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Neoadjuvant chemotherapy for osteosarcoma of the extremity: long-term results of the Rizzoli's 4th protocol

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Abstract

From January 1993 to March 1995, 162 patients with osteosarcoma of extremities were treated according to the IOR/OS-4 protocol. 133 patients had localised disease, while 29 had metastases at diagnosis. These last patients were simultaneously operated upon for their primary and metastatic lesions. Chemotherapy consisted preoperatively of two cycles of high dose methotrexate (HDMTX) and one cycle each of cisplatin (CDP)-doxorubicin (ADM), CDP/ifosfamide (IFO) and IFO/ADM. After surgery, patients were treated with the afore mentioned drugs used as single agents. The mean follow-up of all patients was 6.5 years (5.5–8 years). Surgery was a limb salvage in 94% of cases, and the 5-year event-free survival (EFS) and overall survival (OS) rates were 56 and 71% for patients with localised disease, and 17 and 24% for patients with metastases at diagnosis. These results did not differ from those achieved in our previous study (IOR/OS-3) in which IFO was used only postoperatively in poor responders.

Keywords: Osteosarcoma; Neoadjuvant chemotherapy; Lung metastases; Limb salvage; Metastasectomy

1. Introduction

Today, an aggressive chemotherapy regimen before and after surgery is the standard treatment for patients with osteosarcoma of the extremities. The regimens used for this so-called 'neoadjuvant treatment' generally include high-dose methotrexate (MTX), doxorubicin (ADM), cisplatin (CDP) and ifosfamide (IFO) given in various combinations [1–8].

At the Rizzoli Institute, a neoadjuvant treatment of osteosarcoma of the extremities was started in 1983 and, until 1992, three different protocols of chemotherapy, modified on the basis of the previous experiences, were investigated. In the first protocol, IOR/OS-1, 1983–1986 [9], the preoperative chemotherapy was a two-drug regimen (MTX/CDP), whereas a three-drug regimen (MTX/CDP/ADM) was used in the two subsequent protocols IOR/OS-2, 1986–1989 [10] and IOR/OS-3, 1990–1992 [11]. Ifosfamide, which was proven to be very effective in this tumour in phase II investigations [12,13], was used in the last two protocols, but only postoperatively in patients who responded poorly to the preoperative treatment.

In neoadjuvant treatment of osteosarcoma that was non-metastatic at presentation, several studies demonstrated that the response of the primary tumour to preoperative chemotherapy is an important risk factor for metastases and local recurrence [1–5,14]; so, when designing the next protocol (IOR/OS-4), we thought the addition of IFO in the preoperative phase might result in a higher percentage of good histological responses to primary chemotherapy, thus achieving an increased cure rate. Moreover, we tried to avoid amputation in all patients considering the low rate of local recurrences and major surgical complications observed in the three previous studies (limb salvage procedures increased from 70% in the first study to 83% in the third).

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The aim of this paper was to report the long-term results achieved in 162 patients, 133 with localised tumour and 29 with metastases at the diagnosis, treated between January 1993 and March 1995 according to this new protocol. The preliminary results of approximately 121 of these patients have been previously reported [15], but the results presented here are from the evaluation of a greater number of patients with a longer follow-up.

2. Patients and methods

2.1. Patient selection

Osteosarcoma patients with the following criteria were entered into the study: (a) typical histological and radiological features of primary central high-grade osteosarcoma; (b) age ≤ 40 years; (c) primary tumour located in the extremities; and (d) no previous treatments.

174 patients were eligible among the 276 newly diagnosed cases of osteosarcoma seen at our institution between January 1993 and March 1995. Reasons for exclusions were: osteosarcoma varieties ($n=48$), age over 40 years ($n=18$), site other than extremities ($n=28$), and previous treatments ($n=8$). Of the 174 eligible patients, 12 refused to enter the trial and moved to other institutions for treatment. Therefore the study involved 162 patients.

2.2. Pre-operative evaluation and preoperative chemotherapy

The diagnosis of osteosarcoma was established by clinical and radiological findings, and confirmed by histological examination of specimens taken from an open biopsy, as well as from the resected specimen.

All patients had a complete history taken and a thorough physical examination. Several laboratory tests, were performed before, during and at the end of treatment. The primary tumour was evaluated by plain roentgenograms, technetium-99 methylene diphosphonate bone scan, computed tomography (CT) scan, and magnetic resonance imaging (MRI). Metastatic disease was looked for by total bone scan and CT chest scans. All these examinations were repeated after primary chemotherapy, before surgery.

