Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide

G. Bacci¹*, A. Briccoli², M. Rocca², S. Ferrari¹, D. Donati³, A. Longhi¹, F. Bertoni⁴, P. Bacchini⁴, S. Giacomini³, C. Forni¹, M. Manfrini³ & S. Galletti⁵

¹Chemotherapy, ²General Surgery, ³Orthopaedic Surgery, ⁴Pathology and ⁵Ultrasonography, Department of Musculoskeletal Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy

Received 19 November 2002; revised 4 February 2003; accepted 14 March 2003

Background: Effective adjuvant or neoadjuvant regimens of chemotherapy have dramatically improved the prognosis of patients with high-grade osteosarcoma of the extremity, localized at diagnosis. Currently, little is known about patients with metastatic disease at presentation.

Patients and methods: From May 1995 to May 2000, 57 patients with osteosarcoma of the extremity, metastatic at presentation, were treated according to the following scheme: primary chemotherapy, restaging, simultaneous resection of primary tumor and metastatic lesions, and maintenance chemotherapy.

Results: Thirty-five patients achieved remission. At a follow-up ranging from 2 to 7 years, seven remained continuously free of disease, one died of chemotherapy-related toxicity and 27 patients relapsed. Twenty-one of the 22 patients who never achieved remission died as a result of the tumor, as well as 20 of the 27 who achieved remission but then relapsed. Of the remaining seven relapsing patients, six are alive with uncontrolled disease, while one is alive and free of disease 24 months after the last post-relapse treatment. Two-year event-free survival (EFS) and overall survival (OS) were 21% and 55%, respectively. These results are significantly poorer than those achieved in 128 contemporary patients with non-metastatic disease at presentation, treated with the same chemotherapy protocol (2-year EFS and OS of 75% and 94%, respectively).

Conclusions: The results of our study confirm that the prognosis of patients with osteosarcoma of the extremity, metastatic at presentation, remains poor, despite the use of aggressive treatments.

Key words: limb salvage, lung metastases, metastasectomy, neoadjuvant chemotherapy, osteosarcoma

Introduction

High-grade osteosarcoma of the extremity (HGOE) is a malignancy that used to be fatal in up to 90% of cases when treated only by surgery [1, 2]. The development of effective adjuvant or neo-adjuvant regimens of chemotherapy has dramatically improved the prognosis of patients with localized disease at presentation, leading to a cure rate of 50–70% [3–12]. Moreover, while in the past surgery consisted of amputation in most cases, local treatment now involves limb salvage in >80% of patients [13–15]. However, ~20% of HGOE patients present with detectable metastatic disease at diagnosis. To date, neither the optimal management of these patients nor the assessment of their prognosis are well established. In fact, since most clinical osteosarcoma trials exclude patients with overt metastatic disease, these patients typically do not receive consistent treatment.

At our institution (Istituto Ortopedico Rizzoli, Bologna, Italy), osteosarcoma of the extremities with detectable metastases at presentation is treated according to the following scheme: induction chemotherapy, restaging, simultaneous resection of primary and metastatic lesions when feasible, followed by further chemotherapy. In a previous study of 23 patients with metastatic disease located only in the lung, treated between January 1993 and June 1995 with a protocol of chemotherapy including high-dose methotrexate, doxorubicin, cisplatin and standard doses of ifosfamide, we achieved a 2-year overall survival (OS) of 53% [16]. It has recently been demonstrated that there is a steep dose–response curve when using ifosfamide in the treatment of osteosarcoma [17–19]. In May 1995 we initiated a new protocol using the four-drug regimen of the previous study, but doses of ifosfamide were increased from the conventional 10 g/m² to 15 g/m², and doses of methotrexate, according to the serum level at the end of infusion, were increased from 12 g/m² to 18 g/m².

The purpose of this paper is to report the results achieved in 57 patients with osteosarcoma of the extremity, metastatic at presentation, treated between July 1995 and May 2000, following this
new protocol. The results have been compared with the updated results of the previous study [16], as well as with the results obtained in 128 contemporary patients with non-metastatic osteosarcoma of the extremity treated at our institution according to the same protocol used in the 57 metastatic patients of the present study.

