A pilot study of short-course intensive multiagent chemotherapy in metastatic and axial skeletal osteosarcoma

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Background: This pilot study was undertaken to assess the feasibility, toxicity and response to short-course multiagent chemotherapy followed by high-dose chemotherapy (HDC) in patients with poor prognosis osteosarcoma.

Patients and methods: A total of 30 patients entered the study. Chemotherapy consisted of four blocks of multiagent chemotherapy administered sequentially over a short period in a dose-intensive manner. This therapy was followed by HDC which consisted of carboplatin at an AUC8 × 3 days, etoposide 400 mg/m² × 3 days and cyclophosphamide 60 mg/kg × 2 days.

Results: A total of 227 cycles of chemotherapy were administered. The main toxicity (for blocks 1–4) was haematological. There were two treatment-related deaths: one post HDC due to sepsis and one during surgery. High-dose chemotherapy was administered to 11 patients (10 with extremity tumours and only one with a pelvic tumour). Twenty-seven patients underwent surgery to the primary. Histological response was assessed in 23 patients. Seven patients (30%) had >90% necrosis. Eight patients underwent pulmonary metastatectomy. The median survival time for the whole group was 16 months. The 2- and 3-year survival rates were 50% and 21% for those with extremity tumours and 19% and 13% for those with axial skeletal tumours.

Conclusions: Dose-intensive multiagent chemotherapy though feasible in the group of patients with extremity tumours did not significantly improve the treatment outcome compared with conventional relapse therapy. Inferior survival rates in the axial skeletal group are attributed to less intensive treatment and poor local tumour control.

Key words: dose-intensive therapy, high-dose chemotherapy, metastatic osteosarcoma, pelvic osteosarcoma, poor prognosis osteosarcoma

Introduction

During the past 25 years significant progress has been made in the management of localised, extremity osteosarcoma with the combined use of surgery and chemotherapy. This treatment has substantially improved the prognosis for those patients with no detectable metastases at diagnosis, who have long-term relapse-free survival rates of 55–76% [1–5]. In contrast, for those patients with radiologically detectable metastases at first presentation (approximately 10–20% of all cases) and for those with unresectable pelvic or axial primary tumours, the prognosis remains poor with 3-year survival rates ranging between 11% and 56% [6, 7]. Little information exists on the role of multiagent neoadjuvant chemotherapy in patients with extremity osteosarcomas and metastatic disease at presentation, since most clinical trials exclude such patients, and this group of patients may therefore not receive consistent and homogeneous treatments. However, there is evidence in the literature suggesting that intensive chemotherapy coupled with aggressive surgical resection may improve the prognosis for this group. A retrospective analysis reported a progressive improvement in survival when three cohorts of patients presenting with pulmonary metastases were treated with increasingly intensive chemotherapy. Despite this, those patients treated most intensively still fared badly and all had evidence of persistent disease [8]. Thus, although crude survival may have been improved, the rate of cure has not.
Patients with pelvic and other axial skeletal osteosarcomas also have a poor prognosis, the main reasons for which include large size, often due to a delayed diagnosis, the unresectability of the tumour and a high incidence of metastases present at diagnosis [9–11].

Better approaches to treatment are therefore needed for such patients. The goals of any new strategies should be first, to improve rates of radiological and histological response; second, to improve the number of patients suitable for resection of pelvic and axial skeletal tumours; and third, to avoid prolonged and ineffective treatments for patients destined not to be cured. The key factor in an improved strategy may be to achieve a rapid and maximal chemotherapy response before definitive local treatment, be it surgery or radiotherapy, is applied. The purpose of this phase II study was to examine the feasibility, toxicity and response to short-course multiagent chemotherapy involving a number of agents with proven activity against osteosarcoma in four successive blocks. The addition of recombinant haemopoietic growth factors (G-CSF) to each block facilitated the delivery of planned cytotoxic dose on time. Finally, the administration of high-dose chemotherapy (HDC) with peripheral blood stem cell (PBSC) rescue at the end of treatment was introduced in an attempt to improve overall results.