As reported in Fig. 1, preoperatively, patients received two cycles of high-dose (HD) MTX, and one cycle of CDP/ADM, IFO/CDP and IFO/ADM. HDMTX, ADM and IFO were given intravenously (i.v.), while CDP was delivered either i.v. or intra-arterially. MTX was administered in a 6-h infusion at the dose of 12 g/m^2, and increased by 2 g/m^2 if the 6-h serum level of the drug in the previous course was less than 1.000 μmol/l. Citrovorum factor rescue (15 mg every 6 h, 11 times) was started 24 h after the beginning of MTX. Hydration during and after infusion of the MTX followed the guidelines suggested by Rosen and colleagues [16]. CDP (120 mg/m^2) was delivered in a 72-h continuous infusion, and ADM was given at the dose of 60 mg/m^2 in a 6-h infusion (when associated with CDP), and at the dose of 30 mg/m^2/day for 2 days in a 4-h infusion (after IFO). IFO, associated with 2-mercaptoethane sulphonate sodium (MESNA) uroprotection, was delivered at the dose of 3 g/m^2/day in 1-h infusion for 2 days.

Haematopoietic, renal, metabolic and liver functions were checked before each course of chemotherapy. No dose reduction was scheduled by the protocol, but if the absolute granulocyte count was less than 1×10^9/l (0.8×10^9/l for MTX cycles), and/or the platelet count was less than 100×10^9/l (80×10^9/l for MTX cycles), chemotherapy was delayed until haematological recovery.

Blood counts were monitored every 2 days, starting a week after the beginning of the cycle of the chemotherapy. Patients were generally transfused if the platelet count dropped below 10×10^9/l or the level of haemoglobin dropped below 60–70 g/l.

2.3. Surgery and pathological evaluation

After primary chemotherapy, all patients were radiologically re-evaluated. The surgery for all primary tumours was always scheduled as a limb salvage, apart from very large tumours with pathological fractures or neurovascular bundle involvement who were treated with amputation or rotation plasty. Reconstructions of the resected bones (prosthesis, bone graft and vascularised fibula), were chosen according to tumour location and extension, patient's age, lifestyle and preferences [14,15]. 146 patients were operated upon at Rizzoli institute and 14 in Florence.

In patients with metastatic disease at presentation, simultaneous surgery of primary and metastatic lesions was performed, if metastases were deemed resectable after the preoperative treatment. The rationale for the simultaneous resection of primary and metastatic disease performed at our institution since 1983, was: to avoid leaving in place metastatic nodules that could harbour clones of cells that have become chemoresistant after more than a 2-months course of preoperative chemotherapy, to avoid further stress on patients that would result from a second surgical procedure, and to reduce the postoperative time during which the patient cannot receive chemotherapy, thereby increasing the dose-intensity of treatment. Patients who had unresectable metastatic disease despite chemotherapy were generally only operated upon for the primary tumour, and then moved to other institutions for experimental treatments targeted at the metastatic disease.

Surgery for pulmonary lesions consisted of wedge resection or lobectomy, if necessary, performed through

an anterolateral thoracotomy. The lungs were sequentially and thoroughly palpated by the surgeon. Thin gloves were used to allow the detection of pinpoint lesions, and any suspicious nodule was resected with minimal normal surrounding pulmonary tissue.

After surgery, surgeons and pathologists reviewed the gross specimens to determine the surgical margins that were classified according to Enneking's criteria [17] as intralesional (whenever the tumour was peeled off its capsule or pseudocapsule or broken), marginal (when the tumour as removed in block but, even in a small area of its surface, is only covered by the capsule and pseudocapsule), wide (when the tumour was removed en-block entirely enwrapped by a continuous layer of normal tissue), radical (when the tumour was removed en-block with the entire anatomical compartment of origin). If during surgery, the tumour was accidentally broken, and the surgeon had to widen the resection, the procedure was defined as wide (or marginal or radical), but contaminated. The response to chemotherapy of the primary tumour and/or bone metastases was performed according to a method previously reported [18] and classified as 'poor' (less than 90% tumour necrosis), 'good' (90–99% tumour necrosis), and 'total' (no viable cells left). The histological evaluation of the response of the lung metastases involved the assessment of tumour necrosis in 5–15 histosections of each pulmonary nodule. An attempt was also made to assess the extent of tumour cell destruction in the metastatic lesions and the response was classified as 'good' (calcified osteoid matrix with complete lack of viable tumour cells or only small foci of viable cells) or 'poor' (no necrosis or large areas of viable tumour cells).

2.4. Postoperative chemotherapy and follow-up

Postoperative chemotherapy was started within 5 days after surgery for patients operated upon for the primary tumour alone and within 2 weeks after surgery for patients operated upon for metastatic lesions as well. As shown in Fig. 1, all the drugs used postoperatively 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 a 8-h infusion for 2 days, and IFO at the dose of 2 g/m^2/day in 1-h infusion for 5 consecutive days. In the postoperative treatment, drugs and schedules were the same for all patients, but in patients with localised disease: when the histological response was a total necrosis the last three cycles were omitted.

