Eur J Cancer Clin Oncol, Vol. 20, No. 4, pp. 495–499, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Phase II Trial of Epirubicin in Advanced Squamous, Adeno- and Large Cell Carcinoma of the Lung

RUDOLF A. JOSS,* HEINE H. HANSEN,† MOGENS HANSEN,‡ JOSETTE RENARD§ and MARCEL ROZENCWEIG‖
For the EORTC Early Clinical Trials Group¶

**Institut für Medizinische Onkologie, Universität Bern, Inselspital, CH—3010 Bern, Switzerland, †Finsen Institute, Strandboulevarden 49, DK—2100 Copenhagen, Denmark, ‡Bispebjerg Hospital, Medical Department C, Bispebjerg Bakke 23, DK—2400 Copenhagen, Denmark, §EORTC Data Center, Institut Jules Bordet, B—1000 Brussels, Belgium and ‖Service de Médecine et Laboratoire d'Investigation Clinique Henri Tagnon, Institut Jules Bordet, B—1000 Bruxelles, Belgium*

Abstract—*Epirubicin, a stereoisomer of doxorubicin with suggested lower potential for cardiotoxicity in animal tumor systems, was evaluated in a disease-oriented phase II trial in non-small cell lung cancer. The drug was given as a direct i.v. injection of* 90 mg/m^2 *repeated every* 3 weeks. *Four partial remissions were observed among* 75 *evaluable patients. Forty-two of the* 75 *patients had received no prior chemotherapy. The predicted true response rate is equal to* 5% (0.2–10%). *Leucopenia* (75% *of patients), gastrointestinal disturbances* (76% *of patients) and alopecia* (53% *of patients) were common side-effects observed. Four patients had cardiac abnormalities after treatment with epirubicin (one sinustachycardia, two premature beats, one biopsy-proven cardiomyopathy with congestive heart failure). One patient developed a peripheral neuropathy possibly related to epirubicin. We conclude that epirubicin in the present dose and schedule is an inactive agent in patients with non-small cell lung cancer.*

INTRODUCTION

SINGLE-AGENT chemotherapy has been extensively tested in lung cancer [1]. Data suitable for analysis indicate that, by current standards, response rates to such treatment range from 5 to 20%. As the development of effective combination chemotherapy regimens depends primarily on the individual activity of its components, careful clinical screening of new, hopefully more active agents deserves high priority [2].

Accepted 28 September 1983.

¶Other participants in this study were: Wim ten Bokkel Huinink (Netherland Cancer Institute, Amsterdam, The Netherlands), Jan B. Vermorken (Academisch Ziekenhuis der Vrije Universiteit, Amsterdam, The Netherlands), Reto Abele (Hôpital Cantonal, Genève, Switzerland), Pierre Siegenthaler (Hôpital des Cadolles ,Neuchâtel, Switzerland), Reto Obrist (Kantonsspital, Basel, Switzerland), Eduard Holdener (Kantonsspital, St. Gallen, Switzerland), Franco Cavalli (Ospedale San Giovanni, Bellinzona, Switzerland), Uta Bruntsch (Medizinische Klinik, Nürnberg, Germany), Edward Newlands (Charing Cross Hospital, London, U.K.) and Herman Høst (Det Norske Radiumhospital, Oslo, Norway).

Doxorubicin is one of the most widely used agents in current cancer chemotherapy. However, drug induced cardiac damage, related to the total cumulative dose administered, may result in the occurrence of frequently irreversible and fatal congestive heart failure [3]. A number of anthracycline derivatives with lower cardiotoxicity in various animal models have been developed with great expectations [4]. Accurate verification of these experimental findings in humans should be preceded by early clinical trials screening for antitumor activity of the new analogues.

