applicable to our patients. Other factors which are likely to have contributed to our low response rate are the relatively advanced age of our patients in comparison with those in the two previous reports (Powles *et al.*, 1991: mean age 55; Jodrell *et al.*: mean age 51) and the significant proportion of patients in our study with a Karnofsky score < 70. In consequence, we have used a slightly reduced target dose of all three drugs in our schedule in comparison with previous reports.

Our own studies [7,8] and those of others [9] have shown that locally advanced breast cancer responds well to mitozantrone-containing chemotherapy. Thus, Mansi *et al.* [9] reported a 60% response rate in locally advanced breast cancer. Gazet *et al.* [8] using the 3M regime found 16/30 patients (53%) achieved a response. This previously untreated category of patients may respond as well to the 2M regime with less toxicity.

In conclusion, we feel that patients with advanced breast cancer should receive the less toxic 2M regimen as first-line cytotoxic therapy and only if no response is seen should mitomycin C be added to the regime. Haematological toxicity should be monitored carefully in patients who receive the 3M regime.

1. Powles TJ, Ashely SE,Forgeson GV, *et al.* Treatment of advanced breast cancer with mitomycin-C, mitoxantrone and methotrexate (3M) compared to vincristine, anthracycline and cyclophosphamide (VAC). In: Bonadonna, ed. *Clinical Progress with Mitoxantrone*. Royal Society of Medicine Services International Congress and Symposium Series No. 110, 1987.
2. Powles TJ, Jones AJ, Judson IR, Hardy JR, Ashley SE. A randomised trial comparing combination chemotherapy using mitomycin C, mitozantrone and methotrexate (3M) with vincristine, anthracycline and cyclophosphamide (VAC) in advanced breast cancer. *Br J Cancer* 1991, **64**, 406–410.
3. Hayward JL, Carbonne PP, Heuson JC, *et al.* Assessment of response to therapy in advanced breast cancer. *Cancer* 1977, **39**, 1289–1294.
4. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
5. Jodrell DI, Smith IE, Mansi JL, *et al.* A randomised comparative trial of mitozantrone/methotrexate/mitomycin C (MMM) and cyclophosphamide/methotrexate/5 FU (CMF) in the treatment of advanced breast cancer. *Br J Cancer* 1991, **63**, 794–798.
6. Tannock IF, Boyd NF, De Boer G, *et al.* A randomised trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–87.
7. Coombes RC. Treatment of advanced breast cancer with systemic therapy. In: Robinson R, Cordon S, Cozens L, eds. *Proceedings of the 4th United Kingdom Novantrone Symposium–Current Status of Clinical Research*. Media Medica, West Sussex, 1990, 7–9.
8. Gazet J-C, Ford HT, Coombes RC. Randomised trial of chemotherapy versus endocrine therapy in patients presenting with locally advanced breast cancer (a pilot study). *Br J Cancer* 1991, **63**, 279–282.
9. Mansi JL, Smith IE, Walsh G, *et al.* Primary medical therapy for operable breast cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 1623–1627.

Acknowledgement—The Institute of Cancer Research is funded by the Cancer Research Campaign (CRC) and the Medical Research Council funded COMPACT computer software used for data management.

Eur J Cancer, Vol. 28A, No. 12, pp. 1965–1967, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
© 1992 Pergamon Press Ltd

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

E.F. Smit, D.A. Piers and P.E. Postmus

25 consecutive patients with advanced non-small cell lung cancer (NSCLC) were treated with high-dose epirubicin (HDE) 135 mg/m² and etoposide 60 mg/m² (days 1–3) every 3 weeks. 121 courses, (median 6, range 1–7), were administered and evaluable for toxicity: WHO grades III/IV leukocytopenia in 60/36 (80%) courses, thrombocytopenia in 18/6 (20%) and grades II/III anaemia in 31/6 (31%). Median (range) left ventricular ejection fraction (LVEF) fell from 63% (53–73, $n = 25$) to 60% (48–73 $n = 16$) after 5 courses ($P < 0.02$). 2 patients had a drop of more than 15% in LVEF with an epirubicin dose of 675 mg/m². Apart from 1 patient who had tachycardia 6 months after the last course, no patient had congestive heart failure. There were 2 complete and 7 partial responses [total 9/25 (36%, 95% confidence interval: 18–57.5%)]. Median survival is 31.8 (4.3–75) weeks. Combination HDE and etoposide in NSCLC offers no advantage over HDE alone and is more toxic.
Eur J Cancer, Vol. 28A, No. 12, pp. 1965–1967, 1992.