During postoperative chemotherapy, in addition to clinical evaluation, patients were followed-up every 2 months with radiographs of the chest and of the operated limbs. Additional evaluations were made when indicated by clinical situations. After completion of chemotherapy, all patients were followed-up in the outpatient

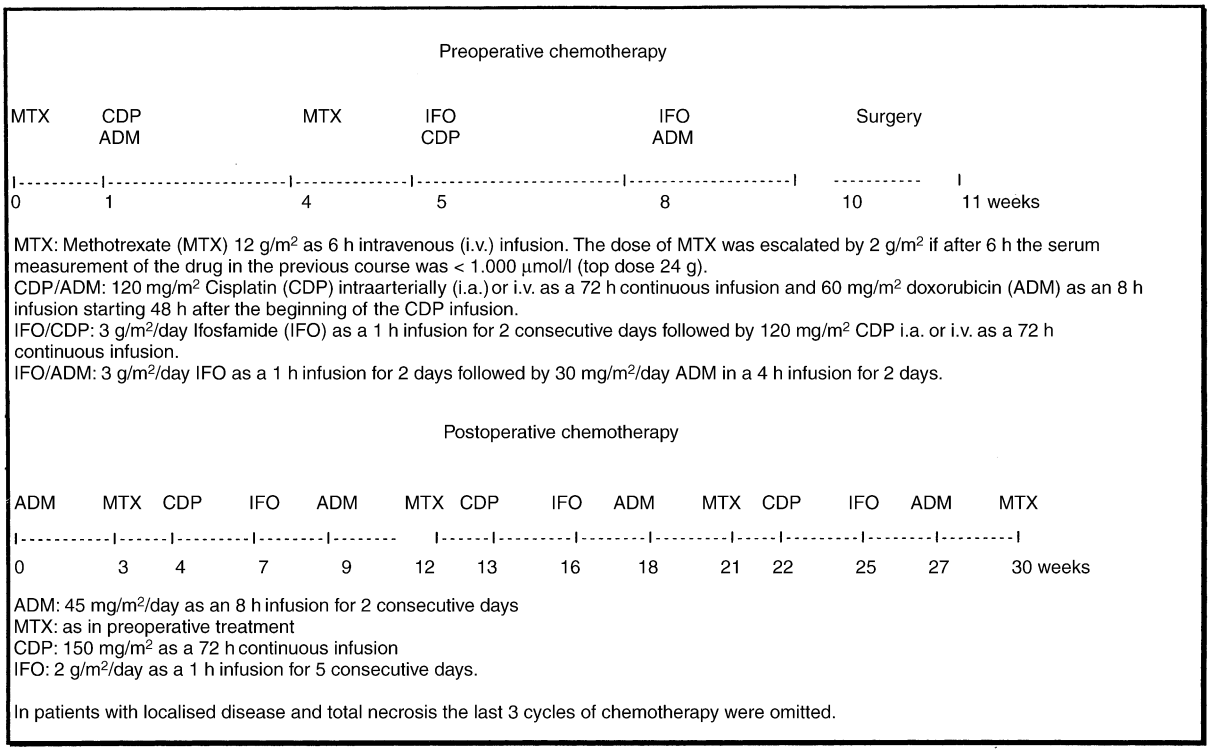

Fig. 1.

clinic with radiographs every 2 months for 2 years, every 3 months in the third year, and subsequently every 6 months.

2.5. Outcome analysis

The endpoint of the study was the event-free survival (EFS). Overall survival (OS) was also evaluated, but the relative data should be considered with caution because, in the case of recurrent disease, many patients moved to other institutions, thus postrelapse treatments were not homogeneous.

EFS was calculated from the first day of preoperative chemotherapy to the first adverse event (relapse or death from toxicity) or the most recent follow-up examination. Overall survival was calculated from the first day of chemotherapy until death or last follow-up. The survival curves were calculated according to the Kaplan–Meier method and compared by means of the log-rank test. The frequency of distribution of different parameters was compared among groups of patients by means of the Chi-square test. Significance was set at $P < 0.02$.

2.6. Comparison with the previous 'Rizzoli' neoadjuvant study (IOR/OS-3)

The results of this study have been compared with the results achieved in 95 patients with localised disease at presentation, treated according to the Rizzoli's IOR/OS-3 protocol carried out between January 1990 and October 1992 [11]. In the IOR/OS-3 protocol, patients received preoperatively only HDMTX (i.v.), CDP (i.v. or i.a.) and ADM (i.v.). Postoperatively, patients with 90% or more tumour necrosis received the same three drugs used before surgery, whereas patients with less than 90% tumour necrosis received also IFO.