**Patients and methods**

Between April 1995 and April 1999 a total of 30 patients from two centers entered the study. Eligibility criteria to be registered onto the study included the following: (i) histological and radiological diagnosis of high-grade osteosarcoma either with metastases (pulmonary, bone, other) at initial diagnosis or a primary unresectable tumour of the pelvis or the axial skeleton; (ii) no previous treatment with chemotherapy or radiotherapy; (iii) <50 years of age; (iv) adequate renal status, defined as a glomerular filtration rate (GFR) of >70 ml/min; (v) adequate hepatic function, defined as an AST level ≤1.5 × upper normal limit (UNL), total bilirubin level ≤1.5 × UNL; (vi) a white blood cell (WBC) count of ≥4.0 × 10^9/l, platelet count of ≥100 × 10^9/l and haemoglobin level of ≥10 g/dl; (vii) adequate cardiac function (left ventricular ejection fraction >50%); (viii) signed informed consent. For patients <16 years of age, a written informed consent was obtained from the parents or legal guardian, and verbal assent obtained from the patient.

Exclusion criteria included a performance status (PS) of 4 and any co-existing illness precluding the use of intensive chemotherapy.

Chemotherapy consisted of five components (blocks) given in a consecutive fashion, as shown in Figure 1. Block 1 consisted of cisplatin and doxorubicin administered between days 1 and 3. Granulocyte colony stimulating factor (G-CSF; lenograstim 263 mg/kg for body weight <100 kg) was administered from day 4 until the absolute neutrophil count (ANC) was over 1.0 × 10^9/l. For patients weighing >100 kg the dose of G-CSF was doubled. Block 1 was repeated once in 2 weeks. Block 2 consisted of cisplatin, ifosfamide and etoposide administered once on week 4 and followed by G-CSF from days 2 to 11. Patients had a daily complete blood count from day 9 and stem cell harvesting was attempted on day 11 if the total WBC was >3.0 × 10^9/l. If the WBC was below this level, the count was repeated daily and the procedure carried out when WBC count was adequate. G-CSF was continued until harvesting was completed. Harvesting was considered successful if CD34+ cell count was >2 × 10^6/kg. Block 3 consisted of ifosfamide administered as a daily 4-hour infusion for 6 consecutive days followed by G-CSF administered from day 7 until

**Figure 1.** Chemotherapy schedule for patients with poor risk osteosarcoma.
the ANC was over $1.0 \times 10^9/l$. Block 4 consisted of high-dose methotrexate given over 4 h repeated three times at 7–10 day intervals. Folinic acid rescue was started 24 h after the start of high-dose methotrexate at a dose of 15 mg/m² and continued 6 hourly until serum methotrexate levels were below $1.0 \times 10^{-7}$. Block 5 (HDC) consisted of carboplatin, etoposide and cyclophosphamide administered around week 21 and after the planned surgery for operable primary tumours.

Chemotherapy was delayed for up to 1 week without modification if the ANC was <1 × 10^9/l or the platelet count was <80 × 10^9/l on the day of scheduled therapy. The dose of chemotherapy during blocks 1, 3 and 4 was reduced to 80% if during the preceding cycles there was documentation of febrile neutropenia, grade 3 to 4 mucositis or gastrointestinal toxicity, or thrombocytopenia requiring platelet support (grade 4), or a delay of more than 1 week of the scheduled treatment.

For block 1 the dose of cisplatin was reduced to 80, 60 and 50 mg/m² if the GFR was 79–70, 69–60 and 59–50 ml/min/m², respectively. For block 2 no modifications were performed. For block 3, the initial dose of ifosfamide was reduced to 12 g/m² if the GFR was <75 ml/min/m². A further reduction of the dose of ifosfamide to 9 g/m² was done if despite a dose reduction during cycle 1 severe toxicity occurred, and also for somnolence at any dose. For block 4, the dose of methotrexate was reduced to 8 g/m² if the GFR was <75 ml/min/m² and discontinued if the ANC was <10 × 10⁹/l.

Disease assessment at entry included both a complete medical history and thorough physical examination, a series of laboratory tests including a complete blood count with differential, a complete renal function assessment with EDTA clearance, a cardiac function assessment by radionuclide scan, hepatic function, audiogram, serum immunoglobulin levels, serological tests for HIV, hepatitis B and C and cytomegalovirus. Imaging tests for the primary site included plain X-rays, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans. Metastatic disease was investigated using Technetium 99m diphosphonate bone scan and CT scans of the lungs.

Radiological response to treatment was assessed after the completion of each block of chemotherapy, and before block 5 (HDC) unless the time elapsed since previous scans was <4 weeks. Definition of response was as follows: complete response (CR), radiological disappearance of all evidence of tumour. Any residual bone changes even in the presence of a complete disappearance of extraosseous disease excluded a CR. Partial response (PR), ≥50% reduction, compared with baseline, of tumour volume(s) (sum of all lesions) according to MRI; minor response (mR), ≥25% but <50% reduction of tumour volume(s); stable disease (SD), a decrease of ≥25% or an increase of <25%, compared with baseline, of tumour volume(s) for at least 4 weeks and progressive disease (PD), any increase of >25%, compared with the smallest measurement, in the sum of volume of measurable lesions or the appearance of new lesions.

