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Primary Chemotherapy and Delayed Surgery for Non-metastatic Telangiectatic Osteosarcoma of the Extremities. Results in 28 Patients

G. Bacci, P. Picci, S. Ferrari, L. Sangiorgi, A. Zanone and A. Brach del Prever

28 patients with telangiectatic osteogenic sarcoma of the extremities were treated between March 1983 and March 1990 with neoadjuvant chemotherapy according to two different protocols activated successively. With the first protocol, patients preoperatively received high dose methotrexate (HDMTX)–cisplatinum (CDP) and postoperatively, depending on the histological response, either HDMTX–CDP-doxorubicin (ADM) or ADM–"BCD". With the second protocol patients were preoperatively treated with HDMTX–CDP–ADM and postoperatively either with the same drugs or with the same drugs plus ifosfamide and VP-16. Preoperatively, CDP was delivered intraarterially. A good histological response (tumour necrosis >90%) was observed in 25 patients (89%) and at a mean follow-up of 5 years (2–9 years) 23 patients (82%) remained continuously disease-free and 5 developed lung metastases. These results are better than those obtained in 272 contemporary cases of conventional osteosarcoma of the extremities treated with the same protocols (62% good histological responses and 61% continuously disease-free survival).

Key words: chemotherapy, telangiectatic osteogenic sarcoma
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INTRODUCTION

TELANGIECTATIC OSTEOSARCOMAS represent a rare subtype of high grade osteosarcoma with distinctive radiological gross and microscopic features, and certain prognostic implications [1, 2]. According to several authors [1, 3, 4], the prognosis of telangiectatic osteosarcoma, when treated with surgery alone, is worse than that of conventional high grade osteosarcoma. In a series from a major centre where large numbers of patients with bone tumours were seen, only 1 of the 25 patients treated with surgery alone survived for more than 5 years [4].

In the last few years, many papers have demonstrated that adjuvant and neoadjuvant chemotherapy dramatically improve prognosis of conventional osteosarcoma [6–10]. There are only two conflicting reports in the literature concerning the efficacy of adjuvant and neoadjuvant chemotherapy in telangiectatic osteosarcoma. In fact, while Rosen and colleagues [11], in a series of 16 patients treated according to two different protocols of neoadjuvant chemotherapy, found that this rare variant of

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osteosarcoma was even more sensitive to chemotherapy than the other more common varieties of osteogenic sarcoma, Mervack and colleagues [12], in a series of 17 patients treated with surgery alone or surgery and chemotherapy, reported that survival of patients was not influenced by the administration of chemotherapy.

In this paper, we report the results achieved in 28 patients with non-metastatic telangiectatic osteosarcoma of the extremities, treated at our institution with two different protocols of neoadjuvant chemotherapy between March 1983 and May 1990. These results were compared to those achieved in 279 patients with primary conventional high grade osteosarcoma of the extremities treated during the same period using the same protocols.

PATIENTS AND METHODS

The diagnosis of telangiectatic osteosarcoma was established by radiological and histological analysis of an incisional biopsy, and confirmed by macroscopic and microscopic evaluation of the entire excised specimen after surgery.

The criteria used for the diagnosis of telangiectatic osteosarcoma were: (1) radiologically; a completely lytic, destructive bone lesion with no definitive areas of sclerosis; (2) grossly: a haemorrhagic and often cystic lesion without areas of intramural bone tissue; (3) histologically: a tumour with single or multiple cystic cavities containing blood or necrotic tissue, with septa composed of anaplastic sarcoma cells.

Fine, lace-like osteoid material between cells was always present even if in minimal amounts. Conventional osteosarcomas, even with large areas of telangiectasia, were not included in this study.

Of the 301 patients with primary, high grade, central, non-metastatic osteosarcoma of the extremities, treated between March 1983 and May 1990 at the Rizzoli Institute and at the Pediatric Department of the University of Turin (all patients were initially observed and evaluated at the Rizzoli Institute, where all surgical procedures, anatomical evaluations of margins and necrosis were also performed. Chemotherapy was given in 22 cases at the Rizzoli Institute and in 6 cases at the Pediatric Department of Univeristy of Turin), according to the two protocols of neoadjuvant chemotherapy reported below, 29 (9.6%) satisfied the cited criteria for the roentgenographic and histological diagnosis of telangiectatic osteosarcoma. One of these patients was not considered in this report because, due to severe toxicity after the first cycle of methotrexate, he refused any further chemotherapy. The clinical features of the remaining 28 patients are summarised in Table 1.

