Eur J Cancer Clin Oncol, Vol. 19, No. 7, pp. 885–890, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00

Intra-arterial Adriamycin Followed by Surgery for Limb Sarcomas. Preliminary Report

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Abstract—*A multimodal treatment schedule for operable soft tissue sarcomas is ongoing in our institution. The main purposes are to achieve an easier radical surgery with limb preservation and to lower the risk of local relapses. Patients with documented untreated soft tissue sarcoma of the lower limb are given continuous intra-arterial regional infusion with adriamycin consecutively for* 8 days *up to a dose of* 100 mg/m^2. *Radical surgery is performed by the fourth day after infusion. Preliminary data on* 13 *cases are available: after infusion only* 6 *patients presented reduction of the tumor diameters, but almost all postoperative histological examinations revealed wide areas of necrosis (up to* 100%*) of tumor tissue (in* 9 *cases* >50%*). In* 4 *patients surgical treatment was completed with radiotherapy. In* 2 *cases the preliminary indication to disarticulation could be modified in wide excision after the postinfusional tumor reduction. The toxicity of adriamycin was typical and acceptable. Further data will be available after adequate follow-up and when more patients enter the study. These data document the feasibility of this multimodal treatment and its validity in terms of specific tumor tissue toxicity and improved surgical approach.*

INTRODUCTION

AT THE Istituto Nazionale Tumori, Milan a new multimodal rationale has been outlined for the treatment of operable soft tissue sarcomas of the limbs to achieve a better surgical approach in terms of limb salvage, to reduce the theoretical risk of metastatic spread during surgical manipulation of the tumor and to evaluate possible tumor tissue chemosensitivity.

MATERIALS AND METHODS

The treatment schedule (Table 1) consists of a preoperative infusional therapy with adriamycin delivered by 24-hr intra-arterial continuous infusion for 8 consecutive days up to a total dose of 100 mg/m^2. A polyethylene catheter was inserted into the homolateral external iliac artery through the homolateral femoral artery (anti-blood stream) according to the accessibility of the angiograms; in two cases of buttock lesions the catheter was inserted into the common iliac artery. The only patient with a tumor of the upper third of the arm was incannulated through the homolateral brachial artery. The drug was given by means of a suitable infusional pump. Radical surgery was performed within 6 days after termination of the infusional chemotherapy. When radicality was considered inadequate, radiotherapy was used.

Eligible patients had a histologically proved operable soft tissue sarcoma of a limb larger than 8 cm in diameter, and had not previously received chemotherapy or radiotherapy. Relapses after non-radical surgery were also candidates.

Table 1. *Treatment regimen*

Preoperative infusion	intra-arterial adriamycin, 100 mg/m^2 (given continuously for 8 days)
Surgery	wide or radical operation, performed within the sixth day after the end of infusion
Radiotherapy	mandatory for marginal, non-radical or contaminated operations; feasible in any case

Accepted 28 January 1983.
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Table 2. Characteristics and therapy performed in the series

No.	Sex	Age (yr)	Histology	Site	Total dose*	Clinical response	Type of surgery	Radicality	Histologic necrosis	Postoperative RT	Follow-up (months)
1	F	43	liposarcoma myxoid	mid thigh	176	<50%	wide excision	yes	>50%	no	living, NED (19)‡
2	F	57	liposarcoma polymorphous	upper thigh	160	<50%	disarticulation	yes	>50%	no	living, NED (19)
3	F	43	malignant fibrous histiocytoma	mid thigh	116	none	wide excision	yes	>50%	no	living, NED (18)
4	F	30	malignant fibrous histiocytoma	buttock	160	none	wide excision	yes	>50%	no	lung metastases (8), living (15)
5	M	23	undifferentiated sarcoma	buttock	170	<50%	marginal excision	dubious	>90%	yes	lung metastases (3), dead (10)
6	M	35	malignant fibrous histiocytoma	mid thigh	178	none	marginal excision	dubious	>50%	yes	living, NED (15)
7	M	50	liposarcoma myxoid	upper thigh	185	none	wide excision	yes	50%	no	local relapse (12), disarticulation, living, NED (14)
8	M	24	synovial sarcoma	upper thigh	173	<50%	marginal excision	dubious	0%	refused	lung metastases (9), living (15)
9	F	55	rhabdomyosarcoma	upper thigh	184	none	wide excision	yes	>90%	no	lung metastases (4), living (10)
10	M	15	clear cell sarcoma	upper thigh	165	<50%	wide excision	yes	100%	no	living, NED (10)
11	M	13	malignant schwannoma	shoulder	128	<50%	marginal excision	dubious	50%	yes	living, NED (6)
12	F	56	malignant fibrous histiocytoma	upper thigh	166†	none	disarticulation	yes	100%	no	synchronous lung metastases, living (6)
13	F	57	liposarcoma myxoid	upper thigh	180	none	marginal disarticulation	dubious	0%	yes	living, NED (5)

*In mg of adriamycin.
†See text.
‡NED = No evidence of disease.

