Neoadjuvant Chemotherapy for Extremity Osteosarcoma

Preliminary Results of the Rizzoli's 4th Study

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A neoadjuvant chemotherapy protocol (1/93–1/95) for extremity osteosarcoma preoperatively using high-dose methotrexate (HDMTX) as single agent per cycle and three different combinations of other drugs (CDP/IFO,CDP/ADM,IFO/ADM) is reported. The four drugs were used postoperatively as single agents. Treatment was uniform, but suspended earlier if total necrosis was attained. An improvement was found in the results of the previous study using only IFO postoperatively, with 16/119 patients (97%) avoiding amputation, and 38 (32%) attaining complete necrosis. At a 3-year (2–4 years) mean follow-up, 92 patients (76%) remained continuously disease-free, 2 died of chemotherapy-related toxicity and 25 suffered relapse. Projected 3-year DFS also improved (75% vs. 60%; $p = 0.04$). Despite limb salvage, local recurrences (6.3%) and infections were few, although postoperative chemotherapy was restarted within a week. Therefore, until new effective drugs are found, expertise in using the four known drugs may improve cure rate and help to avoid amputation in almost all patients.

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After introduction of aggressive neoadjuvant chemotherapy given with various drug combinations (high-dose methotrexate (HDMTX), doxorubicin (ADM), cisplatin (CDP), and ifosfamide (IFO)), long-term survival of patients with high-grade osteosarcoma of the extremities has dramatically improved, rising from 15% to 70% (1–9). At the same time, limb salvage surgery has increased and amputations have decreased (1–3, 5).

The value of neoadjuvant chemotherapy in the treatment of this disease seems well established, but two main questions remain unanswered. First, what is the optimal regimen of chemotherapy for these patients, and second, in how many patients is it possible to avoid amputation? Neoadjuvant studies performed in the past ten years (1–13) used different combinations of the four most effective drugs: HDMTX, CDP, ADM and IFO, but to this day none of the chemotherapy protocols has proven its superiority. It is not clear how many patients can avoid amputation, as the percentage of patients treated with limb salvage surgery in these neoadjuvant studies varies between 27% (8) and 100% (10).

The Rizzoli Institute started treatment of non-metastatic osteosarcoma of the extremities with neoadjuvant chemotherapy in 1983, and up until December 1992, 449 patients entered the protocols. On the basis of previous experience, the regimens were modified during these ten years, and after the first protocol (IOR/OS-1) in 1983 another two neoadjuvant protocols (IOR/OS-2, IOR/OS-3) were successively activated in 1986 and 1990.

In the first study (IOR/OS-1) preoperative chemotherapy included a two-drug regimen (HDMTX/CDP) (1), whereas a three-drug regimen (HDMTX/CDP/ADM) was used in the two subsequent studies (IOR/OS-2 and IOR/OS-3) (2, 11). IFO, which in recent years has proved to be very effective in osteosarcoma (12, 13), was used postoperatively only in the last two studies.

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Table 1

Patient characteristics and histologic response to chemotherapy

Characteristics	Variables	No. cases	%	Total necrosis[a]	%	p
Gender	Male	74	61	24/72	33	p ns
	Female	47	39	14/47	30	
Age	<14	46	38	12/46	26	p ns
	>14	75	62	26/73	36	
Site	Femur	64	53	25/64	39	p ns
	Other	57	47	13/55	24	
Size	<150 ml	52	43	20/52	38	p ns
	>150 ml	69	57	18/69	26	
Histology	Osteoblastic	71	59	23/70	33	p 0.01
	Chondroblastic	16	13	0/16	0	
	Fibroblastic	14	11	8/13	61	
	Other	20	17	7/20	35	
Grade	3	4	3	1/4	25	p ns
	4	117	97	37/115	32	
SAP	Normal	70	58	25/68	37	p ns
	Elevated	51	42	13/51	25	
SLDH	Normal	90	74	30/88	34	p ns
	Elevated	31	26	8/31	26	

[a] Two patients died before surgery.

These studies confirmed that a histologic response to chemotherapy strongly correlates with DFS and patients with total tumor necrosis had a significantly better prognosis than those with partial necrosis. Thus, it was thought that to improve the cure rate and increase the number of patients with total necrosis, a possible strategy might be to administer more drugs preoperatively. In 1993 we designed a new chemotherapy protocol (IOR/OS-4) in which IFO was added preoperatively to HDMTX, CDP and ADM. The low rate of LR and major surgical complications in the three previous studies, where limb salvage procedures increased from 70% in the first study to 83% in the third, led us in the fourth study to try to avoid amputation in all patients.