All patients had a complete history taken, a thorough physical examination, and several laboratory tests. The primary tumour was staged by standard X-rays, Technetium 99-MDP bone scan, angiography and computed tomography (CT) scan. These examinations were repeated after preoperative chemotherapy before surgery. Magnetic resonance imaging (MRI) was also performed in about 50% of the cases. Metastatic disease was excluded with bone scan and with CT scan of the lungs.

Neoadjuvant chemotherapy was performed according to the two protocols reported in Figures 1 and 2. 9 patients treated before September 1986 had regimen 1, and 19 patients treated afterwards had regimen 2. The rationale for these schemes of chemotherapy, which was the same used at our institution for the treatment of conventional osteosarcoma, has been illustrated in previous papers [6]. Surgery was scheduled 3 weeks after the end of preoperative chemotherapy, i.e. approximately 2 months after the beginning of treatment.

Table 1. Characteristics of the 28 patients with telangiectatic osteosarcoma of the extremities and comparison with 272 contemporary patients with conventional osteosarcoma

	Telangiectatic osteosarcoma	Conventional osteosarcoma
No. of cases	28	272
Sex		
Male	14 (50%)	149 (55%)
Female	14 (50%)	123 (45%)
Age		
<14 years	13 (46%)	120 (44%)
≥14 years	15 (54%)	152 (56%)
Site		
Femur	19 (68%)	139 (51%)
Tibia	4 (14%)	81 (30%)
Humerus	4 (14%)	32 (12%)
Other bones	1 (4%)	20 (71%)
Size*		
<1/3	22 (79%)	196 (72%)
≥1/3	6 (21%)	76 (28%)
Alkaline phosphatase		
Normal	19 (68%)	78 (29%)
Elevated	9 (32%)	194 (71%)
Pathological fractures	4 (14%)	12 (4%)

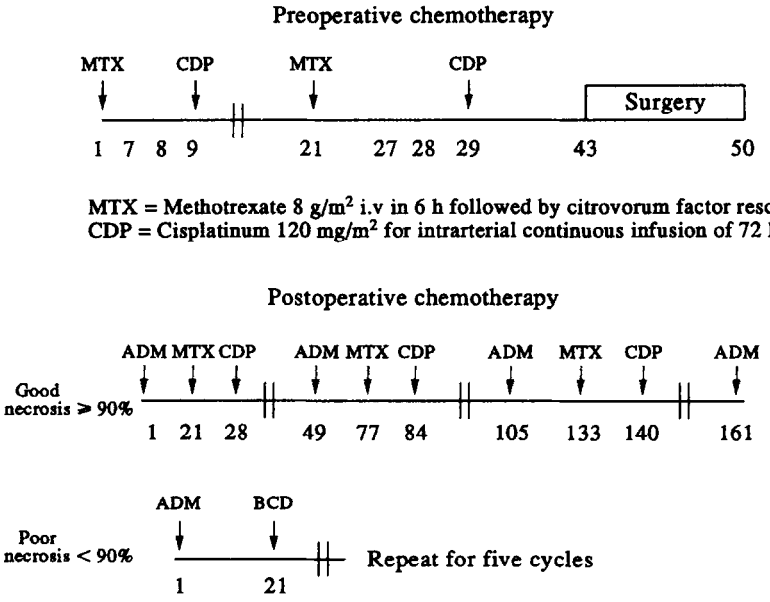
*Proportion of the roentgenographic involved bone length.

The type of surgery (amputation, limb salvage or rotationplasty) and the types of reconstruction (prosthesis, bone graft, rod or plate and cement, vascularised fibula) for resected patients were chosen according to tumour location and extension, patient age and desired life-style. However, for conservative surgery, it was mandatory that preoperative staging assured the possibility of achieving wide surgical margins, preserving at the same time a limb that could at least be partially functional after reconstruction.

