patients was 120 mg/m². Objective remission was accompanied by a subjective improvement.

Limitations of this study are that it was not specifically designed as a dose-objective response study, that the number of patients was low and that many dose levels were used. These limitations, together with the favourable characteristics of the patients, suggest caution in drawing any firm conclusions about the activity of the treatment. However, on the whole the results seem to indicate the existence of an antitumour activity in NSCLC when epirubicin was used at high doses. Our results are in agreement with the recent experiences of other investigators, who have used high-dose epirubicin in NSCLC (Table 4). Although all of these studies are nevertheless limited by their low patient numbers, they have constantly reported a remission rate of about 20% (mean remission rate 23%, 95% confidence limits 15.2–31.6%), thus suggesting that high-dose epirubicin may have a higher antitumour activity than that observed at standard doses.

A detailed description of the side-effects of high-dose epirubicin had been reported in our phase I study [5]. In that study, neutropenia was the dose limiting side-effect. In the present patient series, grade 4 neutropenia was observed in 8 patients (33%): 2 out of 14 (14%) receiving doses of 120–135 mg/m² and 6 out of 10 (60%) receiving doses of 150–165 mg/m². If we exclude alopecia, no other severe side-effect occurred at the two lower dose levels. On the contrary, at the doses of 150 mg/m² and especially 165 mg/m² the treatment became more toxic and impracticable. 1 patient treated with initial dose of 165 mg/m² died after three courses owing to toxicity. The other 2 patients who received 165 mg/m² did not continue the treatment because of a deterioration in performance status.

Radionuclide angiocardiography was monitored in all the patients and in 4 the treatment was stopped because of a reduction in LVEF. None of these patients presented clinical manifestations of cardiotoxicity, either contemporaneously or subsequently. Although clinical implications of decrease in LVEF during anthracycline treatment are still controversial [14], radionuclide angiocardiography is likely the most reliable non-invasive technique to detect anthracycline cardiotoxicity before clinical signs of left ventricular dysfunction [15]. On the basis of a large experience in monitoring the cardiac function in cancer patients treated with doxorubicin, Schwartz *et al.* [16] developed guideline criteria for cumulative dose-related scheduling of serial radionuclide angiocardiography and for discontinuing of doxorubicin treatment. In particular, in patients with normal baseline LVEF (≥ 50%), discontinuation of doxorubicin should occur when there is an absolute decrease in LVEF ≥ 10% associated with a decline to a level ≤ 50%. The criteria for treatment suspension adopted by us have been more prudent. By the above-mentioned criteria, 1 of the 4 patients could have continued treatment. However, a 12.5% (3/24) cardiotoxicity rate, even if mild, cannot be ignored. Epirubicin has definitely shown a lower cumulative cardiotoxicity than doxorubicin [17], and, when used at high doses, does not seem to be associated with an increase of cardiotoxicity [18]. However, the question as to whether or not high-dose epirubicin implies a higher risk of cardiotoxicity than standard doses is open and should be clarified by comparative prospective studies.

In summary, these data indicate that at the dose of 120–135 mg/m² epirubicin exhibits an antitumour activity in NSCLC. We thus believe that it is worth reassessing high-dose epirubicin in this kind of tumour and that its inclusion in multidrug regimens containing drugs with mild myelotoxicity ought to be studied.

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MMAF for Advanced Gastric Cancer

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65 patients with metastatic gastric carcinoma were treated with a combination of methotrexate 1.5 g/m² with 5-fluorouracil 1.5 g/m² on day 1 and doxorubicin 30 mg/m² with mitomycin 4 mg/m² on day 14. Cycles of chemotherapy were repeated every 4 weeks. The overall response rate was 29% with 6% complete responses and 23% partial responses. Prognostic factors that individually affected response were Karnofsky performance ($P < 0.002$), and site of the primary tumour ($P < 0.007$). Multivariate analysis showed that only increasing Karnofsky performance ($P = 0.01$) and disease status ($P < 0.02$) (patients with recurrent tumours responding better than patients with postoperative residual disease and those with inoperable disease) were important in predicting response to therapy. The overall median survival was 7 months. All 4 patients with a complete response are alive in remission at 13, 28, 48 and 52 months from the date of starting chemotherapy. Univariate analysis identified increasing Karnofsky performance ($P < 0.0001$), response to chemotherapy ($P < 0.02$) and higher serum albumin ($P < 0.03$) as prognostic indicators for survival. Multivariate analysis, of pretreatment factors and day 14 full blood count showed that only Karnofsky performance ($P < 0.0001$) and day 14 platelet count ($P < 0.03$) were shown to predict survival, higher platelet values being associated with decreased survival.
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INTRODUCTION

SURGERY IS the usual treatment for patients with gastric cancer. However, only half of the patients undergoing a laparotomy are suitable for surgery and still fewer are able to undergo curative resection [1]. The prognosis following the diagnosis of inoperable gastric cancer is poor with a median survival of only 4 months [2, 3]. The median survival of patients with operable tumours is 10–17 months. The 5-year survival was reported to be 6–10% in studies of more than 1000 patients [4].

Patients with inoperable or metastatic gastric carcinoma show a modest response rate to chemotherapy. Single agent therapy is associated with a response rate of 21% for 5-fluorouracil (5-FU), 24% for mitomycin and 22% for doxorubicin [5].

A combination of 5-FU, doxorubicin and mitomycin (FAM) showed a response of 50% [6]. However, a review of 12 studies using FAM has shown a response rate of 33% in 453 patients [4].

Methotrexate and 5-FU have been shown to have synergy when given sequentially [7]. The combination of these two drugs with doxorubicin (FAMTX) was reported to have a response rate of 63% and a median survival of 22 months for responders. 48% of responders were reported to be alive at more than 37 months [8, 9].

We have evaluated a regimen that has included the sequential use of methotrexate and 5-FU in addition to doxorubicin and mitomycin (MMAF) in patients with inoperable, postoperative residual or recurrent adenocarcinoma of the stomach. The aims were to assess toxicity and determine the response rate, duration of response and survival.