**Patients and methods**

**Patient selection**

Patients <40 years of age, with newly diagnosed HGOE with metastases at presentation, and normal renal, hepatic and bone-marrow function were eligible for the study. Of the 78 patients presenting with metastatic osteosarcoma at our institution between July 1995 and May 2000, 12 were ineligible for the following reasons: age >50 years (four), previous treatments (two), and primary tumor located in the pelvis (four) or spine (two). Of the remaining 66 eligible patients, three, after diagnosis, moved to other institutions for treatment. Six patients, initially judged metastatic on the basis of a computed tomography (CT) chest scan, were then excluded because their lung nodules, which were resected during a thoracotomy performed after the preoperative chemotherapy, turned out not to be metastatic lesions. The remaining 57 patients were entered into the present study.

**Preoperative evaluation and preoperative chemotherapy**

The diagnosis of osteosarcoma was always made by histological examination of specimens taken from an open biopsy. Two pathologists (F.B. and P.B.) reviewed the slides and agreed on the diagnosis and subtype, as well as the grade of histological response to chemotherapy of primary and secondary lesions in operated patients.

All patients underwent clinical evaluation and imaging studies, including radiography, CT and/or magnetic resonance imaging, for assessment of the primary tumor, as well as chest CT scan and radionuclide total bone scan to detect pulmonary and osseous metastases. Even though it is well known that results may be false positive in osteosarcoma [21], as with other tumor types [20], we considered metastatic patients, i.e. all those with lung nodules shown by CT scan, regardless of nodule size and number. In the case of positive bone scintigraphy, an evaluation by means of a CT or MRI scan was performed to confirm the bone metastatic lesion. If the diagnosis was still in doubt, a biopsy was performed. Several laboratory tests, including alkaline phosphatase (AP) and lactate dehydrogenase (LDH), were performed before any treatment. Radiological evaluation as well as biopsy had to be performed in the 3 weeks before initiation of chemotherapy.

**Preoperative chemotherapy**

Chemotherapy was performed according to the following protocol: preoperatively, patients received intravenous methotrexate (MTX), cisplatin (CDP), doxorubicin (ADM) and ifosfamide (IFO). As shown in Figure 1. MTX was administered in a 4-h infusion at a dose of 12 g/m², which was increased by 2 g/m² if the 4-h serum level of the drug in the previous course was ≤1000 µM. Citrovorum Factor rescue (15 mg every 6 h, for 11 cycles) was started 24 h after the beginning of MTX. Hydration during and after MTX infusion followed the guidelines suggested by Rosen et al. [22]. Seven days later, patients received CDP (120 mg/m² in a 48-h continuous infusion) followed by ADM (75 mg/m² in a 24-h continuous infusion). After 3 weeks, patients received IFO (15 g/m² in a 5-day continuous infusion, combined with an equivalent dose of Mesna). A second cycle of chemotherapy was given 2 weeks later, then patients underwent surgery.

Hematopoietic, renal, metabolic and liver functions were assessed before each course of chemotherapy. No dose reduction was contemplated by the protocol. If the absolute granulocyte count was <10000/µl (800 for MTX cycles), and/or the platelet count was <100 000/µl (80 000 for MTX cycles), chemotherapy was delayed until hematological recovery.

**Surgery**

After primary chemotherapy, all patients were radiologically re-evaluated. If the metastatic disease was deemed resectable, simultaneous surgery of primary and metastatic lesions was performed within 3 weeks after the end of the last cycle of chemotherapy. Patients who still had unresectable metastatic disease generally only had the primary tumor operated on, and then moved to other institutions to receive experimental treatments for metastatic disease.

With respect to primary lesions, the type of surgery (amputation, rotation plasty or limb salvage) as well as the type of reconstruction (prosthesis, allograft, autograft and vascularized graft) were chosen according to the location and extension of the tumor, patient age and desired lifestyle. However, preoperative staging had to assure the possibility of achieving wide surgical margins before performing conservative surgery.

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

**Radiological and pathological evaluation of the response to chemotherapy**

Clinical evaluation coupled with a standard X-ray of the primary tumor and of metastatic lesions was performed before each cycle of chemotherapy. If there were no signs of progression, patients concluded the scheduled preoperative chemotherapy and response to therapy was assessed radiologically at week 12. This assessment was performed using CT and/or MRI scan of the primary tumor, CT scan of the chest, and bone scintigraphy. If bone metastases were present, these were re-evaluated by CT or MRI. The radiological response of metastases to chemotherapy was graded as ‘complete response’ (total disappearance of tumors), ‘partial response’ (≥50% decrement in the sum of the products of the perpendicular diameter of all measurable lesions), ‘stable disease’ (no substantial change or >50% decrease in tumor size) and ‘progressive disease’ (≥25% increment in the sum of the products of the perpendicular diameters of measurable lesions, or appearance of the disease at a new site or of new nodules in the lungs).