The purpose of this paper is to report preliminary results achieved at the Rizzoli Institute in 121 patients with non-metastatic osteosarcoma of the extremities treated with this new protocol. These results are compared with those of the earlier neoadjuvant study (IOR/OS-3) where IFO was used postoperatively only. The results of the third study, in part previously reported 4 years ago (11), are updated here.

MATERIAL AND METHODS

Patient selection and pathology

As in our previous osteosarcoma trials, patient eligibility fulfilled the following criteria: typical radiographic and histologic features of primary, high grade, central osteosarcoma, tumor located in the extremities, no prior history of cancer, no prior treatment elsewhere, age under 40 years, no associated disease contraindicating chemotherapy, and no evidence of metastases at diagnosis.

Of the 253 newly diagnosed cases of osteosarcoma observed at the Rizzoli Institute between January 1993 and December 1994, 131 were eligible.

After having been informed of the potential advantages and risks, all eligible patients were proposed for the new neoadjuvant chemotherapy protocol (IOR/OS-4). Of the 121 patients who entered the study, ten refused. And two of the eligible patients died of unrelated causes (suicide and car crash), one during pre- and one during postoperative treatment. Another two died of treatment toxicity, one preoperatively and the other postoperatively. The two patients who died during preoperative treatment (one as a result of unrelated causes and one of toxicity) were excluded from the analysis of chemotherapy-induced necrosis and surgery. Patient characteristics are presented in Table 1.

Osteosarcoma diagnosed by clinical and radiologic findings, was always confirmed on histologic slides of tumor tissue obtained from an open or trocar biopsy as well as from the resected specimen.

Preoperative evaluation and preoperative chemotherapy

A complete history of each patient was taken, and all patients underwent a thorough physical examination and several chemical laboratory tests. The primary tumor was evaluated on plain radiograms, Technetium 99-MDP bone scan, angiogram, CT scan and magnetic resonance imag-

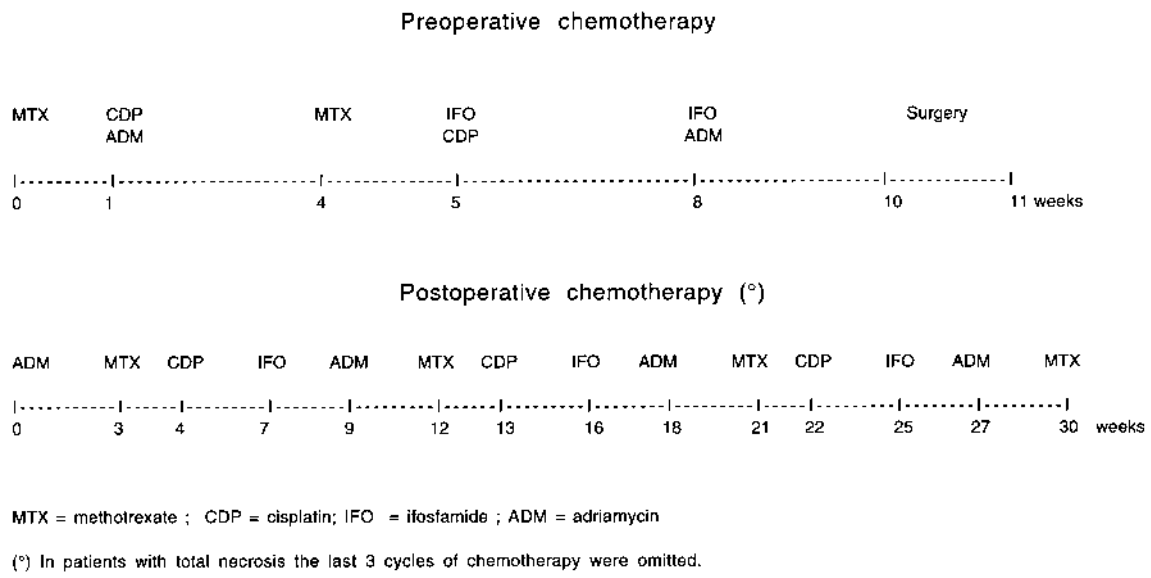

Fig. 1. Pre- and postoperative chemotherapy protocol (OS-4).

ing. These were repeated before surgery. A total body scan was used to detect bone metastases, whereas chest radiograms and a CT scan were used to investigate the lungs.