3. Results

3.1. Patients with localised disease

3.1.1. Surgery, response to chemotherapy and event-free survival

2 patients died during the preoperative treatment, 1 of toxicity and 1 committed suicide.

For the 131 operated patients, surgery was a limb salvage in 123 (94%), an amputation in 5 and a rotation plasty in 3. The surgical margins were radical in one case, wide in 117, marginal in 10 and intralesional in 3. None of the patients had contaminated margins. The histological response to preoperative chemotherapy was poor in 30 patients (23%), good in 60 (46%) and complete (or total) in 41 (31%).

With a follow-up ranging between 5.5 and 8 years (mean: 6.5 years), 74 patients (56%) remained continuously free of disease, 54 (41%) relapsed, 3 patients died of chemotherapy-related toxicity (1 during the preoperative treatment and 2 after surgery), and 2 more patients died of unrelated causes (suicide and car crash). The 7-year event-free survival and overall survival were, respectively, 56% (95% confidence interval (CI) 48–65%), and 69% (95% CI: 59–78%).

The 54 patients who relapsed had metastases (41) and local recurrences (13). All but 2 patients who relapsed with local recurrences also had metastases. The average time to relapse was 26.3 months (range: 9–58 months) and the first site of metastases was the lung in 41 patients, bone in 9, lymph-node in 1, and heart in the remaining patient.

The 7-year EFS (Table 1) was not related to the patient's gender or age, tumour volume or site, serum alkaline phosphatase (SAP) at presentation. Patients with tumours smaller than 150 ml had a better prognosis than patients with larger tumours (7-year EFS: 66% versus 45%; $P < 0.02$). According to the histological response to preoperative chemotherapy, the 7-year EFS was 47% for poor responders, 50% for good responders and 73% for patients with total necrosis. The difference between patients with total necrosis and patients with no total necrosis is statistically significant (73% versus 49%; $P < 0.02$).

3.1.2. Post-relapse outcome

Of the 52 patients who relapsed with metasteses, 32 died of their tumour 12–87 months (mean = 36.4 months) from the beginning of treatment, 1 is alive with uncontrolled disease, and 19 are alive and free of disease 1.5–4 years (mean: 2.8 years) since the last treatment.

Metastatic disease was treated with metastasectomy in 32 patients (19 patients with further chemotherapy), chemotherapy only in 7, and symptomatic treatment in 6. The treatment performed after the appearance of metastases in 7 patients is not known.

3.1.3. Local recurrence

The 13 patients who developed local recurrence had primary tumours in the femur ($n = 8$), in the tibia ($n = 4$), and in the humerus (1). All patients had been treated with limb salvages with wide surgical margins in 9 cases, marginal in 3, and intralesional in 1 case. The histological response was total in 2 patients, good in 5 and poor in 6 patients. Excluding the 3 patients who died of chemotherapy-toxicity or of unrelated causes, the rate of local recurrence for patients treated with limb salvage was 11% (13/120). No local recurrences were seen in the 8 patients treated with amputation or rotation plasty. This difference is not statistically significant. According to the surgical margins, the rate of local recurrence was significantly higher (38%; 4/13) in patients with marginal or intralesional margins than for patients with

Table 1
7-year EFS according to several variables in patients with localised disease at presentation

Variables	Patients *n*	7-year EFS (%)	*P* value	7-year OS (%)	*P* value
Gender					
Male	79	53		70	
Female	54	59	ns	71	ns
Age (years)					
<15	61	54		72	
>15	72	57	ns	70	ns
Site					
Femur	71	58		72	
Tibia	37	54		76	
Humerus	17	59	ns	70	ns
Other sites	8	37		50	
Size					
<150 ml	68	66	<0.02	79	
>150 ml	65	45		63	0.03
SAP					
Normal	86	58		77	
Elevated	47	51	ns	62	ns
Surgery					
Limb salvage	123	56	ns	71	ns
Amputation/rotation plasty	8	62		74	
Histological response					
No total necrosis	90	49		66	
Total necrosis	41	73	<0.02	85	0.02

ns, non-significant; EFS, event-free survival; OS, overall survival; SAP, serum alkaline phosphatase.

radical or wide margins (7%; 9/118). This difference was statistically significant ($P<0.02$). According to the response to preoperative treatment, the rate of poor responders was 50% in the 13 patients with local recurrence and 26% in the other 118 patients. This difference was not statistically significant.

