Eur J Cancer, Vol. 26, No. 2, pp. 139–141, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

Clinical Trial Summary

Doxorubicin in Relapsed Soft Tissue Sarcoma: Justification of Phase II Evaluation of New Drugs in this Disease

An EORTC Soft Tissue and Bone Sarcoma Group Study

G. BLACKLEDGE, A. van OOSTEROM, H. MOURIDSEN, W.P. STEWARD, J. BUESA, D. THOMAS, R. SYLVESTER and J. ROUESSE

INTRODUCTION

SOFT TISSUE SARCOMA represents about 1% of all malignancies. Whilst the disease can be cured by surgical removal, prognosis is poor if the disease relapses. A number of agents have been shown to have first line activity in soft tissue sarcoma including doxorubicin, Ifosfamide and DTIC [1–3]. Most other established cytotoxic drugs, however, have little or no activity in this disease. This lack of activity has been ascertained in a variety of studies, including the use of the drugs in first line and in more formal Phase II studies. The EORTC sarcoma group has evaluated over 15 new compounds over the past 15 years and only Ifosfamide and DTIC, agents already known to be active, showed significant activity in the classical Phase II setting [4].

The question therefore of whether routine Phase II evaluation of a new drug in previously treated patients is worthwhile must be raised in soft tissue sarcoma. It was therefore decided to carry out a Phase II study of doxorubicin, the most active agent against sarcoma, to determine whether this agent could be demonstrated to produce responses following the failure of primary chemotherapy. If this could be demonstrated then it would indicate that further Phase II studies of chemotherapy agents might be justifiable because active agents stood a reasonable chance of being identified.

Accepted 20 October 1989.
Address correspondence to: Dr G. Blackledge, M.D., Ph.D., F.R.C.P., Department of Medicine, Queen Elizabeth Hospital, Birmingham, B15 2TH, U.K.

PATIENTS AND METHODS

Patients with biopsy proven soft tissue sarcoma who had received no more than three previous chemotherapy agents excluding anthracyclines for advanced disease were eligible for entry to the trial. Patients had to have evaluable disease using UICC criteria with white cell count $>3500/\mu l$ and platelets $>125{,}000/\mu l$ prior to treatment.

Doxorubicin was administered at a dose of 75 mg/m^2 by i.v. bolus every 3 weeks. A minimum of two courses was required to assess response. Treatment was continued to a maximum of eight courses, to prevent cardio-toxicity, to progression or to the occurrence of other toxicities which prompted discontinuation of therapy. Data were collected on EORTC forms and analysed by the EORTC Data Center. Response was assessed using UICC criteria and toxicity by WHO criteria.

RESULTS

Twenty-three patients were entered into this study. In two cases there were no evaluable lesions and in a further three cases the eligibility criteria

Table 1. Patient characteristics (in 18 evaluable patients)

Median age in years (range)
46 (24–62)

Male:female
10:8

	PR	NC	PD	Total
Total	3	10	5	18
Previous chemotherapy				
One drug	2	5	2	9
Two drugs	1	4	3	8
Three drugs	0	1	0	1
Performance status				
WHO 0	1	1	1	3
WHO 1	1	8	0	9
WHO 2	1	1	4	6
Sites of disease followed (total 25)				
Primary	1	1	0	2
Nodes	1	0	0	1
Subcutaneous	0	3	1	4
Lung	3	6	4	13
Liver	0	1	1	2
Other visceral metastases	0	3	0	3

were not obeyed (two patients more than three drugs; one patient previous anthracycline). Eighteen patients were therefore eligible and evaluable for the trial. A partial response was seen in three patients (see Table 1) (durations 4, and 6 months) and haematological toxicity was as reported in Table 2.

DISCUSSION

This study confirms that doxorubicin (Adriamycin®) has activity even in patients who are refractory to other chemotherapy agents. Although this was only a small study the number of responses suggests significant activity for doxorubicin. This is even more significant when it is considered that over 200 patients have been studied in different Phase II studies by the EORTC with no responses having been seen [4].

It is also of note that the haematological toxicity profile of doxorubicin given at this dose even after prior chemotherapy was acceptable.

The present study is too small to determine whether factors exist which may influence the likelihood of response to second-line agents. In other diseases factors apart from chemosensitivity appear to influence response to Phase II agents. In gastric cancer, performance status is a highly significant factor, and in ovarian cancer, a recent study has shown that the interval from primary treatment to Phase II treatment was highly important in determining the likelihood of response [5].

Such factors may exist for soft tissue sarcoma, but have not yet been detected. It this is the case, then the number of patients entered into Phase II studies to determine that a drug is inactive may be inappropriately small. In a conventional Phase II study 14 patients are required to show that a drug has a response rate less than 20% and about 19–20 patients to demonstrate complete inactivity. In soft tissue sarcoma, the maximum response rate for a single agent, even as first-line therapy, is approximately 30%. A large proportion of only 14–20 patients could easily have adverse prognostic factors by chance, and therefore a sample size of only 20 patients could be too small to detect a compound with at least minimal activity.

This small study of doxorubicin in sarcoma demonstrates that the present policy of evaluating new drugs after the failure of conventional agents in this disease is probably justified. An additional Phase II study of DTIC has also confirmed the second-line activity of that drug. These do not necessarily support, however, the current methods of Phase II evaluation, and further work is required to determine whether prognostic factors exist in soft tissue sarcoma which may affect sensitivity to chemotherapy in the Phase II setting.

Acknowledgement—We are grateful to Virginia Sykes for her work on data analysis.

Table 2. Haematological toxicity. Total number of courses = 78 (18 patients)

		Hb	WCC	Granulocytes	Platelets
Number of courses [n=number (%)]					
with WHO	Grade 0	56 (72)	37 (47)	25 (32)	66 (85)
	Grade 1	10 (13)	14 (18)	9 (11)	1 (1)
	Grade 2	1 (1)	12 (15)	5 (6)	0
	Grade 3	1 (1)	4 (5)	2 (2)	1 (1)
	Grade 4	0	1 (1)	0	0
	Unknown	10 (13)	10 (13)	37 (47)	10 (13)
	Total	78	78	78	78
Median WHO Grade		0	0	0	0

REFERENCES

1. Gottlieb J, Baker L, O'Bryan R *et al.* Adriamycin® (NSC-123127) used alone and in combination for soft tissue and bone sarcomas. *Cancer Chemother Rep* 1975, **6**, 271–282.
2. Mouridsen H, Somers R, Santoro A *et al.* Doxorubicin versus Epirubicin in advanced soft tissue sarcomas. An EORTC randomized Phase II study. In: Bonadonna G, ed. *Advances in Anthracycline Chemotherapy: Epirubicin.* 1984, 95–103.
3. Bramwell V, Mouridsen H, Santoro A *et al.* Cyclophosphamide versus Ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. *Eur J Cancer Clin Oncol* 1987, **23**, 311–323.
4. van Oosterom A, Santoro A, Rouesse J *et al.* Chemotherapy in advanced soft tissue sarcoma—the EORTC experience. In: Ryan JR, Baker LO, eds. *Recent Concepts in Sarcoma Treatment.* Dordrecht, Kluwer, 1988, 183–190.
5. Blackledge G, Lawton F, Redman C, Kelly K. Response of patients in Phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and the design of Phase II trials. *Br J Cancer* 1989, **59**, 650–653.