Telangiectatic osteosarcoma of the extremity

Neoadjuvant chemotherapy in 24 cases

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ABSTRACT – Between April 1990 and December 1994, we treated 24 patients with telangiectatic osteosarcoma (TO) of the extremities with neoadjuvant chemotherapy using 2 protocols.

Surgery consisted of limb salvage in 21 patients and amputation or rotation plasty in 3. The histologic response to chemotherapy was good (90% or more tumor necrosis) in 23 patients, of whom 12 had total necrosis. With a mean follow-up of 74 (60–96) months, 20 patients remained continuously free of disease and 4 relapsed with lung metastases. There were no local recurrences. Comparing these results to the ones achieved in 269 contemporary patients with conventional osteosarcoma of the extremities using the same protocols for chemotherapy, we found a significantly better histologic response to chemotherapy (96% vs 68% of good histologic response; p= 0.004) and disease-free survival (83% vs 55%; p= 0.01) in the TO group.

We conclude that TO, once considered a lethal tumor, seems to be even more sensitive to chemotherapy than conventional osteosarcoma, and that most of these patients may be cured without amputation.

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Telangiectatic osteosarcoma (TO) is a rare variant of osteosarcoma with distinctive radiographic, gross and microscopic features and prognostic implications (Dahlin 1978, Larson et al. 1978, Huvos et al. 1982, Campanacci 1999). If treated only with surgery, the prognosis is even worse than that of conventional osteosarcoma (Matsuno et al. 1976, Dahlin 1978, Mirra 1989). Since, in the past, patients with TO have usually not been included in chemotherapy trials of osteosarcoma, little is known about the efficacy of surgery combined with chemotherapy in this variant of osteosarcoma. Mervack et al. (1991), in a small series (19 cases) of TO treated at the Mayo Clinic between 1975 and 1983, reported that survival of patients was not affected by chemotherapy. On the contrary, Rosen et al. (1986), in a series of 16 patients who received adjuvant or neoadjuvant chemotherapy at the Sloan Kettering between 1973 and 1980, found that in this variant of osteosarcoma, chemotherapy was even more effective than conventional osteosarcoma.

In a previous paper, we confirmed Rosen's results. In 28 patients with TO of the extremities treated at our institution, we used protocols for neoadjuvant chemotherapy (IOR/OS-N1 and IOR/OS-N2) between March 1983 and March 1990, and found that the rate of good histologic response to preoperative chemotherapy and the rate of 5-year event-free survival were both significantly higher than those obtained in 272 contemporary cases of conventional osteosarcoma treated using the same protocols (Bacci 1994).

We now report the results in a more recent series of 24 new patients with TO of the extremity using two new protocols for neoadjuvant chemotherapy (IOR/OS-N3 and IOR/OS-N4) at our institution from April 1990 and October 1994. These results are compared to those in 269 patients with conventional high grade osteosarcoma of the extremities treated during the same period using the same protocols for chemotherapy.

Table 1. Characteristics of the 24 patients with telangiectatic osteosarcoma of the extremities as compared to 269 patients with conventional osteosarcoma

	Telangiectatic osteosarcoma (24 cases)	Conventional osteosarcoma (269 cases)
Gender		
Male	10	159 (49%)
Female	14	110 (51%)
Age		
< 14 years	8	113 (42%)
> 14 years	16	156 (58%)
Site		
Femur	17	148 (55%)
Tibia	3	80 (30%)
Humerus	4	26 (10%)
Other sites	–	15 (5%)
Serum alkaline phosphatase		
Normal	17	151 (56%)
High	7	118 (44%)
Volume of tumor		
< 150 mL	12	106 (39%)
> 150 mL	12	163 (61%)
Pathologic fracture		
Yes	4	17 (6%)
No	20	252 (94%)

Patients and methods

Patient selection

The diagnosis of TO was suggested by clinical and radiographic findings and confirmed on histologic slides of the tumor tissue from an open biopsy and from the surgical specimens. Two pathologists (P.B. and F.B.) reviewed the radiographs and the slides and agreed on the diagnosis.

