Eur J Cancer Clin Oncol, Vol. 24, No. 9, pp. 1439–1443, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

A Phase I–II Study of Ifosfamide in Combination with Adriamycin in the Treatment of Adult Soft Tissue Sarcoma

JANINE L. MANSI, CYRIL FISHER, EVE WILTSHAW, SHEILA MACMILLAN, MICHAEL KING and ROBIN STUART-HARRIS*

The Sarcoma Unit, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K.

Abstract—*Fifty-four patients with advanced soft tissue sarcoma were treated with a combination of ifosfamide* (5 g/m^2) *and adriamycin* (40–60 mg/m^2) *at 3 weekly intervals. Of the* 50 *evaluable patients a response was seen in* 11 (22%) *patients* (3 *complete and* 8 *partial responses*), *stabilization of disease occurred in* 17 *patients and the remaining* 22 *patients progressed whilst on treatment. Of the* 22 *patients receiving adriamycin* 60 mg/m^2 12 (55%) *required a dose reduction due to toxicity compared to* 11 (39%) *of the* 28 *patients who received* 40 mg/m^2. *For the patients who had a response the median relapse-free interval was* 7 *months* (*range* 2–17+) *and the overall median survival was* 12 *months* (*range* 5–29+). *The combination does not appear to show an advantage over either drug used as a single agent.*

INTRODUCTION

IFOSFAMIDE and adriamycin are the most active single agents in advanced soft tissue sarcomas. Adriamycin was introduced into the treatment of soft tissue sarcomas over a decade ago, and early studies reported response rates ranging from 9 to 70% [1]. Incorporation of adriamycin into regimens such as CYVADIC (cyclophosphamide, vincristine, adriamycin, dacarbazine) was received with initial enthusiasm because of a response rate of 59% [2], however this has not been sustained [3] and more recent studies report poorer results [4, 5]. Ifosfamide was introduced more recently and response rates ranging from 18 to 38% have been reported [6–8].

The urothelial toxicity of high dose ifosfamide can be reduced considerably by the incorporation of mesna into the regimen [6], and the toxicity of adriamycin is well established both alone and in combination with other cytotoxic agents. This study was conducted to evaluate the use of these two agents in combination, at maximum safe doses, with the aim of increasing the response rate and improving the relapse-free interval and overall survival without an appreciable increase in toxicity.

Accepted 26 April 1988.
*Present address: Department of Medical Oncology, The Westmead Centre, Westmead, NSW 2145, Australia.
Name and address for correspondence and reprints: Dr E. Wiltshaw, The Sarcoma Unit, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K.

PATIENTS AND METHODS

(a) *Patients*

All patients with soft tissue sarcoma attending the Sarcoma Clinic at the Royal Marsden Hospital (Fulham Road) btween 1984 and 1987 were considered for the study. Patients were included provided they had a proven histological diagnosis of sarcoma (all cases reviewed by C.F.), measurable disease, no chemotherapy within the previous 4 weeks, no radiotherapy to the sole index lesion within the previous 8 weeks, no history of cardiac or renal disease (as shown by an EDTA of <50 ml/min). The median age of the patients entered into the study was 43 years (range 13–72), 27 were female and 23 male. The majority of patients were performance status WHO grade 1 (36), six were grade 0, 11 grade 2 and 1 grade 3. No patient had received radiotherapy to the sole index lesion but eight had received chemotherapy previously [ifosfamide (2), methotrexate (4), vincristine, adriamycin, cyclophosphamide (2)]. Four of these patients had progressed on previous treatment, three had stable disease and one had received adjuvant chemotherapy. The histological subtypes are shown in Table 1.