For all patients, surgeons and pathologists reviewed gross specimens and histological material to determine surgical margins after surgery. Histological evaluation of the primary tumor response or of bone metastases was performed according to a method previously reported in detail [23]. Responses were defined as ‘good’ (>90% tumor necrosis) or ‘poor’ (<90% tumor necrosis). The histological evaluation of the response in lung metastases involved the assessment of tumor necrosis in five to 15 histosections of each pulmonary nodule. An attempt was also made to assess the extent of tumor cell destruction in metastatic lesions of the lung, and the response was classified as ‘good’ (calcified osteoid matrix with complete lack of viable tumor cells or only small foci of viable cells) or ‘poor’ (no necrosis or large areas of viable tumor cells).

**Postoperative chemotherapy and follow-up**

Postoperative chemotherapy was started approximately 10–15 days after surgery. As shown in Figure 1, MTX and IFO were applied as in the preoperative treatment, whereas CDP (120 mg/m² in a 48-h infusion) and ADM (90 mg/m² in a 24-h infusion) were given as single agents for that administration.

After surgery and during postoperative chemotherapy, patients underwent X-ray of the operated limb and CT of the chest every 2 months. After the completion of chemotherapy, all patients were followed up with roentgenograms of the primary sites and a CT scan of the chest, in the outpatient clinic at our institution, at 3-month intervals for the first 3 years and thereafter once every 6
months. Additional evaluations were performed when indicated by specific clinical situations.

Statistics

The focus of this study was event-free survival (EFS). Local and/or systemic recurrence and death due to toxicity were all considered adverse events. Overall survival (OS) was also evaluated, but the relative data should be considered with caution since when remission was not achieved after induction chemotherapy or when patients relapsed, treatments were not homogeneous and were often performed in other institutions. Therefore, for all patients we know the results of the follow-up at the time this paper was written, but do not know which treatments, if any, were applied after unsuccessful induction chemotherapy or relapse.

EFS was calculated from the first day of preoperative chemotherapy to the first adverse event or to the most recent follow-up examination. OS was calculated from the first day of chemotherapy until death or last follow-up control.

Kaplan–Meier survival curves were plotted and compared using the log-rank test. The frequency of distribution of different parameters was compared among groups of patients using the \( \chi^2 \) test. Significance was set at \( P < 0.05 \).

Results

Features of the study population

Fifty-seven patients aged 6–39 years (median 18.1 years) entered the study. Thirty-eight patients were male (67%) and 19 female (33%). The most common primary site of the tumor was the femur (34), followed by the tibia (10) and the humerus (10). The remaining three patients had tumors located in the radius, fibula and astragalus, respectively. Thirty-four patients had an osteoblastic tumor, nine a chondroblastic and seven a fibroblastic subtype. In the remaining seven patients it was not possible to classify the tumor. Serum alkaline phosphatase values were elevated in 46 patients (81%) and normal in 11 (19%). The serum LDH values were normal in 36 patients (63%) and elevated in 21 (37%). Eleven patients had a pathological fracture at diagnosis. Metastases were located only in the lung in 43 patients, only in the bone in three, in lung and bone in nine, and in lymph nodes in two. Lung metastases were detected by conventional roentgenograms in 16 patients, while in 36 they were found only by CT. Lung metastases were monolateral in 32 patients and bilateral in 20.

General treatment

In two patients with lung and bone metastases, there was a progression of the primary and metastatic lesions after the first two cycles of treatment. Both patients moved to other institutions to receive palliative treatments.

Of the 43 patients with metastases only in the lung, in five they disappeared after induction chemotherapy, while in seven they remained unresectable. These 12 patients underwent surgery only on the primary lesion. The remaining 31 patients underwent simultaneous resection of primary and metastatic lesions.

The two patients with metastatic disease located in the lymph nodes underwent contemporary operation on both primary and metastatic tumors, as did two of the three patients with only bone metastases (in both cases metastases were located in the rib). The remaining patient with bone metastases had five different bones involved and received only palliative radiotherapy. With respect to the nine patients with metastases located in lung and bone, no one was deemed completely resectable after induction chemotherapy. For these patients the primary tumor was treated with surgery in seven cases and with radiotherapy with palliative intent in two.