Following surgery, in all cases, the gross specimens were reviewed together by the surgeon and the pathologist to evaluate surgical margins. These were defined, according to Enneking's classification [13], as radical, wide, marginal or intralesional. The percentage of tumour necrosis induced by chemotherapy was evaluated by a thorough histological examination of an entire coronal slice of the tumour. As previously reported [14], coronal sections were photographed, and representative coronal sections cut into multiple blocks which were numbered and submitted for histological preparation. Between five and 25 blocks (average nine) were reviewed for each specimen, and at least two haematoxylin and eosin-stained slides were made for each block. The response to chemotherapy was rated "good" if tumour necrosis was greater than or equal to 90%, and "poor" if it was less than 90%.

Postoperative chemotherapy was started 3 to 5 days after surgery in amputated patients, and 10–21 days after surgery in patients who had limb salvage or rotation plasty. As illustrated in Figures 1 and 2, the postoperative chemotherapy regimen was chosen according to the histological response.

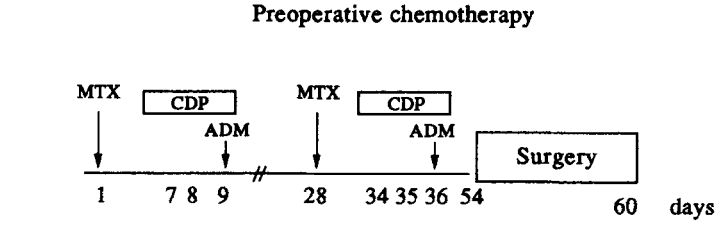
During postoperative chemotherapy, patients were evaluated clinically, and controlled every 2 months with X-rays of the operated limb and of the chest. Additional investigations were performed in case of suspected relapse. At the end of chemotherapy, all patients were followed and monitored with the



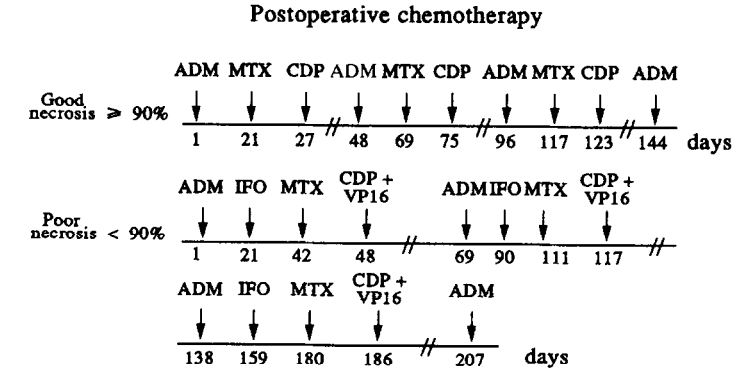
MTX = Methotrexate 8 g/m^2 i.v in 6 h followed by citrovorum factor rescue
CDP = Cisplatinum 120 mg/m^2 for intrarterial continuous infusion of 72 h

MTX, CDP = The same doses used preoperatively, i.v
ADM = Doxorubicin 45 mg/m^2/day i.v for 2 days
BCD = Bleomicin 15 mg/m^2/day, cyclophosphamide 600 mg/m^2/day, dactinomycin 600 mg/m^2/day i.v for 2 days

Figure 1.



MTX = Methotrexate 8 g/m^2 i.v in 6 h followed by citrovorum factor rescue
CDP = Cisplatinum 120 mg/m^2 for intrarterial continuous infusion of 72 h
ADM = Doxorubicin 60 mg/m^2 for i.v infusion of 8 h starting 48 h after the beginning of CDP



ADM = Doxorubicin 45 mg/m^2/day i.v for 2 consecutive days in 4 h infusion
IFO = Ifosfamide 2g/m^2/day i.v for 5 consecutive days in 90 min plus MESNA
CDP = Cisplatinum the same doses used preoperatively, i.v
VP16 = Etoposide 120 mg/m^2/day in 1 h infusion for 3 days
MTX = Methotrexate the same dose used preoperatively.