Each patient on admission to the study had a full blood count, electrolytes, liver function tests, EDTA clearance, ECG (and ECG gated blood pool scan in selected cases), chest X-ray and relevant CT scans where indicated. Nadir blood counts were taken on day 10 and all routine tests were repeated

Table 1. Histological type and response to treatment

Histology	Total No. patients	Previously untreated				Pre-treated			
		CR	PR	NC	PD	CR	PR	NC	PD
Malignant fibrous histiocytoma	8		1	6	1				
Synovial sarcoma	11		1	3	6				1
Leiomyosarcoma	13	1		3	7		1		1
MPNST	2						1	1	
Rhabdomyosarcoma	4	1		1	2				
Liposarcoma	2		1				1		
Sarcoma N.O.S.	5	1	2	1				1	
Haemangiopericytoma	1			1					
Angiosarcoma	2				1				1
Fibrosarcoma	1				1				
Epithelioid sarcoma	1				1				
Total	50	3	5	15	19		3	2	3

CR = complete remission; PR = partial remission; NC = no change; PD = progressive disease; MPNST = malignant peripheral nerve sheath tumour.

prior to each course. CT scans were repeated at regular intervals.

(b) *Methods*

Fifty-four patients received 5 g/m^2 of ifosfamide and 5 g/m^2 mesna with either 40 mg/m^2 or 60 mg/m^2 of adriamycin. Four patients were not evaluable (two lost to follow-up, one died first day of first course and one only received one course).

The method of administration of ifosfamide has been described in previous publications [6, 7]. To reduce urothelial toxicity mesna was given with the ifosfamide (1/5th of total dose as bolus prior to infusion, 3/5th as an infusion with the ifosfamide, and 1/5th as an infusion following the chemotherapy). In the first 28 patients adriamycin was given by bolus at an initial dose of 40 mg/m^2 but increased to 60 mg/m^2 in the subsequent 22 patients. Regular antiemetics (dexamethasone and metoclopramide) were administered with the treatment. Treatment was repeated at 3 weekly intervals up to a maximum of eight courses provided (i) the haematological parameters had returned to adequate levels (leucocyte count $\geq 3 \times 10^9$/l and platelets $\geq$100,000/mm^3), (ii) renal function remained adequate and (iii) there was no evidence of cardiac toxicity. In the face of progressive disease or unacceptable toxicity the treatment was discontinued. In responders or patients with stable disease therapy was continued for eight courses. The median number of courses given was six (range 2–8).

(c) *Dose modifications*

The dose of adriamycin was reduced by 25% if treatment was delayed by failure of the leucocytes or platelets to return to specified levels 3 weeks after the chemotherapy was given. In the presence of a reduced EDTA or persistent micro- or macroscopic haematuria the dose of ifosfamide was reduced by 25%.

(d) *Evaluation of response*

The criteria used for assessing response and toxicity were those defined by the World Health Organization [9].

RESULTS

For the whole group a response was seen in 11 (22%) patients, stable disease in 17 (34%) patients and progressive disease in 22 (44%) patients (Table 1). Of the patients receiving 60 mg/m^2 of adriamycin 9/22 (41%) achieved response compared to 2/28 (7%) who received 40 mg/m^2 (Table 2). The median dose and range of adriamycin given in the two treatment groups are shown in Table 2. A response was seen in three of the eight patients who had received treatment previously (Table 1). Two of these patients had progressed on methotrexate.

The duration of response to treatment is shown in Table 3. Of the three patients who had a complete response to treatment the median relapse-free interval was 14 months (range 7–17+) and median overall survival 17 months (range 10–21+). The relapse-free interval and overall survival was shorter in those patients who either had a partial response or stabilization of disease following chemotherapy. Only two of the 22 patients with progressive disease on treatment are still alive; the median survival, measured from entry to the study, of those who have died was 5 months.

Toxicities encountered by the 50 patients are shown in Table 4. With the increased dose of adriamycin the toxicity of the treatment was also increased, such that 12 of the 22 patients receiving 60 mg/m^2 adriamycin required a dose reduction

Table 2. Response to treatment according to dose of adriamycin

Response	Ifosfamide 5 g/m² Adriamycin 40 mg/m²	MD (range)	Ifosfamide 5 g/m² Adriamycin 60 mg/m²	MD (range)
Complete remission	1	40	2	330 (300–360)
Partial remission	1	320	7	360 (180–480)
No change	11	230 (120–330)	6	195 (120–360)
Progressive disease	15	120 (80–120)	7	200 (120–420)
Total	28		22	

MD = median of cumulative dose of adriamycin given.