Preoperative chemotherapy included MTX, ADM, CDP and IFO as reported in Fig. 1. MTX, ADM and IFO were given intravenously, while CDP was delivered either intra-arterially or intravenously.

MTX was administered intravenously in a 6-h infusion (12 g/m^2 escalated by 2 g/m^2 if the 6-h serum level of the drug in the previous course was less than 1.000 μm/l) with Citrovorum Factor rescue (15 mg every 6 h 11 times starting 24 h after the beginning of MTX). Hydration during and after MTX infusion followed the guidelines suggested by Rosen et al. (14).

CDP was delivered intravenously or intra-arterially at the dose of 120 mg/m^2 over a 72-h continuous infusion, while ADM was always given intravenously at the dose of 60 mg/m^2 in a 6-h infusion when the drug was associated with CDP and at the dose of 30 mg/m^2/day for 2 days in a 4-h infusion, when the drug followed IFO. IFO, associated with MESNA uroprotection, was delivered intravenously at 3 g/m^2/day in a 1-h infusion for 2 days.

Hematopoietic, renal, metabolic, and liver functions were controlled before each chemotherapy administration. No dose reduction was contemplated by the protocol. If the absolute granulocyte count was less than 1 000/ml (800 for MTX cycles), and/or the platelet count was less than 100.000/ml (80 000 for MTX cycles), chemotherapy was delayed until recovery.

Blood counts were monitored every 2 days, starting a week from the end of the chemotherapy cycle. Patients were transfused if the platelet count dropped below 10 000/ml or the hemoglobin level of HBg dropped below 6 g/dl.

Surgery and pathological evaluation

Before surgery the lesion was completely restaged to assess tumor extension after preoperative treatment. Except for very large tumors with pathologic fractures and/or neurovascular bundle involvement, surgery was always scheduled as limb salvage. Reconstruction (prosthesis, bone graft, rod or plate and cement, vascularized fibula) was chosen according to tumor location and extension, patient age, lifestyle and preferences.

After surgery, surgeons and pathologists reviewed the gross specimens to determine surgical margins that according to Enneking's classification (15) were radical, wide, marginal, intralesional or contaminated. Tumor response was evaluated histologically, following the criteria previously reported (16). Response to chemotherapy was classified: poor (less than 60% tumor necrosis); fair (60–89% tumor necrosis); good (90–99% tumor necrosis), and total (complete necrosis). These groups roughly correspond to grades I, II, III and IV of the descriptive classification proposed by Rosen et al. (6, 7).

Postoperative chemotherapy and follow-up

Postoperative chemotherapy was started within 5 days after surgery according to the schemes reported in Fig. 1. All drugs were given as single agents per course. MTX and CDP were administered as in the preoperative treatment, while ADM was given at the dose of 45 mg/m^2/day in an 8-h infusion for 2 days and IFO at the dose of 2 g/m^2/day in a 1-h infusion for 5 consecutive days. Postoperative drugs and schedule were the same for all patients, but when necrosis was total the last three cycles were omitted.

Chemotherapy dose intensity was calculated by dividing the amount of drugs given (mg/m^2) by the duration (in weeks) of treatment. As described by Hryniuk & Bush

(17), dose intensity was calculated by combining the value of each drug in a single value. The received dose intensity was expressed as the percentage of the projected dose intensity according to the protocol (i.e. the dose intensity of a patient with no dose reductions or delays in treatment).

During postoperative chemotherapy, in addition to the clinical evaluation, patients were followed up every 2 months using radiograms of the chest and operated limb. Additional investigations were performed only if a clinical and/or radiographic relapse was suspected. After completion of chemotherapy, patients were followed in the outpatient clinic with the above-mentioned radiograms every 2 months for 2 years, every 3 months in the third year, and subsequently every 6 months.

The major endpoint of the study was the event-free survival (EFS). Overall survival was also evaluated, but the relative data should be considered with caution. In cases of recurrent disease, some patients preferred to move to other institutions, thus postrelapse treatment tended to be unhomogeneous.

The actuarial method was used to calculate the cumulative probability of disease-free and overall survival as a function of time, and the curves were compared by log-rank test. EFS was calculated from the first day of preoperative chemotherapy to the first adverse event or to the most recent follow-up examination. Adverse events included the development of recurrent tumor at any site. The results were updated in January 1997.