INTRODUCTION

THE PROGNOSIS of patients with advanced non-small cell lung cancer (NSCLC) remains poor and requires development of active drug regimens. Recently, high-dose epirubicin (≥ 120 mg/m²) as a single agent was found to have significant antitumour activity in NSCLC. Response rates in five studies varied from 17% to 36%, while toxicity was moderate [1–5]. Among other active single agents in NSCLC producing partial response rates exceeding 15% is etoposide [6, 7]. In this study we report on the efficacy of the combination of HDE and etoposide in advanced NSCLC.

In December 1989, a dose-range finding study was started with the aim of finding a safe dose for the combination of HDE and etoposide. The first 6 patients were treated with epirubicin

135 mg/m^2 and etoposide 60 mg/m^2 on days 1, 3 and 5 every 3 weeks. 4 of these patients experienced WHO grade IV leukocytopenia for more than 5 days, which was defined as unacceptable. 3 patients had to be admitted because of leukocytopenia-associated fever. Because we considered 60 mg/m^2 etoposide as a minimum required for activity, etoposide was administered on days 1–3. 2 out of 6 patients treated at this dose had grade IV myelosuppression in their first course. Therefore the phase I study was stopped and the study continued in phase II to evaluate the toxicity and efficacy of the combination of HDE and etoposide in patients with advanced NSCLC.

PATIENTS AND METHODS

Between April 1990 and April 1991 25 patients with histologically proven NSCLC unsuitable for curative therapy were entered into this study. These included 6 patients from the phase I part treated at the same dose level and schedule as prescribed for the phase II study. Additional eligibility criteria were: no previous chemotherapy, radiotherapy compromising ≤ 25% of the bone marrow stopped at least 4 weeks before entry, life expectancy of at least 3 months, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, white blood cell (WBC) count ≥ 4000/μl, platelet count ≥ 100 000/μl, serum creatinine < 120 μmol/l, serum bilirubin < 25 μmol/l, normal cardiac function (left ventricular ejection fraction (LVEF) > 45% as measured by MUGA scan (normal 55–65%)), measurable lesions and informed consent according to local ethical committee regulations.

Before treatment patients were subjected to staging procedures including physical examination, chest X-ray, complete blood cell counts, electrolytes, liver function chemistries, serum creatinine, electrocardiogram (ECG), measurement of LVEF at rest and tumour measurements. Additional studies were performed to document disease when clinically indicated. Staging was according to criteria of the American Joint Committee for Cancer Staging [8]. Some of the characteristics of the patients entered are listed in Table 1.

Epirubicin (135 mg/m^2, day 1) and etoposide (60 mg/m^2, days 1–3) were administered as an intravenous bolus infusion, both lasting 30 min on a 3-week schedule. Dexamethasone (8 mg orally every 6 h for 36 h) was prescribed to all patients to control emesis. Complete blood cell counts were performed on days 12, 15 and at retreatment (day 21). In case of incomplete bone marrow recovery (WBC < 3000/μl and/or platelets < 100 000/μl) at the time of the next planned dose, therapy was delayed for 1 week (maximally 2 weeks). If after 2 weeks delay there was still insufficient bone marrow recovery the patient was taken off study and was followed for survival. Treatment was to be continued until disease progression, a maximum cumulative dose of epirubicin of 945 mg/m^2 or cardiac toxicity (see below). The whole treatment was performed in the outpatient clinic.