Table 3. Duration of response to treatment and survival

Response	Median response (range)	Overall survival (range)	Number alive
CR $n = 3$	14 (7–17+)	17 (10–21+)	2
PR $n = 11$	6 (2–11+)	12 (5–29+)	5
NC $n = 17$	3* (1–12)	11 (4–36+)	9
PD $n = 22$		5 (2–13)	2

*Progression-free interval.

compared with only 11 of the 28 patients receiving 40 mg/m². The toxicities experienced by the pretreated group of patients are shown in Table 4. There was only one treatment-related death caused by severe neutropenia and this was in a patient with extensive metastatic disease. No cardiovascular side-effects apart from transient tachycardias occurred in either group. Seven patients had haematuria on ward testing and two patients had haemorrhagic cystitis; no renal toxicity occurred. Central nervous system toxicity was encountered in three patients, two experienced drowsiness for 24 h and one had epileptiform episodes culminating in drowsiness for 26 h; all three patients recovered fully.

DISCUSSION

The use of ifosfamide and adriamycin together in the treatment of adult sarcomas has been reported

Table 4. Toxicity according to dose of adriamycin

	Adriamycin 40 mg/m² (%) Total $n = 28$		Pretreated $n = 3$	Adriamycin 60 g/m² (%) Total $n = 22$		Pretreated $n = 5$
Alopecia	28	(100)	(3)	22	(100)	5
N and V (gd 3)	2	(7)	2	5	(23)	1
Leucopenia*						
gd 3	8	(29)	1	7	(32)	2
gd 4	3	(11)	1	10	(45)	2
Thrombocytopenia*						
$<90 \times 10^9$/l	1	(4)	0	1	(5)	0
Anaemia* <9.4 g/l	12	(43)	2	10	(45)	5
Septicaemia	1	(4)	0	5	(23)	2
Infections requiring i.v. antibiotics	4	(14)	0	12	(55)	5
Haematuria						
gd 1	6	(21)	0	1	(5)	0
gd 2	0		0	2	(9)	1
Encephalopathy						
gd 3	2	(7)	0	1	(5)	1
Tachycardia	4	(14)		6	(27)	

*Myelotoxicity data reflects blood counts taken immediately prior to each course of chemotherapy.

Table 5. Comparison with other studies using ifosfamide and adriamycin

Dose/m²		No. of	Response rate (%)			Reference
I	A	patients	CR	PR	Overall	
5	20/40/60	50	13	23	36	[7]
5	50	33	3	21	24	[10]
5	50	126	6	29	35	[11]
7.5	50	14	21	50	71	[12]

I = ifosfamide; A = adriamycin.

by other groups and similar response rates have been obtained (Table 5). The studies by Dombernowsky *et al.* [10] and Schütte *et al.* [11] yielded results, in terms of toxicity and response, directly comparable to this study because of their drug doses and method of administration. Conversely, in the study by Hartlapp *et al.* [12] the ifosfamide was given as a daily infusion over 5 days to a total dose of 7.5 g/m² and adriamycin was given in divided doses over 3 days, however only 14 patients were entered and although preliminary results are encouraging, both with regard to remission rate and toxicity, the results of a larger group of patients will be awaited with interest.

A dose–response relationship with ifosfamide has been investigated previously but a higher response rate was not seen when the dose of ifosfamide was increased from 5 to 8 g/m², although the toxicity was greater at the latter dose [6]. Conversely, higher doses of adriamycin have been shown to increase the response rate, with doses of 60 mg/m² or more giving better results than 50 mg/m² or less [13]. Increasing the dose of adriamycin from 40 to 60 mg/m² in this study increased the overall response rate but the numbers in each group are small and a statistical comparison cannot be made. It is of note that the median total dose of adriamycin received in each patient group is well below the maximum tolerated dose (usually 550 mg/m²) (Table 2).

The toxicity of the combination was predictable from experience when either agent is used singly. There was, however, an increase in toxicity with the higher dose of adriamycin, particularly myelosuppression. Conversely, there was no evidence of increased cardiac toxicity with the higher dose of adriamycin.