Primary tumor

Clinical and radiological response to chemotherapy. A clinical radiological response of the primary tumor was observed in 45 patients (79%). Generally, it consisted of a decrement or disappearance of pain (when present), a reduction of tumor size (when palpable), a decrement or normalization of serum alkaline

---

**Figure 1.** Chemotherapy protocol. MTX = methotrexate: 12 g/m² as a 4-h infusion, increased by 2 g/m² if the hour-4 level of serum MTX in the previous course was <1000 µmol/l. CDP = cisplatin: 60 mg/m²/day as a 48-h continuous i.v. infusion (total dose 120 mg/m²). ADM1 = doxorubicin (adriamycin): 75 mg/m² as a 24-h continuous i.v. infusion. ADM2 = doxorubicin (adriamycin): 90 mg/m² as a 24-h continuous i.v. infusion. IFO = ifosfamide: 3 g/m²/day as a 120-h (5 day) continuous i.v. infusion (total dose 15 g/m²).
phosphatase (when high), and an increased density on plain roentgenograms and CT scan. In 10 patients, a small reduction in the size of the primary lesion, due to a decrease in the surrounding inflammatory response rather than to an actual reduction in the size of the tumor, was also seen. In the other 12 patients the primary lesion was stable in 10, while in two there was a progression. 

**Surgery and histological response.** Of the 54 patients whose primary tumor was operated on, surgery comprised limb salvage in 47 (87%) and a rotation plasty in two (4%). Due to large tumor extension with neurovascular bundle involvement, five patients (9%) were amputated. The histological response of the primary tumor was good in 29 patients (54%) and poor in 25 (46%).

**Metastases**

**Radiological response to chemotherapy.** The radiological response to chemotherapy in the 43 patients with only lung metastases was complete in five cases, partial in 10 and stable in 28. In four patients there was a progression of the lesions (appearance of new nodules), while in the remaining three there was a ‘mixed response’, i.e. some nodules disappeared or decreased in size, but new nodules appeared. In patients with bone metastases (three) or bone and lung metastases (nine), the bone lesions remained stable in eight, while in four there was a progressive increase in the number (three cases) or size (one case) of metastases. In the nine patients who had both lung and bone metastases, the lung lesions remained stable in seven, while in two there was a partial response. In the two patients with metastases in the lymph nodes there was a partial response (after a clinical evaluation).

**Surgical treatment and histological response to chemotherapy.** In the 31 patients whose pulmonary metastases were simultaneously operated on alongside the primary tumor, thoracotomy was unilateral in 20 patients and bilateral in 11. The metastasectomy consisted of a wedge resection in 28 patients and a lobectomy in three. In 26 patients the resection of lung metastases was complete (i.e. there was neither gross residual disease nor microscopic evidence of tumor), whereas four patients showed an unexpected widespread unresectable disease so that thoracotomy resulted in a mere exploratory procedure.

In the 26 patients who underwent complete resection of lung lesions, the number of nodules detected at presentation was 169, which dropped to 98 after primary chemotherapy. At the thoracotomy, the surgeon found and resected 191 nodules (93 more than detected by CT scan before surgery), but histological examination revealed that 51 resected nodules were not in fact metastases but benign lesions. Therefore the number of resected lung metastases in these 28 patients was 140.

The histological response of the 140 resected metastases in the 26 patients who had a complete resection of their pulmonary lesions was ‘good’ in 75 nodules (53%) and ‘poor’ in 65 (46%). In 37 nodules there was a total necrosis. In 14 patients (50%), all the resected metastases showed a ‘good’ response, whereas in four patients (15%) none of the resected metastases showed a ‘good’ response. In the remaining nine patients, the response of lung metastases was mixed, i.e. in the same patient there were nodules with both a ‘good’ and a ‘poor’ response. In the two patients in whom bone metastases were operated on, surgery consisted of a resection of the affected ribs. The histological response to chemotherapy was poor in both cases. The two patients with lymph node metastases had resection of the involved lymph nodes. In one case the histological response was good, while in the other it was poor.