As in our previous study (Bacci et al. 1994), the criteria were: (a) radiography, a lytic destructive lesion of bone with no appreciable areas of sclerosis; (b) gross examination, a hemorrhagic cystic cavity-like tumor with no areas of intramural bone tissue; (c) histologically, a tumor with single or multiple aneurysmally-dilated spaces containing blood or necrotic tumor, with septa composed of anaplastic sarcoma cells. Osteoid formation by such cells, appearing as a fine, ice-like material between tumor cells, was always present, even if in small amounts. Osteosarcomas with large areas of telangiectasia, were classified not as TO, but as conventional osteosarcomas.

Of the 293 cases of non-metastatic osteosarcoma of the extremity in patients aged 40 or less treated with neoadjuvant chemotherapy at the Istituto Ortopedico Rizzoli between April 1990 and October 1994, 24 fulfilled the criteria and were included in this study (Table 1).

Preoperative evaluation and chemotherapy

The primary tumor was evaluated on plain radiographs, Technetium 99-MDP bone scan, angiograms, and CT scan. In the 18 more recent cases, MRI was also used. All these examinations were repeated before surgery. Total body scans were done in the search for bone metastases, but chest radiographs and CT scan were used to seek pulmonary metastases.

Chemotherapy was given according to two different regimens (Figures 1 and 2). They were the same as those used at our Institution for conventional osteosarcoma of the extremities. 13 patients were treated between April 1990 and December 1992, following the IOR/OS-N3 protocol, and 11 patients were treated between January 1993 and December 1994, following the IOR/OS-N4 protocol. The main differences between them were that with the IOR/OS-N4 protocol all the active drugs for osteosarcoma (i.e., methotrexate, Cisplatinum, Adriamycin and ifosfamide) were used for all patients starting from the preoperative phase, but with the IOR/OS-N3 protocol, ifosfamide was used only postoperatively and only in patients with tumor necrosis less than 90%. Moreover, the doses of MTX were 12 g/m^2 in the IOR/OS-N4 protocol vs 10 g/m^2 in the IOR/OS-N3 protocol.

Surgery and pathologic evaluation

3 weeks after the last cycle of chemotherapy, the lesions were completely re-staged, then patients underwent surgery. The type of surgery (amputation or limb salvage) and the type of reconstruction (prosthesis, bone grafts, rod or plate and cement, vascularized fibula) were chosen depending on the location and extension of the tumor, patient's age life-style and preferences. However, for limb-sparing surgery, the mandatory condition was the ability to achieve wide surgical margins.

In all cases after surgery, the surgeon and pathologist reviewed the gross specimen to classify the surgical margins by Enneking's method. The percentage of tumor necrosis induced by chemotherapy was evaluated by a thorough histologic