Epirubicin (4′-epidoxorubicin, NSC-256942) is a stereoisomer of doxorubicin differing from the parent compound only by epimerization of the hydroxy group in the position C-4′ of the sugar moiety [5]. Equitoxic doses of epirubicin elicit equal or slightly better antitumor activity in a number of animal tumor systems, and lower cardiotoxicity has been demonstrated in rabbits [6–8]. This suggested lower potential for cardiotoxicity was ascribed to lower retention of

epirubicin in the heart [6]. Phase I trials with epirubicin yielded encouraging results with hints of activity in a variety of malignancies [9–11]. The present phase II trial was undertaken to determine if the drug could achieve complete or partial responses in 'non-small cell' lung cancer and to further characterize its toxic effects.

MATERIALS AND METHODS

Ninety-eight patients with histologically documented and surgically incurable squamous cell carcinoma, adenocarcinoma or large cell anaplastic carcinoma of the lung were entered. Patients had locally advanced or metastatic disease. Previously unirradiated measurable (two perpendicular diameters measurable) or evaluable (one diameter measurable or deeply located lesions measurable in two diameters) parameters were required. Other eligibility criteria included a performance status under 3 (ECOG/Zubrod scale), age of 75 yr or less, no brain involvement or leptomeningeal disease, recovery of all toxic manifestations produced by prior radio- or chemotherapy, no prior anthracycline treatment and adequate renal (creatinine <1.5 mg/dl and/or creatinine clearance >80 ml/min), hepatic (bilirubin <2 mg/dl), marrow (WBC $\geq 4000/mm^3$, platelets $\geq 100{,}000/mm^3$) and cardiac (no congestive heart failure, no significant arrhythmia, no bilateral bundle branch block or history of myocardial infarction) functions.

Epirubicin was supplied by Farmitalia-Carlo Erba S.p.A., Milan, Italy, in 10- and 50-mg rubber disc-capped vials as a sterile red lyophilized powder. The drug was reconstituted with distilled water for i.v. injection at a concentration of 5 mg/ml immediately prior to drug administration. Epirubicin was given at a starting dose of 90 mg/m^2 i.v. q 3 weeks. Drug administration was postponed by 1 week if there was no full hematologic recovery at the time of scheduled retreatment. Dosages were adjusted according to the lowest value of the WBCs and platelets measured weekly during the previous course. If the WBC nadir and the platelet nadir remained $>4000/mm^3$ and $>100{,}000/mm^3$ respectively, the next dose was escalated by 25%. If the WBC and the platelet nadirs were between 2000 and $2999/mm^3$ and 50,000 and $74{,}999/mm^3$ respectively, the next dose was reduced by 25%. With lower counts the next dose was reduced by 50%. If myelosuppression resulted in treatment delay at the time of scheduled retreatment, drug dosage was reduced by 25% if not already indicated by blood counts during the previous course. Response to treatment was first assessed after 6 weeks, according to WHO response criteria [12]. Death before initial response assessment at 6 weeks without severe toxicity was considered as early non-toxic death. Any death to which drug toxicity was thought to have made a major contribution was considered as toxic death. Response duration was calculated from the first day of treatment until documentation of progression.

Of 98 patients entered, 10 were ineligible because of CNS metastases, lack of tumor parameters, age over 75 yr and a WBC count below $4000/mm^3$ (two patients each). In addition, one patient had a performance status of 3 and another had a pancreatic adenocarcinoma detected at autopsy. Thirteen eligible patients were considered not evaluable. Eight died apparently from rapid disease progression on days 11, 12, 17, 19, 20, 25 and 35. Five other patients were excluded from the analysis because of treatment refusal after the first dose (three patients), acute tachycardia and dyspnea (one patient) and inadequate data (one patient).

The median age of the 75 fully evaluable patients was 60 yr (range 37–75 yr). Fifty-seven males and 18 females were included. Nine patients had a performance status of 0, 42 patients a performance status of 1 and 24 patients a performance status of 2. Prior to study entry 37 patients had experienced weight loss $\leq 5\%$ of their usual body weight, 19 patients $>5\%$ and in 19 the degree of weight loss was unknown. There were 40 squamous cell carcinomas, 20 adenocarcinomas and 15 large cell carcinomas. Thirty-five patients had limited disease and 40 had extensive disease using the criteria of the V.A. Lung Cancer Group [13]. Forty-two patients had received no prior chemotherapy (Table 1).