The combination also appears to be of value in pretreated patients. This compares favourably with other studies in which either ifosfamide alone [14] or in combination [15] has been given to previously treated patients with recurrent disease.

The combination of ifosfamide with adriamycin does not improve the response rate of either agent when used alone sufficiently to recommend combination chemotherapy. The complete remission rate for sarcomas remains at between 6–15% in most large studies even when many drugs are used in combination. Since complete regressions are the only ones associated with relatively long term benefit to patients we feel that the increased toxicity associated with the combination ifosfamide and adriamycin does not warrant its use in this palliative setting. Better therapeutic results for metastatic sarcoma will only come with the advent of more active drugs or possibly by using existing drugs in new schedules.

REFERENCES

1. Pinedo HM, Kenis Y. Chemotherapy of advanced soft-tissue sarcomas in adults. *Cancer Treat Rev* 1977, **4**, 67–86.
2. Gottlieb JA, Baker LH, O'Bryan RM *et al.* Adriamycin (NSC-123127) used alone and in combination for soft tissue sarcomas. *Cancer Chemother Rep* 1975, **6**, 271–282.
3. Yap BS, Baker LH, Sinkovics JG *et al.* Cyclophosphamide, vincristine, adriamycin and DTIC (CYVADIC) combination chemotherapy for the treatment of advanced sarcomas. *Cancer Treat Rep* 1980, **64**, 93–98.
4. Pinedo HM, Bramwell VHC, Mouridsen HT *et al.* CYVADIC in advanced soft tissue sarcoma: a randomized study comparing two schedules. *Cancer* 1984, **53**, 1825–1832.
5. Bui NB, Chauvergne J, Hocke C, Durand M, Brunet R, Coindre JM. Analysis of a series of sicty soft tissue sarcomas in adults treated with a cyclophosphamide–vincristine–adriamycin–dacarbazine (CYVADIC) combination. *Cancer Chemother Pharmacol* 1985, **15**, 82–85.
6. Stuart-Harris R, Harper PG, Parsons CA *et al.* High-dose alkylation therapy using ifosfamide infusion with mesna in the treatment of adult advanced soft tissue sarcoma. *Cancer Chemother Pharmacol* 1983, **11**, 69–72.
7. Wiltshaw E, Westbury G, Harmer C, McKinna A, Fisher C. Ifosfamide plus mesna with and without adriamycin in soft tissue sarcoma. *Cancer Chemother Pharmacol* 1986, **18** (suppl 2), S10–S12.
8. Bramwell VHC, Mouridsen HT, 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**, 311–321.

9. World Health Organization. *Handbook for Reporting Results of Cancer Treatment.* Geneva, WHO, 1979 (Offset publication No. 48).
10. Dombernowsky P, Mouridsen H, Schütte J *et al.* Phase II study of ifosfamide + adriamycin in advanced soft tissue sarcoma in adults. A preliminary analysis. *Cancer Chemother Pharmacol* 1986, **18** (Suppl 2), S17.
11. Shütte J, Dombernowsky P, Santoro A *et al.* Adriamycin (A) and ifosfamide (I), a new effective combination in advanced soft tissue sarcoma. Preliminary report of a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Proc Am Soc Clin Oncol* 1986, **5**, 145.
12. Hartlapp JH, Munch HJ, Illinger HJ, Wolter H, Jensen JC. Alternatives to CYVADIC combination therapy in soft tissue sarcomas. *Cancer Chemother Pharmacol* 1986, **18** (Suppl 2), S20–S22.
13. O'Bryan RM, Luce JK, Talley RW, Gottlieb JA, Baker LH, Bonnadonna G. Phase II evaluation of adriamycin in human neoplasia. *Cancer* 1973, **32**, 1–8.
14. Magrath IT, Sandlund JT, Rayner A, Rosenberg SA, Arasi V, Miser JS. Treatment of recurrent sarcomas with isosfamide (IF). *Proc Am Soc Clin Oncol* 1985, **4**, C528.
15. Miser JS, Kinsella TJ, Triche TJ *et al.* Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. *J Clin Oncol* 1987, **5**, 1191–1198.