**Comparison of the response to chemotherapy in primary and metastatic tumor**

In the 26 patients who had simultaneous complete resections of primary and metastatic tumors, there was a correlation between the response of the primary lesion and the response of the metastatic tumor, as in our previous study [16]. Indeed, 10 of the 16 patients (62%) with a good histological response of the primary tumor also had a good response in all the resected metastases, whereas a poor response of all metastatic nodules was registered in only one patient. In the remaining five patients the response was mixed. On the contrary, in the 10 patients with a poor histological response of the primary tumor, the response of all pulmonary lesions was poor in three cases, good in two and mixed in five. Therefore a concordant response was seen in 50% of patients, while a discordant one was seen in 11% (P <0.006).

**Outcome**

Of the 57 patients in the study, 36 were freed of disease while 21 never attained disease-free status. The proportions of disease-free patients differed significantly according to the sites of metastases (P = 0.003). The proportion of patients who attained disease-free status was 100% for the two with metastases located in the lymph nodes, 74% (32 out of 43) for those patients with metastases located only in the lung, and 66% (two out of three) for those with metastases located only in the bone. None of the nine patients with lung and bone metastases achieved remission. As reported in Table 1, for the 43 patients with metastases located only in the lung, the rate of remission was significantly correlated with the number of pulmonary nodules at presentation (100% for the 23 patients with less than five nodules compared with 40% for the 20 patients with five or more nodules; P = 0.0001). Moreover, the remission rate was significantly higher for patients with metastases detected only by CT scan compared with those whose metastases were already visible using conventional X-ray (93% versus 9%; P <0.0001), and for patients who had a complete or partial radiological response to preoperative chemotherapy in comparison with patients whose lungs remained the same or had progression metastases after preoperative chemotherapy (100% versus 60%; P <0.02). Twenty out of the 21 patients who were never freed of disease died as a result of the tumor 5–13 months after the beginning of treatment (mean = 11 months). The remaining patient is alive with stable disease (multiple lung metastases confirmed by histological examination) 6 years after the start of treatment.

**Event-free survival**

Up to October 2002, with a follow-up ranging from 2 to 7 years (mean 4 years), seven (20%) of the 36 patients freed of disease remained continuously disease-free, 28 (77%) relapsed, and one died of chemotherapy-related complications. All patients who
remained free of disease had metastases located only in the lung. The 2-year EFS for patients freed of disease was 38% (Figure 2).

In the 27 relapsed patients, the first sign of relapse was pulmonary metastases in 18 cases, bone metastases in five, and lung and bone metastases in four. In three patients, metastases were associated with local recurrence. The median time to relapse was 16.7 months (range 6–29 months).

The 2-year EFS was 28% for patients with metastases located only in the lung and bone, only in bone, or in the lymph nodes. However, this difference is not statistically significant ($P < 0.06$). As reported in Table 1, the 2-year EFS for patients with metastases located only in the lungs was not correlated with any of the following: the number of metastases at presentation; radiological response to chemotherapy; radiological examination to detect metastases (conventional X-ray versus CT scan); or the serum level of alkaline phosphatase and LDH at the time of diagnosis. Of the five patients who entered complete radiological remission of their lung metastases, one remained continuously free of disease and four relapsed. According to the histological response of primary and metastatic lesions, in the six evaluable patients who remained free of disease, the histological response in primary and secondary tumor was 'good/good' in four patients, 'poor/poor' in one, and 'poor/good' in the remaining case.

### Treatment after relapse and outcome in disease-free patients

For the 27 patients who achieved remission but later relapsed, the first treatments after relapse and post-relapse outcome were as

---

**Table 1.** Patients with only lung metastases at presentation, who entered remission and were free of disease after 2 years, evaluated according to several variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Proportion of patients who entered remission (%)</th>
<th>$P$ value</th>
<th>Percentage of patients free of disease at 2 years</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lung metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five or less</td>
<td>23</td>
<td>100</td>
<td>$&lt;0.0001$</td>
<td>27</td>
<td>$&lt;0.49$</td>
</tr>
<tr>
<td>Six or more</td>
<td>20</td>
<td>40</td>
<td></td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Radiological response to chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial or complete</td>
<td>13</td>
<td>100</td>
<td>$&lt;0.02$</td>
<td>40</td>
<td>$&lt;0.28$</td>
</tr>
<tr>
<td>Stable or progression</td>
<td>30</td>
<td>60</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Metastases detected by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT scan</td>
<td>14</td>
<td>93</td>
<td>$&lt;0.0001$</td>
<td>38</td>
<td>$&lt;0.07$</td>
</tr>
<tr>
<td>Conventional X-ray</td>
<td>29</td>
<td>9</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>9</td>
<td>89</td>
<td>$&lt;0.39$</td>
<td>29</td>
<td>$&lt;0.14$</td>
</tr>
<tr>
<td>Elevated</td>
<td>34</td>
<td>68</td>
<td></td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Serum LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td>76</td>
<td>$&lt;0.66$</td>
<td>38</td>
<td>$&lt;0.07$</td>
</tr>
<tr>
<td>Elevated</td>
<td>14</td>
<td>64</td>
<td></td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** EFS in patients who achieved disease remission.