Figure 2.

radiographs mentioned above in an out-patient clinic every 2 months for 2 years, every 3 months for the third year and subsequently every 6 months.

The major study endpoint was disease-free survival. The overall survival was also evaluated, but the relative figures are to be considered with caution. In fact, in the presence of recurrent disase, no homogenous treatment was performed.

Event-free survival was calculated from the first day of preoperative chemotherapy until the first adverse event (if any) or until the date of the most recent follow-up examination.

Adverse events included the development of recurrent tumour at any site or death in remission. Results have been updated to May 1992.

RESULTS

Clinical, radiological and histological response to preoperative chemotherapy

After preoperative chemotherapy, a clinical and radiological response of the tumour was observed in 26 patients. In 1 patient there were no significant changes, and another showed clinical and radiological tumour progression. This patient, whose limb was amputated after the first cycle of chemotherapy (regimen 1), despite postoperative salvage chemotherapy, developed pulmonary metastases at 8 months from the beginning of treatment and died 10 months later.

The 26 patients who showed a clinical and radiological response to chemotherapy generally showed complete disappearance of pain (if present), a decrease, usually to normalisation, of serum alkaline phosphatase (if elevated), and an increased density on plain X-rays, associated with a decreased vascularity on angiograms. Clinical and radiological reduction in tumour size—usually due more to a decrease of the surrounding inflammatory tissue rather than to an actual reduction in the tumour itself—was observed in 21 patients.

Histologically, a good response (more than 90% of tumour necrosis) was observed in 25 of the 28 patients considered in the study (89%) (Table 2). According to the chemotherapy protocol, there were seven good histological responses in the 9 patients treated with regimen 1 (78%) and 18/19 in the patients treated with regimen 2 (95%). The small number of patients in the two groups did not allow a statistical analysis.

The correlation between the clinical-roentgenographic response and the percentage of necrosis histologically observed on the surgical specimen was generally good but not constant. Both patients who did not show a clinical and radiological response to chemotherapy had a poor necrosis. However, a poor necrosis was also observed in 1 patient who had shown a clinical and radiological response.

Surgery

22 patients were treated with limb salvage procedures (79%), 5 patients had an amputation (18%) and 1 patient had a rotationplasty (34%). In 1 patient who had limb salvage for a tumour located in the proximal fibula, no reconstruction was required, while in the remaining 21 patients treated with conservative surgery, reconstruction was performed with prostheses (12 cases), Kuntscher rod plus cement (3 cases), allografts (4 cases) and vascularised fibulas (2 cases).

Amongst the 5 patients treated with amputation, radical surgical margins were observed in 4 cases and wide margins in the remaining case. For the patients treated with limb salvage, 17 had wide margins, 4 marginal and 1 intralesional. In the patient treated with rotationplasty, the margins achieved were wide but contaminated.

Although 6 patients had inadequate surgical margins, to date no local recurrences have been seen.

Table 2. Type of surgery, surgical margins and histological response according to the two protocols

	Conventional osteosarcoma			Telangiectatic osteosarcoma		
	Regimen 1 $n=117$	Regimen 2 $n=155$	Total $n=271$	Regimen 1 $n=9$	Regimen 2 $n=19$	Total $n=28$
Surgery*						
Amputation	27	14	41	4	1	5
	23%	9%	15%	44%	5%	18%
Resection	86	130	216	5	17	22
	74%	84%	80%	56%	89%	79%
Rotation plasty	3	11	14	0	1	1
	3%	7%	5%		5%	4%
Surgical margins*						
Radical	9	8	17	3	1	4
	8%	5%	6%	33%	5%	14%
Wide	95	124	219	5	13	18
	81%	80%	81%	56%	68%	64%
Marginal	9	16	25	0	5	5
	8%	10%	9%		26%	18%
Intralesional	4	7	11	1	0	1
	3%	5%	4%	11%		4%
Histological response*						
Good (tumour necrosis	54	113	167	7	18	25
>90%)	47%	73%	62%	78%	95%	89%
Poor (tumour necrosis	62	42	104	2	1	3
<90%)	53%	27%	38%	22%	5%	11%

*One patient who developed lung metastases during preoperative chemotherapy was locally treated with radiotherapy.

