Pharmacol 1984, **12**, 179–182.
7. Italian Multicentre Breast Study. Epirubicin: phase III randomized study of fluorouracil, epirubicin and cyclophosphamide vs. fluorouracil, doxorubicin and cyclophosphamide in advanced breast cancer. *J Clin Oncol* 1988, **6**, 976–982.
8. French Epirubicin Study Group. A prospective randomized phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil and either doxorubicin or epirubicin. *J Clin Oncol* 1988, **6**, 679–688.
9. Miller AB, Hoogstraten B, Staquet H. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
10. Feld R, Wierzbick K, Walde D, *et al.* High dose epirubicin daily × 3 in NSCLC. A phase I study. *Proc ECCO* 1987, **4**, 79.
11. Holdener EE, Jungi WJ, Fiebig H. Phase I of high dose epirubicin in NSCLC. *Proc Am Soc Clin Oncol* 1988, **7**, 806.
12. Walde D, Case A, Lassus M, *et al.* High dose epirubicin in previously untreated patients with advanced metastatic cancer: a phase I study. *Proc Am Soc Clin Oncol* 1988, **280**.
13. Karp D, Colajori E, Fiore R, *et al.* A phase I trial of high dose epirubicin in advanced cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 325.
14. Blackstein M, Wilson K, Merchand J, *et al.* Phase I study of epirubicin in metastatic breast cancer. *Proc Am Soc Clin Oncol* 1988, **7**, 87.
15. Jain KK, Casper ES, Geller NL, *et al.* A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol* 1985, **3**, 818–826.
16. Shepherd FA, Feld R, Blackstein M, *et al.* Administration of high dose bolus epirubicin (EPI) is not associated with increased cardiotoxicity. *Proc Am Soc Clin Oncol* 1989, **8**, 335.

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

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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.

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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

radiological examination of the thorax were repeated after each cycle. Treatment was continued until progression or severe toxicity but the maximum number of cycles was six. The trial was done according to "good clinical practice" guidelines [6].

RESULTS

Between March 1988 and October 1989, 25 patients were entered. 1 patient was not eligible, because re-evaluation of the pathology revealed mesothelioma instead of NSCLC (Table 1). 2 patients with stage III disease who did not fulfil the strict eligibility criteria were kept in all analyses. 1 of these patients was aged 80 and the other had been treated for myelomatosis 5 years earlier and appeared to be still in remission.

A median of four cycles (range one to six) was administered. Dose was escalated in 12 patients. The median cumulative dose of epirubicin was 560 mg/m^2 (135–870). The major toxicity was myelosuppression (Table 2). WHO grade 4 leukopenia in at least one cycle occurred in 17% of the patients. The median day of the nadir was day 12 (6–14) with, in most cases, rapid recovery within 48 h. 2 patients died after the first cycle due to tumour progression. 1 patient developed a perforation of the tumour in the oesophagus with massive bleeding and the other had evident tumour progression at necropsy. Other toxicities included grade 3 nausea/vomiting in 5%, and grade 3 mucositis in 19% of the patients. All patients had complete alopecia. There was no clinical cardiotoxicity and no significant drop in ejection fraction.

6 patients (25%) had partial responses. 3 of these patients had adenocarcinoma, 2 had squamous cell carcinomas and 1 had large cell carcinoma. 11 patients were stable after two cycles and 7 patients had primary progression, 4 after only one cycle. All responses were externally reviewed. All responses occurred in the patients who strictly fulfilled the eligibility criteria. The median duration of response was 3 months (2–5). The median survival of all patients was 6 months (1 to over 16).

Table 1. Patients' characteristics

M/F	17/7
Median age (yr; range)	64 (44–80)
Median performance status	Grade 1 (0–2)
Median weight loss (% of healthy body weight)	5–10% (0– >10%)
Stage of disease	
IV	17
III	7
Histology	
Squamous	14
Adenocarcinoma	8
Large cell anaplastic	2

Table 2. Toxicity in 24 patients

	WHO grade			
Side-effect	1	2	3	4
Leukopenia	17%	25%	33%	17%
Mucositis	5%	19%	19%	0%
Nausea/vomiting	21%	21%	5%	0%
Alopecia			100%	

DISCUSSION

In a previous phase II study we obtained a 55% response rate in stage IV NSCLC with a combination of cisplatin 60 mg/m^2 and etoposide 600 mg total dose and epirubicin 60 mg/m^2 [5]. The additive effect of epirubicin in that trial was not evident because that response rate was within the confidence limits of other studies with cisplatin plus etoposide only. The present trial demonstrated that epirubicin has activity in the same range as that seen with other single agents.

The results of combination chemotherapy in the treatment of advanced NSCLC are poor and the impact on survival remains limited. Cisplatin plus etoposide achieved remission rates of 30–40%. In one study no significant differences were obtained between an intermediate dose (60 mg/m^2) of cisplatin vs. a high dose (120 mg/m^2) in combination with etoposide. The remission rates were 25% and 29%, respectively, with no differences in survival [7]. Another trial by the same group did not reveal major differences between cisplatin alone and cisplatin combined with etoposide, although there was a strong trend in favour of the combination, especially in patients with limited disease [8].

Although it has not unequivocally been demonstrated that combination chemotherapy results in a survival benefit, some randomised studies in patients with NSCLC strongly suggest that appropriate combination regimens produce higher response rates and improved survival than single agents or no treatment [9]. Further randomised studies should reveal whether the incorporation of epirubicin in combination chemotherapy enhances treatment outcome.

1. Karp D, Colajori E, Karpovsky B, *et al.* A phase I trial of high dose epirubicin (epi) in advanced cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 83.
2. Feld R, Wierzbicki R, Walde D, *et al.* High dose epirubicin daily ×3 in NSCLC. A phase I study. *Proc ECCO* **4**, Madrid, 1987, abstr 79.
3. Blackstein ME, Eisenhauer E, Wierzbicki R, *et al.* Phase II study of epirubicin in untreated patients with extensive small cell lung cancer. *Proc ECCO* **4**, Madrid, 1987, abstr 85.
4. Walde D, Case A, Lassus M, *et al.* High dose epirubicin in previously untreated patients (pt) with advanced metastatic cancer: a phase I study. *Proc Am Soc Clin Oncol* 1988, **7**, 73.
5. Wils J, Utama I, Smeets J. Chemotherapy consisting of epirubicin, cisplatin and etoposide followed by irradiation in stage III non-small lung cancer and chemotherapy alone in stage IV non-small lung cancer. *Oncology* 1988, **45**, 413–416.
6. Hvidberg EF. Good clinical practice: a way to better drugs. Rules for clinical drug research that offer a prospect of better trials. *Br Med J* 1989, **299** 580–581.
7. Klastersky J, Sculier JP, Ravez, P, *et al.* A randomized study comparing a high and a standard dose of cisplatin in combination with etoposide in the treatment of advanced non-small cell lung cancer. *J Clin Oncol* 1986, **4**, 1780–1786.
8. Klastersky J, Sculier JP, Bureau G, *et al.* Cisplatin versus cisplatin plus etoposide in the treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 1989, **7**, 1087–1092.
9. Gralla RJ. Issues in the treatment of advanced non-small cell lung cancer. In: Gralla RJ, Einhorn LH (eds). *Treatment and Prevention of Small Cell Lung Cancer and Non-Small Cell Lung Cancer*. London, Royal Society of Medicine, 1989, 73–82.

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