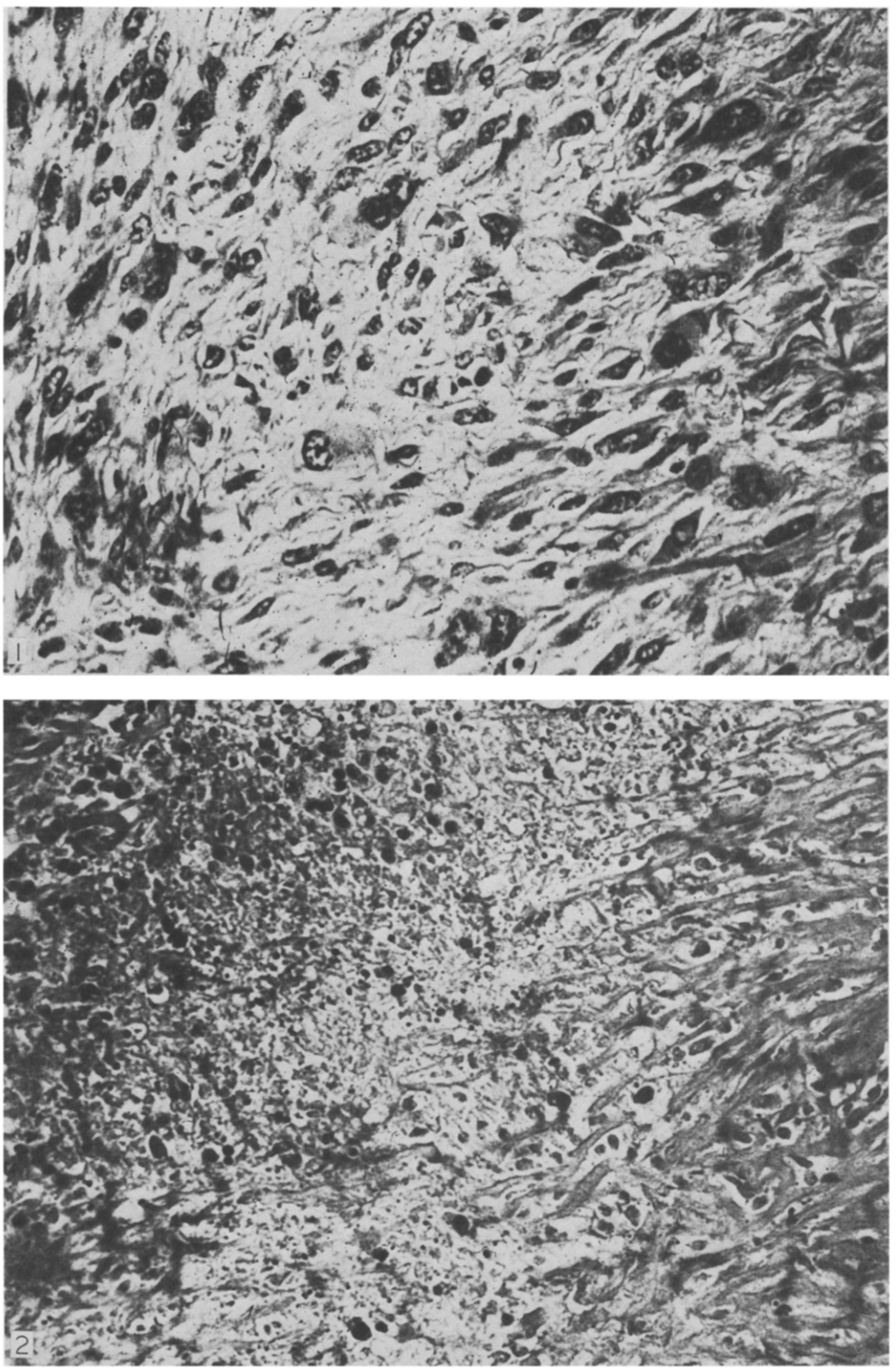

Fig. 1. Postinfusional specimen. Case No. 3: malignant fibrous histiocytoma. Area of residual tumor. Hematoxylin and eosin, ×225.

Fig. 2. Same case. Area of complete necrosis of the tumor. Hematoxylin and eosin, ×225.

RESULTS AND DISCUSSION

Our small series collected 13 patients in 17 months. Their age ranged from 13 to 57 yr (mean age 38.5 yr), and no sex predilection was revealed. All the patients were given the infusional drug at the proposed dosage: mean total dose, 165.7 mg of adriamycin, range 116–185 mg.

Our data are summarized in Table 2. No complications occurred during the infusional treatment; only a 13-yr-old boy, who was given chemotherapy through the brachial artery, revealed a reduction in the pulse and a peculiar reddish color of the homolateral hand, but no vascular deficit occurred. The toxicity from adriamycin was typical and acceptable in all cases (Table 3). It is noteworthy that no complication occurred after surgery, even if the operation had been performed in the presence of leukopenia. Wound healing was normal in all the patients.

Histological response was proved in 11 of 13 evaluable specimens, and in 4 it was more than 90%: in 2 of these no residual neoplastic tissue was found in the necrotic areas. In contrast, only 5 patients revealed a clinical reduction in dimension and consistency of the tumor, and only in 1 case was it judged to be more than 50%. This discrepancy among clinical and pathological results is probably due to the interval between infusional treatment and surgery, which was too short to achieve a significant clinical evaluation of a possible response.