Comparison with the previous 3rd Rizzoli neoadjuvant study

In the 3rd study (IOR/OS-3), carried out at the Rizzoli Institute between January 1990 and December 1992, two cycles of MTX, CDP and ADM were administered preoperatively. MTX was given intravenously (10 g/m^2 in 6 h) followed a week later by CDP (120 mg/m^2 i.v. or i.a. over a 72-h continuous infusion), and ADM (60 mg/m^2 i.v. in an 8 h infusion, starting 48 h after the beginning of CDP infusion).

Postoperatively 'good responder' patients (90% or more necrosis) received one course of ADM (45 mg/m^2/day for 2 days in an 8-h infusion) followed by three courses of MTX and CDP/ADM according to the schedules and doses used preoperatively, while 'poor responder' patients (less than 90% tumor necrosis) had an additional three cycles of IFO (2 g/m^2/day in a 1-h infusion for 5 days) alternated with the other drugs. In September 1991 the protocol was modified: the MTX dose was increased to 12 g/m^2 and, postoperatively, all patients, regardless of histologic response, received treatment with IFO; 98 patients were treated with the first part of the study regimen and 43 with the modified protocol.

RESULTS

Treatment compliance and chemotherapy dose intensity

Of the 2 118 cycles of chemotherapy performed, 254 were postponed for more than 7 days (range 8–19 days) owing to delayed bone marrow recovery (205), delayed clearance of MTX (11), surgical complications (14), abnormal laboratory findings (4), and patient or organizational problems (20).

A dose escalation of MTX was necessary in 13 patients. CDP was delivered intravenously in 91 patients and intra-arterially in 26, while the remaining four patients had one cycle intravenously and one intra-arterially.

Although the protocol did not account for dose reductions, these were performed in 72 cycles ranging from 15% to 30% (mean 21%) of the fixed dose. Owing to delays and dose reductions, only 27 patients (23%) received the scheduled dose intensity, 61 (51%) received between 90 and 99%, and the remaining 31 patients (26%) received a dose intensity between 63% and 89%.

As expected, chemotherapy dose intensity was higher in patients with total necrosis who had a shorter postoperative treatment compared to those who had a partial necrosis. The median dose intensity in the two groups was respectively 97.1% and 92.8% of the scheduled dose intensity.

Clinical and radiologic response to preoperative chemotherapy

Two patients died during preoperative treatment, one of a chemotherapy-related cause (sepsis caused by myelosuppression) and the other of an unrelated cause. The remaining 119 evaluable patients had a good clinical and radiologic response in 104 cases (87%), whereas 13 (11%) had no significant changes, and two (2%) had a radiographic progression of the tumor.

Surgery

One-hundred and thirteen patients (97.5%) had a limb salvage, and three a rotationplasty. Owing to the large tumor extension with neurovascular bundle involvement, three patients had to have an amputation.

In limb salvage procedures, reconstruction was prosthesis (72), Kuntscher rod or plate plus cement (2), vascularized fibula combined with allograft (6), allograft (21), and autograft (8). No reconstruction was necessary in four patients with tumors located in the fibula.

In the three patients who had amputations, surgical margins were radical in one and wide in two. In patients treated with limb salvage the surgical margins were wide in 100, marginal in ten, and intralesional in three. All three patients treated with rotationplasty had wide margins. None of the patients had contaminated margins.

Histologic response to preoperative chemotherapy

The histologic response to chemotherapy was 'total' necrosis in 38 patients (31.9%), 'good' in 61 (51.2%), 'fair' in 11 (9.2%), and 'poor' in nine (7.5%). Therefore, in 99 patients (83%) tumor necrosis was at least 90%.

As observed in previous studies, histologic response was not related to patient gender or age, site, size and tumor grade, or serum levels of alkaline phosphatase (AP), and LDH at presentation (Table 1). Chondroblastic tumors showed a significantly lower percentage of total necrosis compared with other subtypes (0/16 vs. 38/113; $p = 0.0001$).

Survival

At a median follow-up of 36 months (range 24–48 months), 92 patients (76%) remained continuously event-free, 25 suffered relapse (21%), two died of chemotherapy-related toxicity and two, already cited, died as a result of unrelated causes. The projected 3-year EFS was 75% (Fig. 2) and the projected 3-year overall survival was 91%.

The first signs of relapse were metastases in 18 cases and LR in seven. The latter group of patients also developed metastases.