Continuously disease-free survival (CDFS)

At a mean follow-up of 5 years (2–9 years), 23 patients (82%) remained continuously event-free (CEF) and 5 patients developed metastases (Table 3). The actuarial 5-year continuously disease-free survival is 79%.

For all patients who relapsed, the first site of metastatic disease was the lung. In these patients, the histological response had been good in 4 and poor in 1. The post-relapse course of these 5 patients was the following: 2 are alive and free of disease 10 and 28 months after a thoracotomy with a wedge resection of lung metastases; 1 is alive with uncontrolled disease and 2 died, respectively, 18 and 45 months after the beginning of treatment.

Comparison with conventional osteosarcoma

As illustrated in Table 1, age and sex distribution, tumour location and size of the 28 cases of telangiectatic osteosarcoma considered in this study were identical to those of the 272 cases of conventional osteosarcoma observed at our institution in the same period, and treated with the same two neoadjuvant protocols. In telangiectatic osteosarcoma, however, there was a higher percentage of patients with normal values of serum alkaline phosphatase at presentation (68 versus 29%) and a higher percentage of pathological fractures (14 versus 4%). Even if these differences are not statistically significant, they probably reflect the peculiar telangiectatic osteosarcoma histological features and its aggressive behaviour.

Surgically, the percentage of limb salvages performed in patients with telangiectatic osteosarcoma and in the contemporary patients with conventional osteosarcoma was the same (79 versus 80%).

In terms of results, the comparison between the two groups (Tables 2 and 3) demonstrated that the percentage of good responders was higher in the telangiectatic group (25/28, 89%) than in the conventional group (167/272, 62%). This difference is significant ($P > 0.01$). In the telangiectatic group, as well as in the conventional group, the percentage of good responders was higher in the patients treated with regimen 2, in whom doxorubicin was added during preoperative chemotherapy in addition to methotrexate and cisplatinum (95 and 73% versus 78 and 47%, respectively). In the conventional group, this difference is statistically significant ($P > 0.0021$), but probably due to the small number of patients, it is not significant in the telangiectatic group.

The percentage of patients who remained continuously disease-free was higher in those with telengiectatic osteosarcoma (82%) than in those with conventional osteosarcoma (61%). This difference is statistically significant ($P < 0.01$). In both groups the disease-free survival rate was greater in patients treated with regimen 2 (Table 3). However, it must be outlined that the follow-up period for patients treated with regimen 2 was shorter than that of patients treated with regimen 1 (4 versus 7 years).

Chemotherapy toxicity and surgical complications

For the 28 patients, the major toxicities related to chemotherapy were a transient grade 4 haematological toxicity observed in about 1/3 of the cycles. For this haematological toxicity, on six occasions it was necessary to hospitalise the patient for an aggressive treatment with antibiotics and transfusions.

There were three minor and two major surgical complications, all observed in patients treated with limb salvage procedures. The minor complications consisted of wound slough (2 cases) and one subluxation of the prosthesis. Surgically treated, these complications healed with no further problems. The two major complications were a permanent peroneal palsy and a deep periprosthetic infection. This last complication was managed with repeated surgical debridements, but ultimately it required amputation.

DISCUSSION

Telangiectatic osteogenic sarcoma is a high grade variant of osteosarcoma with an incidence that, in different series, ranges between 3 [1, 4] and 1% [3, 15] of all osteosarcomas.

In historical series, in which the only therapy was surgery, the prognosis of telangiectatic osteosarcoma was even worse than that of conventional osteosarcoma, and so the tumour was considered almost uniformly lethal [1, 3–5]. It is difficult to assess if the worse prognosis of telangiectatic osteosarcoma compared to conventional osteosarcoma was due to the tumour itself or to the delay in the definitive diagnosis. In fact, the purely lytic appearance of telangiectatic osteosarcoma on roentgenograms and the consequent, not uncommon confusion with benign bone cysts (particularly aneurismal bone cysts) often led