5 patients had local recurrence and contemporary unresectable metastases (lung in 2 cases and bone in the others); in 1 patient, local recurrence was diagnosed 4 months after lung metastases. These local recurrences were treated with palliative radiotherapy in 3 patients and with amputation in 2 cases. The other 8 patients, who apparently recurred only locally were treated with an amputation in 5 cases and with limb-salvages in 3 cases. 2 of the patients treated with amputation are alive and free of disease 1–3 years from the last operation, while the remaining 6 patients developed lung metastases and died of disseminated disease. The 5-year overall survival rate for patients with local recurrence was significantly lower than the rate of patients who relapsed only with metastases (15% versus 51%; $P<0.02$).

3.1.4. Comparison with our previous study IOR/OS-3

As reported in Table 2, percentages of limb salvages (76% versus 94%; $P<0.0009$) and of total necrosis (16% versus 31%; $P<0.02$) were both significantly lower for the 95 patients treated according to the IOR/OS-3 protocol than for the 131 patients with localised disease of the present study (IOR/OS-4), but also the rate of local recurrence was significantly lower in the previous study (2.1% versus 9.9%; $P<0.02$). None the less, with a longer follow-up there were no differences between the two studies (Fig. 2) in terms of 7-year EFS (54% (95% CI: 44–64%) versus 56% (95% CI: 48–65%)), and 7-year OS (69% (95% CI: 51–71%) versus 71% (95% CI: 49–78%)). This is in contrast with the results reported 3 years ago [15]. In the preliminary report of the IOR/OS-4 study [15], the 2-year EFS rate of the 119 patients considered was significantly higher than the one of patients treated with the previous IOR/OS-3 protocol (85% versus 68%; $P<0.02$).

3.2. Patients with metastatic disease at presentation

Of the 29 patients with metastatic disease at presentation, 24 had lung metastases and 5 bone metastases (i.e. multicentric osteosarcoma). Patients with bone metastases had respectively, 1, 1, 3, 4 and 7 secondary lesions, while on CT scan, each patient with lung metastases showed a mean of 4.5 nodules (range: 1–20). 9 patients had only one or two lung metastases, while 15 had more than two lung metastases.

Among these patients, 27 had the primary tumour resected and a limb salvage performed, whereas the remaining 2 patients with bone metastases had only palliative radiotherapy on the primary and secondary lesions. In the 27 patients that were operated upon, the histological response to chemotherapy of the primary tumour was poor in 9 (33%), good in 11 (41%) and

Table 2
Patients with localised disease. Comparison between the results of the present (IOR/OS-4) and of the previous (IOR/OS-3) neoadjuvant study

	Previous study (IOR/OS-3)	Present study (IOR/OS04)	*P* value
Number of evaluable patients	95	133	
Percentage of limb salvage	76%	94%[a]	<0.0009
Percentage of total necroses	16%	31%[a]	<0.02
Deaths of toxicity	1%	2.2%	ns
Local recurrences	2.1%	9.9%	<0.02
7-year EFS	54%	56%	ns
7-year OS	69%	71%	ns

ns, non-significant; EFS, event-free survival; OS overall survival.
[a] The 2 patients who died before surgery have not been considered.

total in 7 (26%). This kind of response is very similar to that of the patients with localised disease.

So, in the 2 patients with bone metastases at presentation, the secondary lesions were judged unresectable after primary chemotherapy and they had only palliative treatments. They died 8 and 9 months later, respectively. The remaining 3 patients were operated on at the same time on the primary tumour with limb-salvage (the primary lesions were all located in the femur), and on the metastatic foci (located in the humerus (2 patients), and in the other femur and both tibias (1 patient). All these 3 patients relapsed with new lung and bone metastases after 14, 17, and 28 months and all died 8–28 months later (mean = 17.8 months).