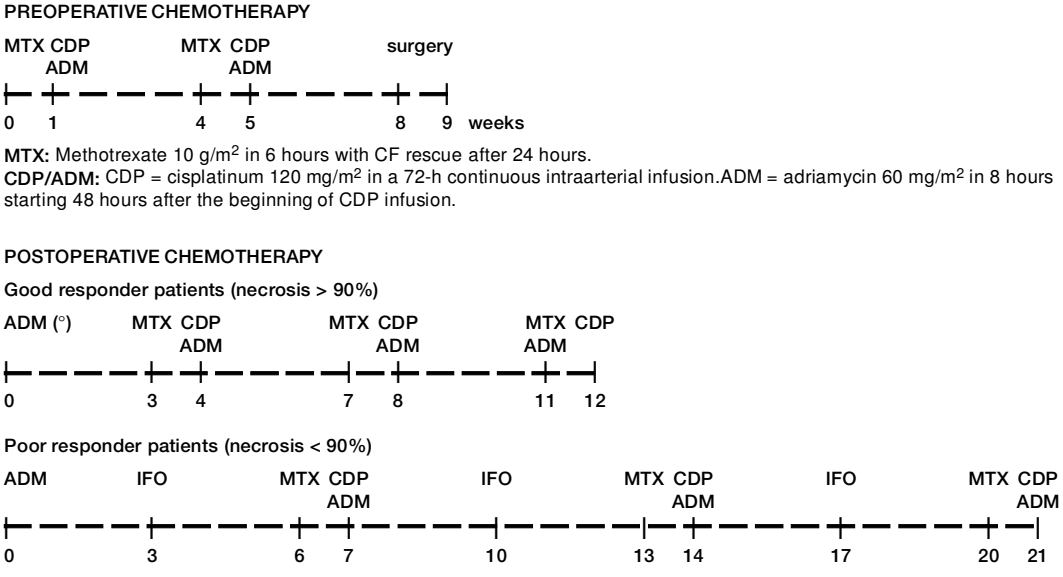

Figure 1. IOR/OS-N3 protocol.

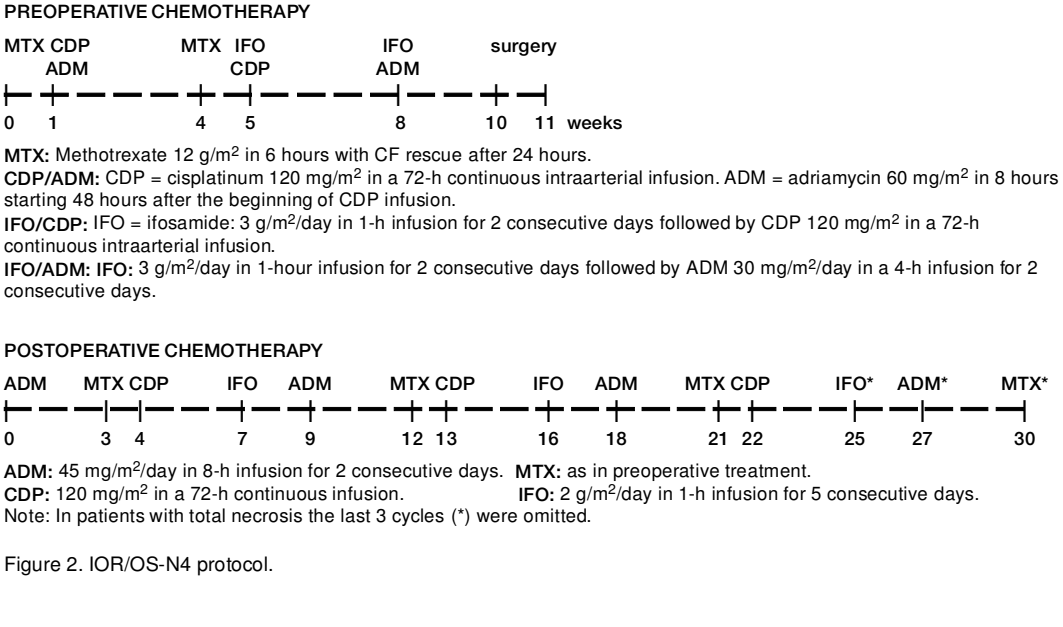

Figure 2. IOR/OS-N4 protocol.

examination of an entire coronal slice of the tumor using a previously reported method (Picci et al. 1985). The response to chemotherapy was rated "good" if tumor necrosis was equal to or greater than 90% and "poor" if it was less than 90%.

Postoperative chemotherapy and follow-up

Postoperative chemotherapy (Figures 1 and 2) was started 4 or 7 days after surgery according to the type of operation (amputation or limb salvage).

During postoperative chemotherapy, apart from clinical evaluation, patients were checked every 2

months with radiographs of the chest and treated limb. Additional investigations were performed only in case of clinical and/or radiographic suspicion of relapse. After chemotherapy, all patients were followed in the outpatient clinic every 2 months for 2 years, every 3 months in the 3rd year and subsequently every 6 months.

The cumulative probability of disease-free survival and overall survival over time were calculated with the actuarial method. The time was calculated from the day of starting preoperative chemotherapy until the first adverse event (if any) or until the date of the most recent follow-up examination. Such events included the development of a recurrent tumor at any site. Results were updated in November 1999.