All the patients underwent radical surgery. In no case was gross residual neoplastic tissue left in the surgical bed, but in 5 cases the operation was classified as marginal, according to Enneking's classification [1]. In 2 cases slight clinical improvement made it possible to perform conservative surgery instead of disarticulation.

Table 3. Postinfusional toxicity

Alopecia	in all patients
Leukopenia	WBC* mean nadir, 1950 (range 700–2500)
Cardiotoxicity	none
Wound healing	normal in all patients

*WBC = White blood cells.

Table 4. Follow-up

	No. of cases	Mean follow-up (months)
Living, NED*	8	13.3
Living with metastases	4	11.5
Dead	1	10.0
Lost to follow-up	0	—
Total	13	12.5

*NED = No evidence of disease.

The first patient entered this study in January 1981, and 8 patients are now in their second year of follow-up. Five patients developed lung metastases, and all were given adriamycin (75 mg/m^2 every 21 days). Four (80%) of these (case Nos 4, 5, 9 and 12 in Table 2), the same cases that revealed good local response to prior chemotherapy, had objective improvement; one died 7 months later. Two, in remission, are waiting for thoracotomy. The metastatic onset occurred after a mean interval of 4.8 months (range 0–9 months). The one patient who developed synchronous metastases (case No. 12) was given 3 cycles of adriamycin, the first intra-arterially and the second and third intravenously, and then radiotherapy was employed. After disarticulation 6 more cycles of adriamycin were delivered and the solitary lesions almost completely regressed; the patient is now waiting for thoracotomy. The 100% histologically proven necrosis of the tumor is suggestive of an effective dose–response relationship, even if radiotherapy could have effected a local response. The high incidence of metastases is probably due to an unfortunate and spontaneous selection of highly malignant histotypes, which included 4 malignant fibrous histiocytomas (two now have metastases), 1 synovial sarcoma, 1 rhabdomyosarcoma and 1 undifferentiated sarcoma (the latter three all with metastases). One patient, who had a poor response to the intra-arterial infusion, recurred locally, and a disarticulation guaranteed radicality; he is alive and free of disease 2 yr after the first treatment.

Pathological features

Histological examination of these neoplasms showed large areas of necrosis involving 50–100% of the tumoral mass in 11 cases. Only a myxoid liposarcoma and a synovial sarcoma showed no therapeutic response. The areas of necrosis were made up of well-demarcated, confluent foci of various sizes; there was scarce or no inflammatory infiltrate. At the edge of the necrotic tumor tissue there was occasionally hemorrhage and fibrosis. Significant cytological changes (hyperchromasia, irregular nuclear shape, cytoplasmic vacuolization) were visible only in the transitional areas between the foci of necrosis and the residual viable tumor, whereas in the latter there were no cytological alterations. The small and medium-sized vessels did not reveal special structural changes. There was a diffuse vascular dilatation and, in one case only, evidence of arterial thrombosis. In contrast, in the areas of regression there were many arterial thromboses with widespread sclerosis of the vascular wall and occlusion of the lumen. In one case of

liposarcoma (No. 13) the comparison of the preoperative biopsy with the surgical specimen revealed no evidence of therapeutic regression except for minimal circumscribed hemorrhages in the surgical specimen. In another case (No. 12) no comparison was possible owing to the complete regression of the tumor in the surgical specimen. Examples of pre- and postinfusional specimens are shown in Figs 1 and 2.

CONCLUSIONS

In our opinion this study is peculiar for the strict selection of operable, similar cases and for the high dose of adriamycin as a single dose, higher than reported by others [2–7]. The number of patients who entered the study is limited. However, new cases of soft tissue sarcomas are not very frequent and, excluding the analysis of Weisenburger *et al.* [7], no other author has presented a larger series of selected cases [2–6].

After this pilot study, and reviewing our former purposes, we can conclude that (1) preoperative intra-arterial chemotherapy is feasible and has no complications or unexpected side-effects; (2) clinical improvement sometimes makes it possible to perform conservative surgery instead of amputation or disarticulation; (3) the early metastatic spread seen in our series suggests the presence of latent metastases at the beginning of therapy; anyhow, this multimodal treatment schedule does not seem to prevent metastatic onset; (4) tumor chemosensitivity to adriamycin was well documented in almost all the patients. It is noteworthy that the response rate (11 of 13 cases) is very high if we consider that the clinical response to adriamycin for advanced sarcomas is less than 30% of the treated cases [8].

A different treatment schedule will give answers to the following questions: (1) What is the real role of preoperative treatment in terms of local or systemic recurrence and related survivals? (2) Is preoperative chemotherapy given intra-arterially more effective than when given intravenously? (3) What histotype, site and size of sarcomas best take advantage of this treatment? (4) What is the optimal therapeutic regimen (1, 2 or more cycles, drug combination and doses) and the validity of postoperative chemotherapy in responders?

Acknowledgements—We thank Dr. Bruno Damascelli and his staff for providing the angiograms and for insertion of the catheters.

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