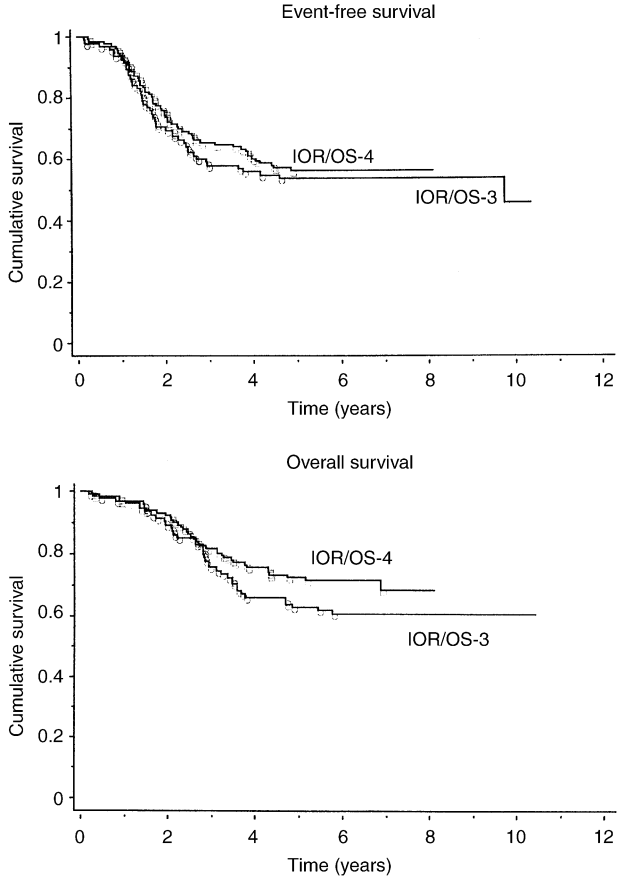

Fig. 2. Comparison of 7-year event-free and overall survival of the two studies IOR/OS-3 and IOR/OS-4.

Considering the 24 patients with lung metastases, CT scan after primary chemotherapy showed disappearance of secondary lesions (4 patients), reduction in size and number (5 patients), no substantial changes (12 patients). In the remaining 3 patients, the lung lesions increased in number and size. The 4 patients whose lung metastases disappeared were surgically treated only for the primary tumours. 1 of them died of toxicity after the first post-operative cycle of cisplatin, another is alive and free of disease 7 years from the beginning of treatment, and 2 relapsed with new metastases after 14 and 16 months, and both died after 28 and 30 months, respectively.

4 patients still had unresectable metastases after primary chemotherapy: after surgery on the primary tumour, they moved to other institutions for experimental treatments for metastatic disease and all died 8–39 months after the beginning of treatment (mean = 20.2 months). 16 patients had a simultaneous resection of primary and metastatic tumour: thoracotomy was monolateral in 12 patients and bilateral in 4 . The metastasectomy consisted of wedge resection in 14 patients and lobectomy in 2. The resection of lung metastases was complete (i.e. neither gross residual disease nor microscopic evidence of tumour at resection margins) in 15 patients, but in 1 patient metastasectomy was not completely performed due to unexpected, widespread, unresectable disease. Considering the 15 successful simultaneous operations: 10 patients relapsed after 11–34 months (mean = 19.2 months) and 9 died from their tumours 18–54 months later (mean = 32.9 months), only 1 is alive with uncontrolled disease after 7 years from the beginning of treatment. The other 5 patients are alive and free of disease 6–7 years after the start of treatment.

In the 15 patients who had a complete resection of lung lesions, the nodules detected at presentation were 61 and dropped to 44 after primary chemotherapy. At the thoracotomy, the surgeon found and resected 82 nodules (38 more than the ones detected by CT scan before surgery), but the histological examination showed that 20 of the 82 resected nodules were not

metastases, but benign lesions. The histological response of the 62 metastases was poor in 20 nodules (32%), 'good' in 25 (40%) and total in 17 (27%). Therefore the histological responses in the primary and metastatic lesions was essentially the same.

In the 18 patients who had simultaneous complete resections of primary tumours and metastases, there was a good correlation between the response of the primary lesion and the response of metastatic tumour. Indeed, 10 of the 14 patients with total or good histological response of the primary tumour had also a complete or good response of all the metastatic lesions, whereas a poor response of all the resected metastatic foci was only registered in 2 patients. In the remaining 2 good responders, both with multiple lung metastases, the response of metastatic lesions was 'mixed' (i.e. the same patient had good response in some nodules and poor in other). However, in the 4 patients with poor histological response of the primary tumour, the response of the metastatic lesions was poor in 2, good in one and mixed in the remaining patient.

In conclusion, among the 29 patients with metastatic lesions at presentation, 7 never achieved complete remission and 22 were apparently free of all their neoplastic lesions. The number of metastatic foci was significantly higher in the 7 patients who were never disease-free than in the 22 who apparently reached a disease-free status (mean = 9.8 versus 2.5; $P = 0.0001$).

The 29 metastatic patients' 5-year EFS and OS rates were 17 and 24%, respectively (23 and 27% for the 22 patients who were apparently free-of-disease). No patients with bone metastases survived, while 6 patients with lung metastases are presently alive, 1 with uncontrolled disease and 5 apparently free-of-disease. According to the number of lung metastases at presentation, the rate of 5-year EFS was significantly higher for patients with one or two lesions than for patients with more than two lesions (4/9, 44% versus 1/15, 7%; $P < 0.02$).

The rate of 5-year EFS and OS for the 29 patients with metastatic lesions at presentation is significantly lower than the one observed in the 131 patients with localised disease (17% versus 56%; $P < 0.0005$ and 24% versus 71%; $P < 0.0001$).