Comparison with conventional osteosarcoma

The results obtained in the 24 patients with TO were compared to those in 269 contemporary patients with conventional osteosarcoma of the extremities treated at our institution in the same period using the same protocols for chemotherapy (IOR/OS-3 and IOR/OS-4). The only difference between the 2 groups of patients was that all patients with TO received preoperative Cisplatinum intraarterially, while those with conventional osteosarcoma received this drug intraarterially (188 cases) or intravenously (81 cases). This was done because patients with conventional osteosarcoma belonged to a previous randomized study aiming to compare intraarterial versus intravenous Cisplatinum infusion. The results in patients with conventional osteosarcoma treated according to the above-mentioned protocols have been reported (Bacci et al. 1998a, Ferrari et al. 1999).

Results

Clinical and radiological responses to preoperative chemotherapy

After preoperative chemotherapy, clinical and radiographic response of the tumor were seen in 19 patients, but in 5 patients there were none. No clinical or radiographic progression occurred.

The response to chemotherapy usually consisted of a reduction, or more often, complete remission, of pain (if present), and reduced vascularity of the lesions on the angiograms. Clinical and radiographic reduction in tumor size—usually due more to a decrease in the surrounding inflammatory tissue rather than an actual reduction in tumor extension—were also observed.

Surgery and histologic response to preoperative chemotherapy

21 patients were surgically treated with limb salvage, 2 with amputation and 1 with rotation plasty. In the 21 resected patients, reconstructions were performed with prostheses (14), vascularized fibula combined with homograft (2), autografts (3) and allografts (2). The surgical margins were adequate (radical or wide) in 22 patients and inadequate (marginal or intralesional) in 2.

In all but one case, the histologic response to chemotherapy was good (90% or more tumor necrosis). In 12 patients, the tumor necrosis was total.

Survival

At a median follow-up of 74 (60–96) months 20 patients remained continuously free of disease and 4 had relapsed with pulmonary metastases. There were no local recurrences (Table 2). All 4 relapsing patients were good responders, but no one had had a total necrosis. The average time to relapse was 24 (16–34) months. The disease-free survival rate was not related to the patient's sex or age, tumor volume or site, regimen of chemotherapy used, or histologic response to chemotherapy.

All 4 relapsed patients were successively treated with metastasectomy, followed by further chemotherapy in 2 cases. 1 of these patients is alive and free of disease 3 years after the relapse, but the other 3 had further metastatic relapses and died of the tumor 6, 16 and 28 months later.

Comparison with conventional osteosarcoma

Age and gender as well as tumor site in patients with TO were similar to those with conventional osteosarcoma (Table 1). Patients with TO had more femoral locations of the tumor, larger lesions, normal values of alkaline phosphatase and pathologic fractures at presentation.

The rate of limb salvage was the same in the two groups of patients (Table 2). The rate of good histologic response, instead, was higher in telang-

Table 2. Type of treatment and results in 24 patients with telangiectatic osteosarcoma and in 269 patients with conventional osteosarcoma

	Telangiectatic osteosarcoma (24 cases)	Conventional osteosarcoma (269 cases)	P-value
Surgery			
Limb-salvage	21	237 (88%)	
Amputation	2	15 (6%)	ns
Rotation plasty	1	17 (6%)	
Protocol of chemotherapy			
IOR/OS3	13	163 (61%)	ns
IOR/OS4	11	106 (39%)	
Histologic response			
Good	23	183 (68%)	0.004
Poor	1	86 (32%)	
Results			
CDFS [a]	20	148 (55%)	0.02
Relapsed	4	121 (45%)	
Time to relapse (months)	24	25 (6-58)	ns
Local recurrence	0	17 [b] (6%)	ns
Site of first metastases			
Lung	4	102 (84%)	
Bone	0	12 (10%)	
Lung and bone	0	4	ns
Lymph nodes	0	2	
Heart	0	1	
Postrelapse outcome			
Alive and free of disease	1	35	
Alive with uncontrolled disease	0	6	
Died	3	80	

[a] Patients continuously free of disease.
[b] Associated with metastases in all but 1 case.

iectatic osteosarcoma: 23/24 vs 68% of tumor necrosis >90% (p= 0.004), and 12/24 vs 24% of total necrosis (p= 0.01). The rate in patients who remained continuously free of disease was also significantly higher in patients with TO than in those with conventional osteosarcoma (20/24 vs 55%; p= 0.02). The 5-year event-free survival and overall survival were 83% vs 55% (p= 0.01) and 87% vs 69% (p= 0.06), respectively.