Table 1. Prior treatment

	No prior chemotherapy	1–2 cytostatic agents	≥3 cytostatic agents
None	31	11	9
Surgery	7	4	2
Radiotherapy	3	4	2
Radiotherapy and surgery	1	1	0
Total	42	20	13

RESULTS

Four patients achieved partial remissions of 2.5, 3, 5 and 9 months duration. All responders had a good performance status, three had experienced ≤5% weight loss upon entry and three had disease confined to one hemithorax (Table 2). Three responders had received no prior chemotherapy and one was pretreated with vincristine for an adenocarcinoma and had responded to this agent. Forty-one patients had unchanged disease for a median of 4 months (range 1.5–9 months) and the remaining 30 patients had progressive disease.

Myelosuppression was the most significant toxic effect (Table 3). The median WBC nadir was 2900/mm^3, with a range of 100–17,400/mm^3. Full recovery was seen by day 21. Two patients had leucopenia related lung infections that promptly recovered with antibiotic treatment. The median platelet nadir was 175,000/mm^3 (range 38,000–836,000/mm^3). The majority of the patients experienced mild to moderate nausea and vomiting. Other toxic effects included alopecia, mucositis, phlebitis, diarrhea, dizziness, neuropathy and cardiac abnormalities. One 70-yr-old female with metastatic adenocarcinoma previously treated with CCNU, cyclophosphamide, methotrexate and vindesine complained of dizziness and had signs of a peripheral neuropathy during the fifth cycle of epirubicin. CT-scan of the brain was negative. After epirubicin-discontinuation the neurological signs improved. Four patients exhibited cardiac abnormalities after epirubicin treatment. One patient developed sinustachycardia and shortness of breath after the first dose of epirubicin. This adverse reaction precluded further drug administration. Within 2 hr after epirubicin two patients had premature beats which disappeared spontaneously. Nine patients received a total dose of epirubicin greater than 500 mg/m^2: 550, 560, 600, 630, 630, 630, 1000, 1160 and 1533 mg/m^2. The latter patient was treated for an unresectable anaplastic large cell carcinoma confined to one hemithorax. No prior radiation therapy was given, but the patient had been pretreated with vindesine. The patient had stable disease over 8 months and was given a total dose of 1533 mg/m^2 of epirubicin. He then developed signs of cardiac decompensation with neck vein distension and moderate liver enlargement. The echocardiogram showed no pericardial effusion, but was compatible with moderate cardiomyopathy. Low voltage was noted on the electrocardiogram. Angiocardiography showed a diffuse decrease of the contraction capacity of the left ventricle. Endomyocardial biopsies showed changes consistent with moderate to severe anthracycline toxicity in the left and right ventricles.

DISCUSSION

Epirubicin was evaluated in this study in a favorable group of patients with 'non-small cell' lung cancer. All patients were ambulatory, half of the patients had experienced no or minimal prior weight loss and almost half of the patients had locoregional disease. Furthermore, 31 patients had received no prior treatment at all and 42 of 75 fully evaluable patients had received no prior chemotherapy. With four partial remissions

Table 2. Antitumor activity of epirubicin according to selected prognostic factors

	No. of patients*				
	Total	CR	PR	NC	P
All patients	75	0	4	41	30
Performance status					
0–1	51	0	4	32	15
2	24	0	0	9	15
Weight loss					
≤5%	37	0	3	15	19
>5%	19	0	1	11	7
Unknown	19	0	0	15	4
Histology					
Epidermoid carcinoma	40	0	2	19	19
Adenocarcinoma	20	0	2	11	7
Large cell anaplastic carcinoma	15	0	0	11	4
Extent of disease					
Locoregional	35	0	3	21	11
Metastatic	40	0	1	20	19

*CR = complete remission; PR = partial remission; NC = no change; P = progressive disease.