The DFS rate was not related to patient gender or age, tumor volume or site, and LDH serum values at presentation. DFS was also unrelated to MTX serum levels at the end of infusion. On the other hand, DFS was significantly higher in patients with normal serum values of AP at presentation than in those with high values of this enzyme (59/66–89% vs. 33/51–64%: $p = 0.002$).

In terms of chemotherapy dose intensity, the 86 patients who received at least 90% of the scheduled treatment had a higher DFS than the 31 who received a lower chemotherapy dose intensity (70/86–81% vs. 22/31–71%). This difference, however, is not statistically significant.

According to the histologic response to chemotherapy 84.2% of the 38 patients with total necrosis remained continuously disease-free compared with 74% of the 81 patients with partial necrosis. No differences in DFS were seen when comparing good responder patients (45/61–73.7%) with fair and poor responders (15/20–75%).

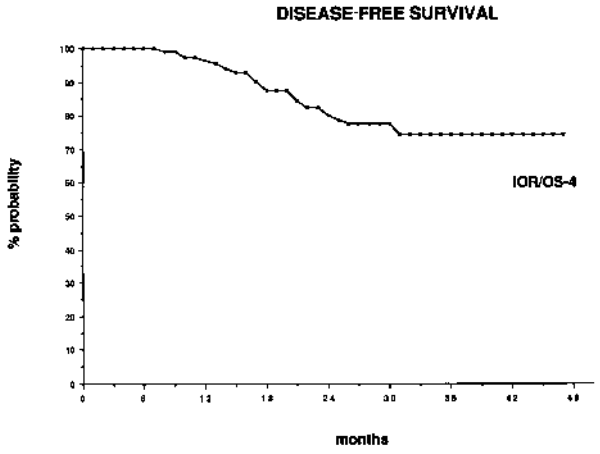

Fig. 2. Disease-free survival for 121 patients treated with the 4th protocol (OS-4).

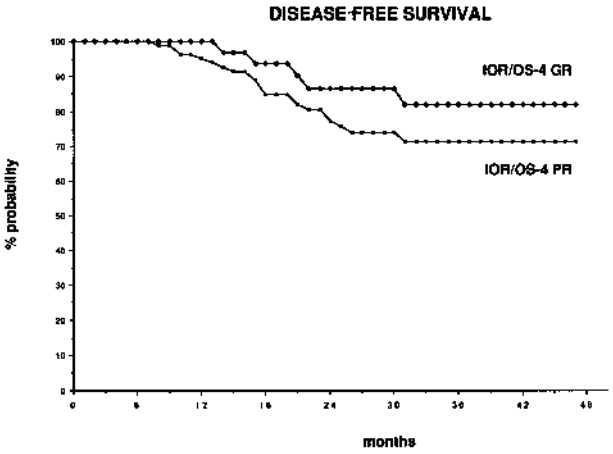

Fig. 3. Disease-free survival for patients with total and partial necrosis treated with the 4th protocol OS-4, excluding the two patients who died preoperatively.

The actuarial 3-year DFS was 82% for patients with total necrosis and 70% for those with partial necrosis (Fig. 3). This difference is not statistically significant.

The average time to the first adverse event was 17.8 months (range 8–31 months), with a difference between the six patients with total necrosis (21.8 months, range 14–31 months) and the 21 patients with partial necrosis (17.8 months, range 8–31 months). The primary site of metastasis was the lung in 22 cases (88%), and the bones in three (12%).

Local recurrence (LR)

Seven LR were registered, primary sites being the femur (5), tibia (1) and humerus (1). In all cases surgery was limb salvage and wide surgical margins in three cases, marginal in three, and intralesional in one case. Histologic response was total in two patients, and partial in five (poor in one, fair in three, and good in one).

Excluding the four patients who died of chemotherapy toxicity or of unrelated causes, the rate of LR was 6.3% for the 111 patients treated with limb salvage, while no LR was seen in the six patients treated with amputation or rotationplasty. This difference is not statistically significant. The rate of LR was significantly higher for the 12 patients with inadequate surgical margins than for the 105 with adequate surgical margins (33.3% vs. 2.8%). This difference is statistically significant ($p = 0.0004$). According to histologic response to chemotherapy, the rate of LR was the same for all patients.