3.3. Chemotherapy toxicity

3 patients with no signs of recurrence, died of treatment-related complications (2 sepsis during neutropenia and 1 venocclusive disease) after the last cycle of MTX 3, 4, 5 and 8 months, respectively, from the beginning of chemotherapy.

Grade 4 haematological toxicity was observed in 15% of all the courses of chemotherapy, and in 2% of cases patients had to be hospitalised for life-threatening febrile myelodepression. Probably due to the number of cycles, in patients with localised disease the rate of Grade 4 haematological toxicity was significantly lower in patients with total necrosis than in other patients (16.1% versus 11.2%; $P < 0.02$).

A severe clinical doxorubicin-cardiotoxicity was observed in 3 patients with localised disease and no total necrosis who received a cumulative dose of ADM of 480 mg/m^2. The clinical symptoms of cardiopathy appeared at the end of chemotherapy (1–3 months after the last cycle). These 3 patients are presently alive, free of disease and in fair cardiological compensation with appropriate therapy 49, 58 and 64 months after the onset of cardiomyopathy. No doxorubicin clinical cardiotoxicities were registered in the 34 patients with total necrosis who received a cumulative dose of ADM of 390 mg/m^2.

Episodes of World Health Organization (WHO) grade 1 and 2 renal toxicity were recorded after 34 chemotherapy cycles, 15 after a delayed MTX elimination, and one in the postoperative phase after CDP and IFO infusion.

No major surgical complications were seen in patients treated with amputation and rotation plasty. In patients treated with limb salvage, there were two major orthopaedic complications (one prosthetic failure and one infection) which required a second surgical procedure (amputation in one case and new limb salvage in the other). Surgical morbidity related to thoracotomy was minimal and was comprised of only transient pneumothorax and/or pleural effusion.

4. Discussion

Although the survival of osteosarcoma patients has been dramatically improved by the addition of chemotherapy to surgery, this combined treatment is still unsuccessful in 30–40% of patients with localised tumours [1–8] and in 80–85% of patients with metastatic disease at presentation [19–21]. Therefore, investigation of innovative therapies is necessary to improve the cure rate, but since there are no new chemotherapeutic agents imminently underway, improvement in treatment may be obtained only by a better use of the four drugs that are the most active against osteosarcoma: HD MTX, ADM, CDP and IFO.

In the neoadjuvant treatment of osteosarcoma, several studies demonstrated that the degree of necrosis in the resected tumour specimen is predictive of subsequent disease-free survival (DFS). Patients with a greater degree of necrosis in the primary tumour had a greater probability of DFS. Thus, the main strategy used in the past to improve prognosis for patients with osteosarcoma was the postoperative employment of a salvage chemotherapy in poor responders based on modifications of the agents given preoperatively. However,

these attempts to alter the DFS of poor responders had limited success in the majority of the studies reported [2–5]. An alternative strategy to salvage chemotherapy might be the use of more aggressive presurgical treatment to increase the percentage of good responders. The cooperative osteosarcoma study (COSS) group was the first to follow this idea. In their third neoadjuvant study, 'COSS-86', IFO was introduced in the preoperative phase of chemotherapy for all but a small selected group of patients believed to be at low risk of relapse [6]. In the 128 patients of the study, they achieved the highest DFS and OS (66 and 72% at 10 years), if considering the data from three studies COSS-80, COSS-82 and COSS-86. Meyers and colleagues [22] performed a randomised study involving 73 patients, comparing a pre-operative chemotherapy with HDMTX and bleomycin + cyclophosphamide + actinomycin (BCD) to a preoperative chemotherapy with HDMTX, BCD, CDP and ADM; they had a higher degree of good histological responses in the second arm of the study, but unfortunately this higher proportion of good responders was not followed by an improvement in EFS.

In our IOR/OS-4 protocol, as in COSS-86 study, we used HDMTX, CDP, ADM and IFO. The study was designed to test whether a more intensive initial therapy of osteosarcoma, might increase the proportion of good responders and whether this increment would result in a better overall EFS. With this preoperative regimen, we significantly increased the rate of total necrosis (31% versus 16%; $P<0.02$) in comparison to the previous protocol IOR/OS-3 [11] in which 95 patients were preoperatively treated with only HDMTX, CDP and ADM and IFO was used only postoperatively for poor responders. However, in contrast with the preliminary results [15], at a longer follow-up, despite the greater number of patients with total necrosis (extensive necrosis) of the primary tumour, the rate of EFS and OS was not significantly different from the rate achieved in the previous study IOR/OS-3 (56% versus 54% ; and 71% versus 69%). Since in our last study, we significantly increased the rate of limb salvage performed (94% versus 76%; $P<0.0009$), but we also had a significant increment in local recurrence (9.9% versus 2.1%; $P<0.02$), it is not clear whether the two protocols had a similar efficacy or if the IOR/OS-4 protocol was better, as results were hidden by the higher rate of local recurrences caused by the higher number of limb salvages performed. It must be remembered that in the present study, as well as in previous ones, local recurrence was generally associated with systemic relapse, and the post-relapse survival of patients who had a local recurrence was significantly worse than the one of patients who relapse with metastases, but without local recurrences. For this reason, we have started a new study for patients with localised disease at presentation, aiming to compare the two previous protocols in a randomised way. If the two arms give similar results, we will be able to avoid the use of IFO in approximately 3/4 of patients, and use this drug only for relapsing patients.