Table 3. Results according to the chemotherapy protocols

	Conventional osteosarcoma			Telangiectatic osteosarcoma		
	Regimen 1	Regimen 2	Total	Regimen 1	Regimen 2	Total
No. of cases	117	155	272	9	19	28
Follow-up (years)	7	4	5	7	4	5
Range	5.5–9	2–5.5	2–9	5.5–9	2–5.5	2–9
CDFS	54	113	167	5	18	23
	46%	73%	61%	56%	95%	82%
Local recurrences						
n	6	3	9	0	0	0
	5%	2%	3%	—	—	—
Time (months)	11.3	29.2	18.5	—		—
Metastases						—
n	62	40	103	4	1	5
	53%	26%	38%	44%	5%	18%
Time (months)	15.4	20.5	17.5	25.7	36	27.8
Died from chemotherapy	1	2	3	—	—	—
toxicity	<1%	1%	1%	—		—

CDFS, continuously disease free survival.

to a delayed definitive diagnosis and adequate surgical treatment compared with conventional osteogenic sarcomas. In addition, the propensity of telangiectatic osteosarcoma to pathological fractures due to its lytic nature may lead to a worse prognosis. The occurence of pathological fractures and the subsequent bleeding around the site of the fracture should indeed predispose to an early systemic diffusion of the tumour.

It is uncertain whether, as in the case of conventional osteosarcomas, the modern combination of chemotherapy and surgery has changed the prognosis of telangiectatic osteosarcoma. In the only paper in the literature on this topic, Rosen and colleagues [11] reported that, when treated with neoadjuvant chemotherapy, the cure rate of telangiectatic osteosarcoma may be even higher than that observed in other more common varieties of osteogenic sarcomas. In fact, 14 of the 16 patients treated by these authors with two different protocols of chemotherapy (consisting, respectively, of HDMTX, BCD and doxorubicin and HDMTX–BCD) remained continuously free of disease at a mean follow-up of 5 years. The results of our present study confirm these data. Of the 28 patients treated with two different protocols of neoadjuvant chemotherapy, 23 (82%) remained continuously disease-free at a mean follow-up of 5 years. This percentage is significantly higher than that (61%) of disease-free survival observed in the 272 consecutive cases of conventional osteosarcoma treated at our institution with the same regimens and during the same period. This better prognosis for telangiectatic osteosarcoma is probably due to a better response of the primary tumour to preoperative chemotherapy. In osteosarcoma treated with primary chemotherapy and delayed surgery, several authors [8–10], including ourselves [5], have demonstrated the highly predictive value of the histological degree of tumour necrosis on disease-free survival. In our present study, the percentage of good histological responses was significantly higher in telangiectatic osteosarcoma (89%) than in conventional osteosarcoma (61%). These data compare favourably with the data reported by Rosen and colleagues [11]. In the 16 cases of telangiectatic osteosarcoma treated with neoadjuvant chemotherapy, these authors reported a rate of good responders of 69%, while the good response rate in 206 contemporary cases of conventional osteosarcoma treated with the same protocols by the same authors was only 41%.

The high responsiveness to chemotherapy of telangiectatic osteosarcoma may be explained by the vascularity of this tumour, resulting in a better perfusion of the neoplastic tissue by the chemotherapeutic agents. However, there is the possibility that factors other than increased sensitivity of telangiectatic osteosarcoma to chemotherapy (compared with conventional osteosarcoma) could have some influence on the better response observed since the different chemotherapy protocol we used achieved the same good results.

Besides having a propensity to metastasise early, telangiectatic osteosarcoma has been reported to frequently recur locally after surgery. In the historical Mayo Clinic series of 25 patients treated with surgery alone, five local recurrences were reported (20%), and four were observed in amputated patients [4]. According to Rosen and colleagues [11], if conservative surgery is performed this tendency to recur locally seems to persist with telangiectatic osteosarcoma even if chemotherapy is added to surgical treatment. In Rosen's series, 2 of the 6 patients treated with limb salvage surgery had local recurrences, and for this reason the authors advise the use of limb salvage procedures only in very selected cases.

The results of our study did not confirm these data. No local recurrences were observed in our 28 patients, despite the fact that 22 were treated with limb salvage procedures, and in six cases the surgical margins that resulted were inadequate. The explanation of the discrepancy between our results and those reported by Rosen and colleagues could be the following.