Two patients had LR contemporary to inoperable metastases (lung in one case and bone in the other). These LR cases were treated with palliative radiotherapy. The

Table 2

Comparison between the results of the present (OS-4) and previous study (OS-3)

	Cases present study OS-4		Cases previous study OS-3		p
	n	%	n	%	
No. cases	119		139		
Limb salvage	113	94.9	115	82.7	0.004
Total necrosis	38	31.9	23	16.5	0.005
Deaths from chemotherapy toxicity	2	1.7	2	1.4	ns
Secondary amputations[a]	1	0.8	1	0.7	ns
Local recurrences	7	5.8	7	5.0	ns
Two-year DFS[b]	101/119	85	94/139	68	0.003
			29/43[c]	67	0.02

[a] Patients initially treated by limb salvage and subsequently amputated for infections.
[b] Real data, no projections.
[c] Data relative to the 43 patients who, regardless of the grade of necrosis, received postoperative ifosfamide.

remaining five patients apparently had no metastases when the LR was diagnosed. Four underwent amputation and one had another limb salvage. All five of these patients successively developed lung metastases (after 3, 4, 4, 6 and 10 months respectively), and despite treatment, all died of disseminated tumor 4–9 months later.

Postrelapse outcome

Of the 25 patients who suffered relapse, 11 died of the tumor 3–19 months ($x = 11.8$) after relapse, four are still alive with uncontrolled disease (4–8 months: $x = 6.5$ after relapse) and ten are alive and disease-free 4–18 months ($x = 9.6$) after the last treatment.

Metastatic disease was treated with metastectomy followed by further chemotherapy in 19 cases, chemotherapy alone in four, while the remaining two patients had palliative therapy only; pulmonary metastases were resected twice in five patients and three times in two.

Chemotherapy toxicity

Two patients with no signs of recurrence, died of chemotherapy-related toxicity (sepsis after the first cycle of preoperative CDP/ADM and venocclusive disease after the fifth course of MTX).

A severe clinical ADM cardiotoxicity was observed in three patients. These had had a partial necrosis and therefore had received a cumulative drug dose of 480 mg/m^2. The clinical symptoms of the cardiopathy appeared at the end of chemotherapy (20 days to 3 months after the last cycle). The patients are still alive, free of disease, and with appropriate therapy in acceptable cardiologic compensation 19, 28 and 34 months after the onset of the cardiomyopathy.

No ADM clinical cardiotoxicities were observed in the 38 patients with total necrosis who received a reduced total dose of the drug (390 mg/m^2). Of the 2 124 courses of chemotherapy given a grade 4, hematologic toxicity was observed in 305 courses (14%) and 42 times (2%) patients had to be hospitalized for life-threatening febrile myelodepression. Probably due to the higher number of cycles performed, the rate of grade 4 hematologic toxicity was significantly higher in patients with partial necrosis compared with those with total necrosis (245/1593–15.3% vs. 60/528–11.3%; $p = 0.02$). Hospitalization for life-threatening bone marrow toxicity was also higher in the first group of patients (34/1593–2.1% vs. 8/528–1.5%). This difference, however, is not statistically significant.

Episodes of WHO grade 1 to 2 renal toxicity were recorded after 30 chemotherapy cycles, 15 occurring after a delayed MTX elimination while the remainder occurred in the postoperative phase after CDP and IFO infusion. The serum creatinine values returned to normal before the subsequent cycles of chemotherapy.

Comparison with our previous study IOR/OS-3

The percentage of limb salvages (82.7% vs. 94.9%, $p = 0.004$) and total necrosis (16.5% vs. 31.9%, $p = 0.005$) were both significantly lower for the 139 patients treated in the

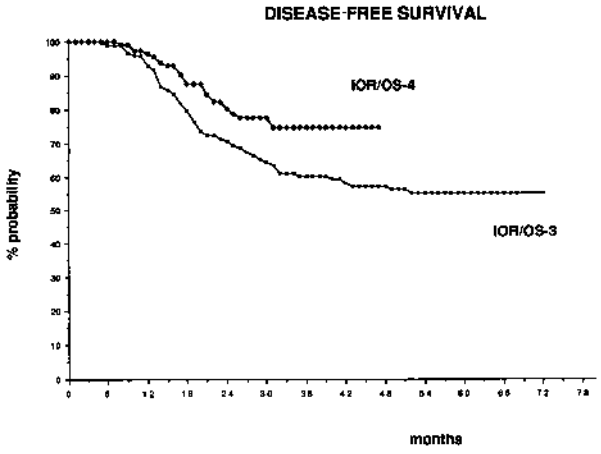

Fig. 4. Disease-free survival for patients treated with the 3rd (OS-3) and 4th (OS-4) protocols.