**Table 2.** Osteosarcoma of the extremity with metastases at presentation: comparison of the results of the present study with updated results of our previous study

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Present study (only patients with lung metastases)</th>
<th>Previous study</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>57</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>Patients who reached remission (%)</td>
<td>61</td>
<td>76</td>
<td>78</td>
</tr>
<tr>
<td>Limb salvage as surgery for primary tumor (%)</td>
<td>87</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>2-year EFS (%)</td>
<td>21</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>2-year OS (%)</td>
<td>55</td>
<td>81</td>
<td>53</td>
</tr>
</tbody>
</table>
follows: (i) the 15 who relapsed with only new lung metastases were treated using thoracotomy in 11 cases (combined with new chemotherapy in eight), while no further treatments (other than palliative cures) were given in four. (ii) The two patients who relapsed with local recurrence and bone metastases received only palliative treatment, while the other patient who developed local recurrence with lung metastases was treated with amputation and simultaneous resection of four lung metastases. (iii) Of the nine patients who relapsed with lung and bone metastases, four received further chemotherapy in different institutions, while four received only palliative treatment.

Of these 27 patients, 20 died as a result of their tumor 9–42 months (mean 25 months) after the beginning of treatment, and six remain alive with uncontrolled disease 14–39 months (mean 32 months) from the beginning of treatment. The remaining patient, who relapsed with lung metastases and was treated with new thoracotomy and new chemotherapy, is alive and apparently free of disease 24 months after relapse.

The 2-year OS for all 57 patients in the study is 55% (Figure 3), and 79% for the 27 patients who achieved disease remission (Figure 4).

Comparison with the results of our previous study

As shown in Table 2, the results of the present study are very similar to those of our previous study [16], which are updated here. In fact, the percentages of patients who achieved remission (61% and 78% in the earlier and present studies, respectively), the rate of limb salvages (87% and 90%), and the rate of good histological responses in the primary tumor (61% and 71%) and in the resected pulmonary metastases (78% and 87%) are all essentially the same. The 2-year EFS (21% and 32%) and OS rates (55% and 53%) were also highly similar.

Comparison with the results in contemporary patients with localized disease at presentation

One-hundred and twenty-eight patients without metastases at presentation were treated at our institution in the same period, with the same protocol used for patients with metastatic disease. In these 128 patients, the rate of limb salvages as well as the rate of good histological response to chemotherapy in the primary tumor were similar to rates observed in the patients with lung metastases at presentation. On the other hand, 2-year EFS and OS were significantly higher than those observed in the group of patients with metastatic disease at presentation in the present study (75% compared with 21%, $P < 0.0001$; and 91% compared with 54%, $P < 0.001$). Even if, among metastatic patients in the present study, we consider only those 36 patients freed of disease, their rates of 2-year EFS and OS remain significantly lower than those of non-metastatic patients (75% compared with 36%, $P < 0.0001$; and 91% compared with 75%, $P < 0.01$). However, in the group of patients with metastatic disease at presentation, for the five patients with only one metastatic lung nodule, the rates of 2-year EFS and OS were the same as those observed in patients with localized disease (67% and 75%, and 91% and 87%, respectively).

Treatment compliance, chemotherapy toxicity and surgical complications

In total, 740 cycles of chemotherapy were performed, of which 133 (18%) were delayed by >7 days (range 8–28 days) due to delayed bone marrow recovery (117 cases), abnormal laboratory findings (eight), surgical complications (five), delayed clearance of MTX (two), and organizational problems (one). A dose escalation of MTX was necessary in three patients.