Table 3. Toxic effects of epirubicin

Toxic effect	No. of toxic patients*
Nausea/vomiting	57 (11)†
Leucopenia	56 (18)
Alopecia	40 (19)
Thrombocytopenia	13 (4)
Mucositis	9 (2)
Phlebitis	6
Cardiac abnormalities	4 (1)
Diarrhea	2 (0)
Dizziness	2
Peripheral neuropathy	1 (0)

*75 patients evaluable for toxicity.
†( ) = No. of patients with WHO grade III or IV toxic effects.

among this group of patients the predicted true response rate was 5%, with a range of 0.2–10%. The response rate according to histological subtypes was 5% (0–11%) for squamous cell carcinoma, 10% (0–23%) for adenocarcinoma and 0% among 15 patients with large cell anaplastic carcinoma. Our results are comparable to those of Kalman and co-workers [14]. These authors observed one partial remission among 34 adequately treated patients.

Epirubicin was generally well tolerated. Most patients had myelosuppression, but 16 (21%) experienced no hematological toxicity. Gastrointestinal disturbances were usually of mild to moderate degree and 18 patients (24%) experienced no nausea and vomiting. Only nine patients received a total dose of epirubicin that was greater than 500 mg/m^2. As mentioned, one patient developed congestive heart failure after a total dose of 1533 mg/m^2 of epirubicin. Further studies in patients receiving this agent will be required to define the true incidence of cardiotoxic side-effects of epirubicin.

Our results with epirubicin in non-small cell lung cancer are disappointing and have prompted us to review the data of disease-oriented phase II trials evaluating anthracyclines in this disease. Adriamycin has been tested in at least five trials (see Table 4), which indicate that this agent has low activity in non-small cell lung cancer. Another anthracycline analogue, 4-demethoxy-daunorubicin, has recently been evaluated in a disease-oriented phase II trial in a favorable group of patients with non-small cell lung cancer. No response was observed among 23 fully evaluable patients [20].

We conclude that epirubicin, in the present dose and schedule, is an inactive agent in patients with non-small cell lung cancer. Furthermore, the role of anthracyclines in the treatment of non-small cell lung cancer has to be reconsidered.

Acknowledgement—The authors are grateful to Miss G. Bachmann for secretarial assistance.

Table 4. Doxorubicin in the treatment of non-small cell lung cancer

Dose and schedule	Performance status	Prior chemotherapy	Histology	Response rate	Response duration (months)	Reference
0.4–0.6 mg/kg × 3/week			squamous	0/ 9		
or	N.S.*	N.S.	adeno	0/ 6	1.5–3.0	[15]
25 mg/m^2 × 3 q 3 weeks			large cell	1 CR + 1 PR/11		
30–35 mg/m^2 × 3 q 3–4 weeks	N.S.	no: 10	squamous	0/ 2		
		yes: 21	adeno	5 PR/17	7.0	[16]
			large cell	1 PR/ 6		
20–25 mg/m^2 × 3 q 3 weeks			squamous	2 PR/18		
or	N.S.	N.S.	adeno	3 PR/18	N.S.	[17]
60–75 mg/m^2 q 3 weeks			large cell	0/12		
20 mg/m^2 × 3 q 3 weeks	ambulatory 67	no: 56	squamous	4 PR/58		
	non-ambulatory 100	yes: 111	adeno	2 PR/45	2.0	[18]
			large cell	2 PR/37		
75 mg/m^2 q 3 weeks	N.S.	no: 46	squamous	11 PR/30		
		yes: 14	adeno	0/ 2	3.0	[19]
			large cell	2 PR/ 2		
			squamous	17 PR/117 (15%)		
Total			adeno	10 PR/ 88 (11%)		
			large cell	1 CR + 6 PR/68 (10%)		

*Not specified.