3rd study (IOR/OS-3) than for the 119 patients in the present study (IOR/OS-4) (Table 2). The projected 3-year DFS (Fig. 4) was also significantly lower in the previous study (60% vs. 75%; $p = 0.04$).

When taking the real follow-up of 2 years into consideration rather than the projections for DFS, the percentage achieved in the present study was significantly higher than that obtained in the previous IOR/OS-3 study (85% vs. 68%: $p = 0.003$). This difference is still significant even taking into consideration only the 43 cases treated with the second part of the IOR/OS-3 protocol, in which, regardless of the grade of necrosis, all patients received IFO postoperatively (101/119–85% vs. 29/43–67%; $p = 0.02$).

DISCUSSION

The prognosis for high-grade osteosarcoma of the extremities has improved dramatically in the past two decades, but for almost a third of the patients neoadjuvant chemotherapy is still unsuccessful and about 75% of the patients who suffer relapse after neoadjuvant treatment will die of the tumor despite further surgical and chemotherapeutic treatment. Investigation of innovative therapies is therefore necessary to improve the cure rate for these patients, but since there are no new active chemotherapeutic agents imminently underway, improvements in treatment can be obtained only by an advantageous use of the four drugs currently considered as the most active for osteosarcoma: i.e. high-dose MTX, ADM, CDP and IFO.

Several papers have stated that histologic response to preoperative chemotherapy at the time of definitive surgery strongly correlates with DFS (1, 3, 5, 6, 8, 9). Thus, the main strategy used in these years to improve prognosis has been to modify the agents given postoperatively in poor-responder patients Unfortunately, the effect of such conventional 'salvage' treatment is questionable, since, with few exceptions (2, 3), the relapse-free survival for poor responders remains in the 40% range (1, 3, 8, 9).

In an attempt to increase the percentage of patients likely to achieve a good histologic response, an obvious alternative strategy to salvage chemotherapy for poor responders could be the use of more aggressive presurgical chemotherapy. Today, preoperative chemotherapy is generally performed with HDMTX, ADM and CDP, used either as single agents or in different combinations of two or three drugs, whereas IFO was sometimes used only as salvage postsurgical chemotherapy for poor-responder patients (2, 3). In this study preoperative chemotherapy was administered using the four active drugs and the preliminary results reported here seem to indicate that this strategy is effective. Using a four-drug preoperative regimen, total necrosis was obtained in 32% of patients and a good response in 51%. These percentages of total and good histologic response are significantly higher than those previously achieved using a three-drug chemotherapy regimen (IOR/OS-3), and are also significantly higher than those reported by other authors who preoperatively used several combinations of MTX, CDP, and ADM only (3–5, 8, 9).

Although this follow-up is still too short to draw definitive conclusions, good response in the primary tumor to primary chemotherapy seems associated with a high rate of DFS. At a median follow-up of three years more than 75% of patients remained free of disease. These results compare favorably with those of other studies that used a variety of different chemotherapy regimens (3–5, 8, 9). Moreover, the 3-year DFS rate in the present study is significantly better than that achieved in the previous IOR/OS-3 study (78% vs. 59%; $p = 0.04$).

A true evaluation of the effectiveness of the two treatments can only be achieved by randomized studies, but we believe that the comparison of two sequential studies referring to a homogeneous group of patients observed in the same institution and treated by the same medical team is as reliable as the comparison of the results of a randomized study involving different institutions and different medical teams.

As in other recent neoadjuvant studies on osteosarcoma, here, too, a differentiated postoperative treatment was used according to the histologic response to chemotherapy. However, instead of performing salvage chemotherapy by changing drugs in poor responders, as is usually done in other studies (1, 3, 6, 10, 13), chemotherapy was reduced in patients with total necrosis, who, according to the authors' previous experience (2), have a lower risk of relapse. This strategy also seems to be effective. Despite the shorter treatment, patients with total necrosis had the same DFS rate as patients with partial necrosis who received longer postoperative chemotherapy. The shorter treatment used in patients with total necrosis was associated with a lower toxicity. The group of patients with total necrosis had no ADM-related cardiotoxicities and the percentage of life-threatening episodes due to myelosuppression was significantly lower. However, it remains to be demonstrated what the DFS rate would have been had these patients been treated in the same way as those with partial necrosis.