In the present study, patients with non-metastatic osteosarcoma of the extremity treated with limb salvage and neoadjuvant chemotherapy had a rate of local recurrence which significantly correlated with the surgical margins. The histological response to chemotherapy was significantly related with the EFS rate, but not with local recurrence, probably due to the small number of patients. In a previous study evaluating a larger series of extremity-osteosarcoma patients ($n=540$), treated at our institution between 1983 and 1994 with five different protocols of neoadjuvant chemotherapy, the rate of local recurrence correlated with surgical margins, and histological response to preoperative chemotherapy [14]. Considering the very poor outcome of patients who locally relapse ($n=13$), we strongly suggest a secondary amputation after a limb salvage with inadequate surgical margins, determined by pathological examination of the resected specimens.

For this reason, we believe that in order to minimise the risk of local recurrence, and its bad prognosis, patients with osteosarcoma of the extremity should always be treated by experienced surgeons in a few selected centres, where also the pathological examination of surgical margins and the histological response to chemotherapy can be accurately performed and evaluated.

If the role of adjuvant and neoadjuvant chemotherapy in patients with non-metasatic osteosarcoma of the extremities has been extensively studied, in patients with osteosarcoma of the extremity with metastatic disease at presentation, the role of multiagent chemotherapy coupled with 'aggressive' surgery has been less investigated, and the results of the few studies on this topic are contrasting. In fact, the 3-year survival rate in patients with synchronous metastases treated with chemotherapy and surgery was 65 and 47% in two series of 9 and 30 cases, respectively [23,24], and only 18 and 15% in the other two series with 62 and 73 cases [20–25]. One of these studies only referred to patients with lung metastases at presentation [19], whereas the other three studies [20,23,24] also included patients with synchronous bone metastases. Chemotherapy was always performed according to different protocols within the same study, i.e. in the same series it was adjuvant for some patients and neoadjuvant for others, and surgery of primary and metastatic tumours, when performed, was always carried out at different times.

In our present study, patients with metastatic disease at presentation received the same chemotherapy as patients with localised disease, followed by simultaneous resection of primary and secondary lesions (when feasible). In 6 of the 29 patients with metastatic disease, it was not possible to operate on the metastatic lesions, and all them died within a few months. 22 of the

remaining 23 patients, achieved a disease-free status thanks to simultaneous complete resection of primary and metastatic lesions or disappearance of lung metastases after the preoperative treatment. None the less, 17 patients relapsed with new metastases. The 5-year EFS rate was 17% for all the 29 patients and 23% for the 22 patients who reached a disease-free status. Both rates are significantly lower than these achieved in patients with localised disease ($P < 0.0001$). No patients ($n = 5$) with multifocal osteosarcoma survived versus 7 of the 24 patients with lung metastases only.

These results are similar to the results reported by Meyers [20] and by Paquement [25] and in contrast with the results reported by Yonemoto [23] and by Harris and colleagues [24]. This discrepancy could be explained by the fact that patients with detectable metastases at diagnosis were a non-homogenous group. In fact, in our present series, none of the 5 patients with bone metastases survived, while for the 24 patients with lung metastases the rate of 5-year DFS was 44% for the 9 patients with only one or two pulmonary lesions, and only 7% for the 15 patients with more than 2 lesions ($P > 0.02$). In other words, while the rate of EFS for patients with one or two lesions was similar to that observed in contemporary patients without metastases at presentation (44 versus 56%), the prognosis of patients with multiple metastases was much worse.

These results, as well as the results of another study by us [21], indicate that, in spite of an aggressive treatment, the prognosis for patients with osteosarcoma of the extremity with bone and/or multiple lung metastases at presentation remains poor, and significantly worse than the prognosis of patients with localised disease or only one or two lung metastases. We believe that for the first group of patients the idea of abandoning standard regimens of chemotherapy in favour of experimental treatments should be considered.

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