There were no differences between the two groups as regards the site of first metastases, and the time of the relapse. No local recurrences were seen in the telangiectatic group, but 269 with conventional osteosarcoma had 17 local recurrences. In both groups, the event-free survival rate was the same in patients treated according to protocol IOR/OS-N3 and protocol IOR/OS-N4.

Discussion

Telangiectatic osteosarcoma is a rare, very aggressive variant of osteosarcoma, accounting for about 8% of cases of osteosarcoma seen at our Institution as compared to 2.5% in the Mayo Clinic series (Matsuno et al. 1976), 5% in the Gustave Roussy (Vanel et al. 1987) series and 11% in the Sloan Kettering series (Huvos et al. 1982). Several authors claim that, when the tumor is treated with surgery alone, the prognosis of TO is even worse than that for conventional osteosarcoma (Dahlin 1978, Mirra 1989, Campanacci 1999). In the study of Matsuno et al. (1976), that has received wide publicity and subsequently aroused pessimism in pathologists and surgeons who diagnose TO, only 1 of the 25 patients treated with surgery alone (amputation in 19 cases and resection in 6) survived more than 5 years. These results were confirmed by other "anecdotal" reports (Campanacci and Pizzoferrato 1971).

There are very few papers about the efficacy of chemotherapy in TO (Rosen et al. 1986, Mervak et al. 1991). In a series of 28 patients with TO of the extremities treated at our institution between 1983 and 1990 using two protocols for neoadjuvant chemotherapy, 23 remained continuously free of disease at a mean follow-up of 5 years (Bacci et al. 1994). In the present study of 24 more recent cases treated at Istituto Ortopedico Rizzoli between 1992 and 1994, we confirmed that this rare variant of osteosarcoma responds even better to chemotherapy than the conventional tyme. The high responsiveness to chemotherapy of TO may reflect the marked vascularity of this tumor, resulting in a better perfusion of the neoplastic tissue by the chemotherapeutic agents.

Besides having a propensity to metastasize early, TO has often been reported to recur locally. In the historical Mayo Clinic series (Matsuno et al. 1976) of 25 patients treated with surgery, alone, despite 19 amputations, 5 developed local recurrences. According to Rosen et al. (1986), when limb-sparing surgery was performed the tendency to recur locally seemed to persist even when chemotherapy was added to the surgical treatment; 2 of the 7 patients treated surgically with a limb salvage had a local recurrence. Our recent study does not confirm these data. Despite the fact that ampu-

tation was avoided in 21/24 patients, no local recurrence occurred in our previous series of 28 patients with TO (22 with limb salvage), no local recurrences were seen (Bacci et al. 1994). There may be an explanation for the discrepancy in local recurrence between our series and Rosen's. It is well known that in patients treated with neoadjuvant chemotherapy, local recurrences are particularly frequent in those who do not have a good histologic response to preoperative chemotherapy (Picci et al. 1994, Bacci et al. 1998b). In Rosen's series, 9 patients had no preoperative chemotherapy and, of the 16 patients who had preoperative treatment, only 11 had a good histologic response. On the contrary, in our present series, all 24 patients received preoperative treatment and all but one had a good histologic response to chemotherapy. This interpretation seems to be confirmed by the fact that even in Rosen's series, none of the 11 patients who had a good histologic response to chemotherapy developed a local recurrence.

As in our previous paper we conclude that the prognosis for TO is no worse than that for conventional OS, as suggested by previous reports concerning patients treated with surgery alone. When treated with neoadjuvant chemotherapy, most patients with TO can be cured and, in most cases, amputation may be avoided.

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