Although the protocol did not provide for dose reductions, they were necessary in 60 cycles (8%), with decrements ranging from 18% to 33% of the fixed dose. Owing to delays and dose reductions, only seven patients actually received the scheduled dose intensity; 12 received a dose intensity between 90% and 99%, and the remaining 38 patients received a dose intensity between 72% and 89% of the scheduled treatment. One patient with no signs of recurrence died of chemotherapy-related toxicity (veno-occlusive disease after the first postoperative cycle of MTX).

In all courses of chemotherapy, a hematological toxicity grade 4 was observed on 155 occasions (21%), and patients had to be hospitalized a total of 32 times (4%) for life-threatening febrile myelodepression. Episodes of grade 1 or 2 renal toxicity were recorded after 12 cycles, one occurring after a delayed MTX
elimination, and the others in the postoperative phase after IFO in (5 pts) and CDP in (6 pts) infusion. In all but one case the serum creatinine values returned to normal before subsequent cycles of chemotherapy.

No major surgical complications were seen in patients treated with amputation and rotation plasty. In patients treated with limb salvage there were four major orthopedic complications (two prosthetic failures and two infections) that required a second surgical procedure. Surgical morbidity related to thoracotomy was minimal, and comprised only transient pneumothorax and/or pleural effusion.

Discussion

The addition of aggressive adjuvant or neoadjuvant chemotherapy to surgery has dramatically improved the long-term disease-free survival and the cure rate of patients with osteosarcoma of the extremity without evident metastatic disease at presentation from 10–15% to 50–70% [3–12]. Moreover, in patients who relapse after this combined treatment, the surgical removal of lung metastases with or without further chemotherapy gives good results and approximately 25–30% of these patients are rescued [24–29].

In contrast, the prognosis of osteosarcoma of the extremity in patients with synchronous metastases, treated with chemotherapy and surgical removal of the primary tumor and all detectable metastatic lesions, is not well known and controversial. In 10 recently published series, the 5-year OS for this group of patients ranged from 11% to 53% [30–37]. These differences in prognoses observed in various institutions are most likely attributable to the small number of patients in most studies, as well as the different selection criteria of patients: some studies only consider patients with metastatic disease located in the lungs [30, 31, 33], while others evaluated also patients with metastases located in the bone and/or other sites [32, 35–38].

The lungs are by far the most common location of osteosarcoma metastases, and to stage the pulmonary disease, CT of the chest is the standard diagnostic technique, even if, especially for some neoplasms, a strong inter-observer variability has been reported, as well as false-positive examinations [20]. In osteosarcoma, CT of the chest has two limits: (i) not all lung nodules found during surgery are evident on the CT scan; and (ii) not all nodules seen on the CT scan are true metastatic lesions. In our series, 27 patients had complete resection of their lung lesions and at the thoracotomy the surgeon resected 191 nodules, while the number of lesions evident on the CT scan before surgery was only 98. In other words, the surgeons found almost double the number of nodules detected by CT scan. However, of these 191 resected nodules, only 140 (73%) were true metastases while the remaining 51 were benign lesions. Moreover, seven patients who presented with metastatic disease and were simultaneously operated upon were successively reclassified and excluded from this study, as the histological examinations of their resected nodules showed that they were non-tumoral lesions. The presence of "pseudometastases" in osteosarcoma is not a rare event. In a recent review undertaken at our institution [21], ~51 patients with osteosarcoma underwent simultaneous thoracotomy for metastatic disease at presentation, on the basis of CT of the chest; histological study of the resected lesions confirmed metastatic nodules in only 29 (57%).

It is important to underline that only four out of 13 patients (31%) with one nodule found during surgery had a true metastatic disease; however, all patients presenting with more than seven nodules had real metastases. Therefore we cannot be sure that the five patients in the present series whose lung nodules disappeared after preoperative treatment had a real metastatic tumor. However, even if CT has limitations, it remains the best technique available today. In addition, it should be remembered that aggressive pulmonary surgery is probably the only way to cure patients with osteosarcoma and contemporary pulmonary metastases. This means that today, a patient with lung nodules evident upon CT scan has no better choice than lung surgery, even if this implies useless thoracotomies for some patients.