REFERENCES

1. COHEN MH, PEREVODCHIKOVA NI. Single agent chemotherapy of lung cancer. In: MUGGIA F, ROZENCWEIG M, eds. *Lung Cancer: Progress in Therapeutic Research*. New York, Raven Press, 1979, 343–374.
2. CAPIZZI RL, KEISER LW, SARTORELLI AC. Combination chemotherapy—theory and practice. *Semin Oncol* 1977, **4**, 227–253.
3. VON HOFF DD, LAYARD MW, BASA P. Risk factors for doxorubicin induced congestive heart failure. *Ann Intern Med* 1979, **91**, 710–717.
4. ROZENCWEIG M, DE SLOOVER C, VON HOFF DD. Anthracycline derivatives in the new drug development programs. *Cancer Treat Rep* 1979, **63**, 807–808.
5. GANZINA F. 4′-Epi-doxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1983, **10**, 1–22.
6. CASAZZA AM. Experimental evaluation of anthracycline analogues. *Cancer Treat Rep* 1979, **63**, 835–844.
7. CASAZZA AM, DI MARCO A, BERTAZZOLI C. Antitumor activity, toxicity, and pharmacological properties of 4′-epiadriamycin. In: SIEGENTHALER W, LUTHY R, eds. *Current Chemotherapy*. Washington, DC, American Society of Microbiology, 1978, 1257–1260.
8. ZBINDEN G, BRÄNDLE E. Toxicologic screening of daunorubicin (NSC-82151), adriamycin (NSC-123127) and their derivatives in rats. *Cancer Chemother Rep* 1975, **59**, 707–715.
9. BONFANTE V, BONADONNA G, VILLANI F. Preliminary phase I study of 4′-epi-adriamycin. *Cancer Treat Rep* 1979, **63**, 915–918.
10. BONFANTE V, BONADONNA G, VILLANI F. Preliminary clinical experience with 4′-epiadriamycin in advanced human neoplasia. *Recent Results Cancer Res* 1980, **74**, 202–209.
11. SCHAUER PK, WITTES RE, GRALLA RJ. A phase I trial of 4′-epi-adriamycin. *Cancer Clin Trials* 1981, **4**, 433–437.
12. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO, 1979.
13. ROSWITT B, PATNO ME, RAPP R. The survival of patient with inoperable lung cancer: a large-scale randomized study of radiation therapy versus placebo. *Radiology* 1968, **90**, 688–697.
14. KALMAN LA, KRIS MG, GRALLA RJ. Phase II trial of 4′-epi-doxorubicin in patients with non-small cell lung cancer. *Cancer Treat Rep* 1983, **67**, 591–592.
15. BONADONNA G, TANCINI G, BAJETTA E. Chemotherapy of lung cancer. The experience of the National Cancer Institute of Milan. *Cancer Chemother Rep* 1973, **4**, 231–237.
16. CORTES EP, TAKITA H, HOLLAND JF. Adriamycin in advanced bronchogenic carcinoma. *Cancer* 1974, **34**, 518–525.
17. O'BRYAN RM, LUCE JK, TALLEY RW. Phase II evaluation of adriamycin in human neoplasia. *Cancer* 1973, **32**, 1–8.
18. KNIGHT EW, LAGAKOS S, STOLBACH L. Adriamycin in the treatment of far advanced lung cancer. *Cancer Treat Rep* 1976, **60**, 939–941,
19. KENIS Y, MICHEL J, RIMOLDI R. Results of a clinical trial with intermittent doses of adriamycin in lung cancer. *Eur J Cancer* 1972, **8**, 485–489.
20. JOSS RA, OBRECHT JP, ALBERTO P. Phase II trial of 4-demethoxydaunorubicin (IMI-30) in patients with non-small cell lung cancer (NSCLC). Abstract, 13th International Congress of Chemotherapy, Vienna, 1983.