It is now well known that after primary chemotherapy and limb salvage, local recurrences are particularly frequent in patients who did not show a good histological response to preoperative chemotherapy [6, 16]. In comparison to Rosen's series, we had a higher percentage of good responders (89 versus 69%), and the only 3 patients who had a poor histological response to chemotherapy were surgically treated with an amputation. The higher percentage of good responders observed in our study could be because in our patients cisplatinum was preoperatively used in addition to methotrexate. In our opinion, another important factor is that we delivered cisplatinum intraarterially. While it is recognised that equivalent systemic levels of this drug result from intravenous or intraarterial infusion, by intraarterial delivery, the tumour is exposed to two to four times higher concentrations [17, 18]. Therefore, the intraarterial route could improve local effects without sacrificing the systemic effects of chemotherapy that are crucial to microscopic control of osteosarcoma.

This hypothesis has been confirmed by our recent randomised study, in which patients with conventional osteosarcoma treated preoperatively with high dose methotrexate, cisplatinum and doxorubicin were randomised to receive cisplatinum intraarterially or intravenously [19]. In this study, with 79 cases, the percentage of good responders was significantly higher in the group of patients who received cisplatinum intraarterially (77 versus 46%). These results contrast with the COSS experience [20]. It must be stressed, however, that in the COSS-86 study, cisplatinum was delivered as a 5-h infusion intravenously and as a 1-h infusion intraarterially. In addition, while in our previously cited study, cisplatinum was given in combination with intravenous doxorubicin, in the German study, it was combined with intravenous ifosfamide.

In conclusion, our results confirm that telangiectatic osteosarcoma is not a uniformly lethal tumour as suggested by prior reports concerning patients treated with surgery alone. When treated with neoadjuvant chemotherapy, a high percentage of patients with this variant of osteosarcoma can be cured. In addition, following primary chemotherapy, a limb salvage procedure is often possible. This conservative surgery is safe and does not adversely affect the long-term disease-free survival.

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The Importance of Dose Scheduling With Mitoxantrone, 5-Fluorouracil and Leucovorin in Metastatic Breast Cancer

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We have studied a mitoxantrone, 5-fluorouracil (5-FU) and leucovorin chemotherapy regimen in metastatic breast cancer. 8 patients received mitoxantrone 10 mg/m² on day 1, leucovorin 200 mg/m² and 5-FU 300 mg/m² on days 1–5 by intravenous bolus every 28 days in a pilot study. Grades 3–4 granulocytopenia followed 55% of the courses, with 2 patients admitted for febrile neutropenia. Only a 29% objective response rate was seen in a subsequent phase II trial using reduced mitoxantrone doses. Comparison with other trials suggested that 5-day bolus 5-FU administration adversely affects the combination's therapeutic index.

Key words: breast cancer, metastatic, chemotherapy
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INTRODUCTION

THE COMBINATION chemotherapy of metastatic breast cancer with mitoxantrone, 5-fluorouracil (5-FU) and leucovorin has been studied in at least seven different clinical trials [1–7]. The potential interest of combining these agents comes from the observations that both mitoxantrone [8–10] and 5-FU/leucovorin [11–14] are active as second-line therapy of metastatic breast cancer, there is no known mechanism of cross-resistance between them, and they have moderate and different toxicity profiles. Each study used different dose schedules, and response rates ranged from 33 to 65%. Interestingly, the toxicity profile was mild in all studies except one, where 75% of the patients had grade 3–4 leucopenia with six episodes of neutropenic sepsis and 19% grade 3–4 thrombocytopenia [3]. Furthermore, these severe side-effects were only associated with a 33% response rate. This clinical trial was the only one in which both 5-FU and leucovorin were administered for 5 consecutive days by intravenous (i.v.) bolus every 4 weeks, suggesting the possible impact of dose scheduling with this chemotherapy combination. We now report another trial in metastatic breast cancer, which confirms the toxicity and relative lack of efficacy of mitoxantrone, 5-FU and leucovorin administered in a similar dose schedule.

PATIENTS AND METHODS

Eight women with evaluable metastatic breast cancer and no prior chemotherapy, except as adjuvant therapy completed more