With respect to chemotherapy, the most active agents against osteosarcoma are: methotrexate, especially if used at high doses [3, 4]; cisplatin [39, 40]; doxorubicin (adriamycin) [41, 42]; and IFO [38, 43]. When these drugs are used as single agents, the response rate ranges from 20% to 40%. When used together from the start of treatment, however, results improve significantly, as shown in our previous study of 23 patients with metastatic disease at presentation located only in the lung [4]. The percentage of patients who achieved a disease-free status was 78%, with a following 2-year EFS and OS of 32% and 53%, respectively. Some studies have demonstrated a dose–response relationship for IFO in metastatic osteosarcoma [17, 18, 36], so in 1995 we started a new study in which doses of IFO were escalated from 10 g/m² to 15 g/m² per cycle. In addition to this, since previous experience [44, 45] had indicated serum concentrations of MTX to be positively linked to improved histological tumor response and survival, the doses of MTX were also increased by 2 g/m² in patients whose serum level of the drug was <1000 μM/L. As in our previous study, surgeries to remove both the primary tumor and metastatic lesions were performed at the same time to reduce the period of time without chemotherapy. The other new feature of the present study is the inclusion of patients with metastases located outside the lung.

Despite this aggressive regimen, the results were disappointing. Of the 57 treated patients, only 35 (61%) achieved disease-free status. It is important to underline that the proportion of patients who attained disease-free status was significantly related to the site of metastases, and, for patients with metastases located only in the lung, with the number of pulmonary lesions and their response to preoperative chemotherapy. The 2-year EFS and OS were only 21% and 41%, respectively. It is important to stress that none of the patients with metastases outside the lungs remained disease-free. In patients with metastases located in the lung only, the 2-year EFS was not related to any of the following: (i) the number of lung lesions; (ii) the radiological or histological response to preoperative chemotherapy; (iii) radiological techniques to detect pulmonary lesions (conventional X-ray or CT scan); or (iv) the serum levels of alkaline phosphatase and LDH. Considering only patients who achieved disease remission, 2-year EFS and OS were 32% and 63%, respectively. These percentages are essentially the same as those of the previous study. Thus, it appears that increasing the doses of IFO and MTX did not improve the prognosis of
patients with metastatic osteosarcoma at presentation, which remains extremely poor. These results are in contrast to those reported recently by Goorin et al. [36]. This group treated 40 patients with metastatic osteosarcoma in the lung and/or other sites, according to a 5-day treatment protocol consisting of high-dose MTX, CDP and ADM, alongside a high dose of IFO (3.5 g/m²/day) combined with etoposide (100 mg/m²/day). Even though significant myelosuppression and nephrotoxicity, sometimes associated with sepsis, and two deaths resulting from therapy toxicity were recorded, the preliminary results were significantly better than those of our study. The projected 2-year progression-free survival was in fact 39% for the 28 patients with lung metastases, and 58% for the 12 patients with bone metastases (with or without pulmonary nodules).

For our patients, an intensive surveillance program comprising 3-monthly CT scans over a period of 3 years was performed. Our experience shows that ~25% of relapsing osteosarcoma patients (with localized disease at presentation, treated with adjuvant and neoadjuvant chemotherapy) can be cured if relapse is detected early. Also, the time to diagnosis seems to affect outcome, particularly in the case of lung metastases [46]. Despite the intensive follow-up program, in the present series of patients presenting with metastases, only one of the patients who relapsed after achieving disease-free status is currently alive and free of disease. In the same patient group, the comparison of the histological response to chemotherapy by both the primary and metastatic tumors, evaluated in 26 patients with lung metastases who underwent simultaneous resection of primary and secondary lesions after chemotherapy, deserves some comment. In contrast to our previous experience [16], a concordant response was observed in only 50% of cases. This low rate of concordant responses, as well as different responses in different nodules in the same patients, is not surprising since several clinical and experimental studies support the idea that, in solid tumors, the primary lesion and the metastatic foci are comprised of clones of cells that differ with respect to ploidy, enzyme profile, karyotype, metastatic potential and chemosensitivity [47].

From the results of the present study, we can conclude that slight variations in the doses of the drugs currently used do not improve the outcome of patients with metastatic osteosarcoma at presentation. Nevertheless, these variations in dose can only be slight, as even if a severe drug-induced myelotoxicity could be prevented by the stem cell support, the adverse effects on vital organs do not allow further incremental increases. Therefore, for these patients, new drugs and new therapeutic avenues arising from biological studies are necessary. Today, as far as we are concerned, new experimental treatments have to be considered as first-line treatment for osteosarcoma patients presenting with extra-pulmonary metastases.

References