All patients were considered evaluable for response and toxicity. Responses were scored according to WHO criteria [9]. For complete and partial responders, duration of response was calculated from the first day of treatment to the first day of occurrence of any new lesion or disease progression was observed. Time to progression was defined as the period from first day of treatment to the date of first observation of disease progression. Survival, for which all patients were evaluable, was from first day of treatment until death. Toxicity was evaluated using the WHO grading system. LVEF, using MUGA scan, was measured prior to initiation of treatment and after course 5 (cumulative dose of epirubicin of 675 mg/m^2) and every 2 months after treatment had been discontinued. If the patient demonstrated an absolute drop of > 15% compared with pretreatment levels or to a LVEF ≤ 45%, the patient went off study and was followed for survival. The same applied to patients who developed clinical signs and symptoms of congestive heart failure (CHF).

Table 1. Patients' characteristics

No. of patients	25	
Male/female	17/8	
Median (range) age	59	(46–69) years
ECOG performance status		
0	9	
1	14	
2	2	
Histology		
Squamous carcinoma	8	
Adenocarcinoma	10	
Large cell carcinoma	3	
Bronchiolo-alveolar carcinoma	4	
Stage		
III^A	2	
III^B	10	
IV	13	
Pretreatment		
Radiotherapy	1	
None	24	

RESULTS

The 25 patients entered into this study received a total of 121 courses (median 6, range 1–7). The major toxicities are listed in Table 2. There were no treatment-related deaths. Myelosuppres-

Table 2. Treatment outcome

	WHO grade				
	0	I	II	III	IV
Leukocytopenia	4*	2	19	60	36
Thrombocytopenia	58	15	24	18	6
Anaemia	25	59	31	6	0
Nausea/vomiting	83	21	16	1	0
Mucositis	51	34	28	8	0
Alopecia	0	3	22	0	0
Infection	94	18	9	0	0
Complete response	2 (8%)				
Partial response	7 (28%)				
No change	12 (48%)				
Progressive disease	4 (16%)				
Median (range) response duration	29.6 (12.1–42.7) weeks				
Median (range) time to progression	23.9(2.9–42.7) weeks				
Median (range) survival	31.8 (4.3–75) weeks				

*No. of courses in which grade was scored.

Correspondence to P.E. Postmus.
E.F. Smit is at the Department of Internal Medicine, Martini Hospital, van Swietenlaan 4, 9728 NZ Groningen; D.A. Piers is at the Department of Nuclear Medicine, University Hospital, Groningen; and P.E. Postmus is at the Department of Pulmonary Diseases, University Hospital, Free University, De Boelenlaan 1117, 1007 MB Amsterdam, The Netherlands.
Revised 4 Mar. 1992; accepted 5 Mar. 1992.

sion in the form of leukocytopenia was the dose-limiting side-effect, with 96 out of 121 (79.3%) courses associated with WHO grades III/IV leukocytopenia. During 14 courses patients ($n=5$) had to be admitted because of leukocytopenia-associated fever requiring IV antibiotics. In 3 patients repeated infectious episodes led to discontinuation of treatment. During 24 (19.8%) courses thrombocytopenia WHO grades III/IV was observed. 3 patients had bleeding episodes during thrombocytopenia. 5 patients received a total of 8 platelet transfusions. In addition, 34 red blood cell transfusions were administered to the study population. In none of the patients was it necessary to postpone the subsequent course of chemotherapy because of incomplete bone marrow recovery on day 21. Mucositis WHO grades II/III were observed during 36 (29.8%) courses. Nausea and vomiting exceeding WHO grade I were seen in 17 (14%) courses despite antiemetic treatment, but were usually of short duration. Phlebitis of the infusion arm occurred in 15 (12.4%) courses. Median LVEF decreased from 63% (range 53–73%) at baseline ($n=25$) to 60% (range 48–73%, $n=16$) ($P< 0.02$, Wilcoxon test for paired observations) after a cumulative epirubicin dose of 675 mg/m^2. 2 patients were taken off study because a decrease of 15% of LVEF was observed after a cumulative dose of epirubicin of 675 mg/m^2. 1 patient showed a decrease of 25% 6 months after the last dose of epirubicin and etoposide. Besides a slight tachycardia this patient had no signs of CHF. None of the other patients developed clinical signs or symptoms of CHF. All patients receiving more than one course had alopecia WHO grade II.

