Eur J Cancer Clin Oncol, Vol. 23, No. 9, pp. 1407–1408, 1987.
Printed in Great Britain

0277–5379/87$3.00+0.00

4′-Deoxydoxorubicin, an Inactive Drug in Small Cell Lung Cancer

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Abstract—*4′-Deoxydoxorubicin was administered to* 27 *evaluable patients with refractory small cell lung cancer. The majority of patients had good initial performance status. One third of patients had never received doxorubicin before, and six had received a single drug alone* (*VM*26).

Myelotoxicity was the main side-effect, and leukopenia was more pronounced than thrombocytopenia. No significant non-hematological toxicity occurred apart from skin necrosis due to drug extravasation in one case. Two patients had partial response (7.4%; 95% *confidence limits* 0–17.2%). *The low response rate obtained in this good prognosis patient population does not support further testing of this drug in small cell lung cancer.*

INTRODUCTION

4′-DEOXYDOXORUBICIN (DXDX) is an anthracycline derivative that differs from doxorubicin by the absence of a hydroxyl group at the C4 position of the aminosugar moiety. DXDX is active against several experimental tumors and human tumors transplanted into nude mice [1, 2]. DXDX also showed efficacy both *in vivo* and *in vitro* in neoplasms resistant to doxorubicin [3, 4].

Phase I trials have established granulocytopenia as the limiting toxicity and several studies suggest a lower cardiotoxicity of DXDX in comparison with doxorubicin [5–7]. Moreover, other non-hematologic side effects (alopecia and gastrointestinal toxicity, in particular) appeard to be less pronounced than those induced by the parent compound [7–9].

We tested DXDX in patients with refractory small cell lung cancer (SCLC).

PATIENTS AND METHODS

Twenty-seven patients with a cytologic or histologic diagnosis of SCLC were entered into the study from October 1984 to June 1986. Eligibility criteria included: presence of measurable disease, an ECOG performance status < 3, life expectancy of at least 2 months, good hepatic, renal, marrow and cardiac functions, no second tumor and no prior treatment in the last 3 weeks.

Accepted 29 April 1987.
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Informed consent was obtained from all patients. There was no age limit in this study.

DXDX was administered i.v. at a dose of 30 mg/m^2 diluted in 100 ml 5% dextrose and infused in 15 min, every 3 weeks. At the start of treatment and before each cycle blood counts, 12 channel profile and electrocardiogram were checked, together with other investigations, as indicated by disease extension. Blood counts were repeated at least once a week during the first two cycles and DXDX was increased to 125% if WBC and platelet nadir counts were above 3000/mm^3 and 100,000/mm^3, respectively. Dose reductions were applied when WBC and platelet counts dropped below 1500/mm^3 and 75,000/mm^3, respectively. Treatment was delayed if WBC and platelet counts were below 3000/mm^3 and 100,000/mm^3 on the day of treatment. At least two cycles were required for response evaluation, unless a rapid progression occurred after one cycle. Criteria for response and toxicity definition were those recommended by the WHO [10]. Response and survival durations were calculated from start of treatment.

RESULTS

All 27 patients were evaluable and their characteristics are summarized in Table 1. All patients were pretreated by chemotherapy; 18 patients had received prior doxorubicin, and six patients had previously received a single drug alone (VM26). Seventy-eight cycles were administered overall (1–8 per patient). Dose could be escalated in 13 patients; dose reduction was required in one patient only.

Table 1. Patient characteristics and treatment outcome

Number of entered and evaluable patients				27
Stage: limited/extensive*				11/16
Median age (range): years				62 (47–74)
Sex: male/female				25/2
Performance status (ECOG): 0–1/2				20/7
Weight loss: less/more than 5%				23/4
Prior treatment:	surgery	2	radiation	7
	chemotherapy	27	doxorubicin	18
			VM26 alone	6
Marrow toxicity (patients):		Grade 3	Grade 4	
WBC		6	2	
Platelets		1	2	
Nadirs ($\times 10^3/mm^3$)	Mean	(range)	Day of nadir	(range)
WBC	3	(0.9–7.1)	15	(9–22)
Platelets	204	(13–351)	14.2	(8–22)
Responses: partial 2; no change 8, progression 17				
Median survival time: 133 days				

Limited disease: disease confined within one hemithorax and regional lymphatics. Ipsilateral supraclavicular nodes and pleural effusion included.
Extensive disease: diseases extending beyond limits mentioned for limited disease.

The drug was generally well tolerated. The main toxicity encountered was marrow toxicity: leukopenia was more pronounced than thrombocytopenia. Transient hemorrhage occurred in a thrombocytopenic patient. Mild alopecia was observed in two patients only. Of two cases of drug extravasation, one required skin grafting. Vomiting occurred in eight patients; mild diarrhea, infection and transaminase increase occurred in occasional patients. No sign of cardiac (maximal cumulative dose reached 292.5 mg/m^2) or renal toxicity was observed.

Two patients had a partial response in lung deposits and in bone which lasted 154 and 97 days, respectively; eight patients had no change and 17 progression. Median survival time was 133 days.

DISCUSSION

Chemotherapy is the mainstay treatment for SCLC and new active drugs are needed.

In our study DXDX was well tolerated and severe non-hematologic toxicity was not encountered. However, the response rate was disappointingly low (7.4%; 95% confidence limits 0–17.2%) in the good prognosis patient population that we studied. Further study of this drug in SCLC patients therefore does not seem to be warranted.

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