Another point to consider is that only 3% of patients had to undergo an amputation. Despite the high number of limb salvages performed, the rate of LR was relatively low (6.3%). When patients with LR are analyzed in detail, it appears that in limb salvage when the surgical margin is less than wide the risk of LR is unacceptably high. While only three of the 99 patients (3%) resected with adequate surgical margins had an LR, the rate of LR was more than 30% for the 12 patients with inadequate surgical margins. Although it is correct to try to avoid amputation, limb salvage always has to be followed by an accurate study of the surgical margins and when surgical margins are inade-

quate, immediate amputation should be considered. Inadequate surgical margins carry a very high risk of LR and, as reported (18, 19) and here confirmed, the prognosis for patients who have had an LR is very poor.

In conclusion, further consistent improvements in the therapy of osteosarcoma of the extremities are likely to occur with the development of new and more active chemotherapeutic agents. However, until then, a better use of the effective drugs already known could improve results to some extent.

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REFERENCES

1. Bacci G, Picci P, Ruggieri P, et al. Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. The Istituto Rizzoli experience in 127 patients treated preoperatively with intravenous methotrexate (high versus moderate doses) and intraarterial cisplatin. Cancer 1990; 65: 2539–53.
2. Bacci G, Picci P, Ferrari S, et al. Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 164 patients preoperatively treated with high doses of methotrexate, followed by cisplatin and doxorubicin. Cancer 1993; 72: 3227–38.
3. Benjamin RS, Chawla SP, Carrasco C, et al. Arterial infusion in the treatment of osteosarcoma. In: Ryan J, Baker L, eds. Recent concepts in sarcoma treatment. Boston: Kluwer Academic Publishers, 1988: 269–74.
4. Bramwell VH, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. J Clin Oncol 1992; 10: 1579–91.
5. Meyers PA, Heller G, Healey J, et al. Chemotherapy for non-metastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol 1992; 10: 5–15.
6. Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982; 49: 1221–30.
7. Rosen G. Preoperative (neoadjuvant) chemotherapy for osteogenic sarcoma: a ten year experience. Orthopaedics 1985; 8: 659–64.
8. Saeter G, Alvegard TA, Elomaa I, et al. Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of preoperative chemotherapy with single-agent high-dose methotrexate: a Scandinavian Sarcoma Group Study. J Clin Oncol 1991; 9: 1766–75.
9. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (Coss-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol 1988; 6: 329–37.
10. Delepine G, Delepine N, Goutallier D. L'amputation conserve-t-elle des indications en 1985? Rev Rhum Mal Osteo-Artic 1986; 53: 539–45.
11. Bacci G, Picci P, Ferrari S, et al. Influence of adriamycin dose in the outcome of patients with osteosarcoma treated with multidrug neoadjuvant chemotherapy: results of two sequential studies. J Chemother 1993; 5: 237–46.
12. Bowman LC, Meyer WH, Douglass EC, Pratt CB. Activity of ifosfamide in metastatic and unresectable osteosarcoma. Proc Am Soc Clin Oncol 1987; 6: 214.
13. Benjamin RS, Legha SS, Patel SR, Nicaise C. Single agent ifosfamide studies in sarcomas of soft tissue and bone: the M.D. Anderson experience. Cancer Chemother Pharmacol 1993; 31 (suppl 2): 174–9.
14. Rosen G, Nirenberg A. Chemotherapy for osteogenic sarcoma: an investigative method, not a recipe. Cancer Treat Rep 1982; 66: 1687–97.
15. Enneking WF, Spanier S, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980; 153: 106–20.
16. Picci P, Bacci G, Campanacci M, et al. Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy. Regional mapping of viable and nonviable tumor. Cancer 1985; 56: 1515–21.
17. Hryniuk W, Bush H. The importance of dose intensity in the chemotherapy of metastatic breast cancer. J Clin Oncol 1984; 2: 1281–8.
18. Delepine N, Delepine G, Alkallaf S, et al. Local relapse following limb sparing salvage surgery for osteosarcoma. Prognostic factors and influence of chemotherapy. Proc Am Soc Clin Oncol 1996; 15: 526.
19. Kempf-Bielack B, Bielack S, Bieling P, et al. Local failure of osteosarcoma: risk factors and prognosis. Results of the cooperative OS study group COSS. Proc Am Soc Clin Oncol 1996; 15: 520.