Response was evaluated in all patients. Complete response was achieved in 2 patients (8%) and a partial response in 7 patients (28%). The overall response rate was 36% (95% CI: 18–57.5%). 12 patients (48%) had stable disease, 4 patients (16%) progressive disease. There was no significant difference in the response rate of patients with squamous histology (3/8) as opposed to non-squamous histology (6/19). The median duration of response ($n = 9$) was 29.6 (range 12.1–42.7) weeks. Median time to progression ($n = 25$) was 23.9 (range 2.9–42.7) weeks.

Median follow-up for the whole group of patients is 39 weeks with 9 patients alive with cancer. Median survival for all patients is 31.8 (range 4.3–75) weeks.

DISCUSSION

This is the first study reporting on toxicity and efficacy of the combination of HDE and etoposide in advanced NSCLC. Toxicity of this regimen is considerable, leading to the removal of 5/25 patients from the study. As was to be expected, myelosuppression was the dose-limiting toxicity, in particular leukocytopenia (79.3% of courses WHO grades III/IV). During 14 courses patients had to be admitted because of leukocytopenia-associated fever. In addition 19.8% of courses were associated with thrombocytopenia WHO grades III/IV. The incidence of non-haematological toxicities was comparable with our previous study with HDE [5], though the rate of mucositis WHO grade II/III was slightly higher in this study. The observed lack of clinically significant cardiotoxicity in this study, in spite of a significant decrease in median LVEF values, confirms the results of our studies [5] and those of others [10] that doses of epirubicin up to 950 mg/m^2 are rarely associated with CHF.

The total response rate obtained with the high-dose epirubicin and etoposide regimen including 2 complete responses was 36% (95% CI: 18–57.5%). Although this is not a randomised trial comparing HDE and its combination with etoposide we feel that it can be concluded that the addition of etoposide at this dose level does not lead to an improved response rate nor to prolonged survival and is associated with significantly more toxicity compared with a similar historical group of patients treated with high-dose epirubicin as a single agent [5]. Consequently, further studies with this combination are not warranted, unless adding haematopoietic growth factors will give the opportunity to increase the dose of etoposide. On the other hand, high-dose epirubicin consistently seems to produce response rates of 25–30% in advanced NSCLC. Therefore, the incorporation of this drug in combination regimens should be the subject of future clinical trials in this disease.

1. Feld R, Wierzbicki R, Walde D, *et al.* High-dose epirubicin given as a daily × 3 schedule in patients with untreated extensive non-small cell lung cancer. *Proc AACR* 1988, **29**, 208 (abstr.).
2. Feld R, Wierzbicki R, Walde D, *et al.* A phase II trial of high-dose epirubicin (E) in patients (pts) with untreated extensive non-small cell lung cancer (NSCLC). *Proc ASCO* 1990, **9**, 930 (abstr.).
3. Martoni A, Melotti B, Guaraldi M, Panutti F. Activity of high dose epirubicin in advanced non small cell lung cancer. *Eur J Cancer* 1991, **27**, 1231–1234.
4. Wils J, Utama I, Sala L, *et al.* Phase II study of high dose epirubicin in non small cell lung cancer. *Eur J Cancer* 1990, **26**, 1140–1141.
5. Smit EF, Berendsen HH, Piers DA, Smeets J, Riva A, Postmus PE. A phase II study of high dose epirubicin in unresectable non small cell lung cancer. *Br J Cancer* 1992, **65**, 405–408.
6. Vokes EE, Vijayakumar S, Bitran JD, Hoffmann PC, Golomb HM. Role of systemic therapy in advanced non small cell lung cancer. *Am J Med* 1990, **89**, 777–786.
7. Bakowski MT, Crouch JC. Chemotherapy of non-small cell lung cancer: a reappraisal and a look to the future. *Cancer Treat Rev* 1983, **10**, 159–172.
8. Mountain CF. A new international staging system for lung cancer. *Chest* 1986, **89**, 225 (suppl.).
9. WHO Handbook for reporting results of cancer treatment. WHO Offset Publication no. 48, Nijhoff Den Haag, 1978.
10. Nielsen D, Jensen JB, Dombernowsky P. Epirubicin cardiotoxicity: a study of 135 patients with advanced breast cancer. *J Clin Oncol* 1990, **8**, 1806–1810.