All histology specimens were reviewed at the Royal National Orthopaedic Hospital. Resected tumours were examined histologically to assess completeness of excision and tumour response to chemotherapy. A slab, including the resection margins, was prepared from the specimen through the plane of maximum tumour diameter, which was then submitted for decalcification and processing. Response to chemotherapy was assessed by estimating the per cent necrosis of tumour surface represented in the processed slab. A >90% necrosis of the tumour indicated a good response while a <90% necrosis of the tumour represented a poor response. Percentage necrosis was assessed according to the methods described by Malcolm et al. [12].

Surgery was planned to be carried out after block 4. Earlier surgery was carried out if disease progression or major toxicity from chemotherapy was encountered. The type of surgical procedure (limb salvage surgery or amputation), as well as the type of reconstruction (prosthesis, allograft or vascularized graft), depended on the location and extension of the primary site, degree of response and the patient’s age. Conversion to operability was recorded for any patient deemed to have an inoperable primary or inoperable metastatic disease at presentation. Surgery for pulmonary lesions comprised wedge resections or, if necessary, lobectomy, performed through an anterolateral thoracotomy. All pulmonary resections were performed by two thoracic surgeons whereas primary tumours were operated on by four different orthopedic surgeons of the same service.

Toxicity was graded according to the National Cancer Institute–Common Toxicity Criteria [13]. To test the differences between groups the two-sample test of proportions was used. Survival analyses were performed using the Kaplan–Meier method [14]. Subgroup analysis was performed using the log rank test.

**Results**

**Patient characteristics**

Table 1 summarises the patients’ characteristics and distribution of the primary site according to age. The median age of patients at diagnosis was 24 years (range 9–46). The median age of patients with extremity tumours and axial skeletal primaries was 17 years (range 8–32) and 30 years (range 9–46), respectively. Male to female ratio was 1.7:1. The disease was localised in 14 patients and metastatic at presentation in 16 patients. The majority (15/16) of patients with metastatic disease had lung metastases and one patient had osseous metastases only. One patient had involvement of more than one site (pulmonary and osseous metastases). Pulmonary metastatic disease was documented in 13 patients with extremity and in two patients with axial skeletal osteosarcoma. In the majority of cases (13/15 patients) the pulmonary metastases were multiple, usually bilateral with a total number of nodules ranging from two to 20. Among the two cases with a single pulmonary metastatic lesion, one patient had a complete radiographic response and the other one underwent resection of the nodule which was found to be an eosinophilic granuloma.

The clinical symptoms at presentation were local pain and swelling of the involved site. Five patients presented with a pathological fracture (four with extremity tumours and one pelvic). Alkaline phosphatase levels were elevated in 14/30 patients (four with extremity, eight with pelvic and two with other axial skeletal primaries). One patient with a malignant fibrous histiocytoma (MFH) of the extremity participated in the study and was assessed for response and survival together with the rest of the patients, since this was a feasibility study. Evidence suggests that MFH has a similar prognostic behavior to osteosarcoma when treated with similar chemotherapy regimens [15].

**Treatment**

A total of 226 cycles of chemotherapy (blocks 1–5) were administered to 30 patients. In one patient with a pelvic primary, cisplatin was substituted by carboplatin (AUC6) due
to impaired renal function and in another patient etoposide (350 mg/m²) was added to block 3 (ifosfamide) and the total dose of ifosfamide was reduced to 9 g/m². Although the total number of chemotherapy cycles administered for blocks 1–4 was not significantly different among the two patient groups (107 versus 108 cycles, respectively) they differed significantly in terms of dose intensity. For blocks 2, 3 and 4 a considerably higher percentage of patients from the group of extremity osteosarcomas received the intended number of chemotherapy cycles compared with patients with axial skeletal tumours (100%, 93% and 70% of patients versus 70%, 75% and 38% of patients, respectively). Patients with extremity tumours were more likely to receive the full planned dose of therapy for blocks 3 and 4 (high-dose ifosfamide and methotrexate, respectively) compared with those with axial skeletal tumours. This difference was more evident for block 3 (57% of patients versus 20% of patients; \( P = 0.04 \)) and less evident for block 4 (50% versus 19%; \( P = 0.07 \)). The percentage of patients who received >80% of the intended dose of chemotherapy for block 3 was significantly higher in patients with extremity tumours (\( P = 0.02 \)), as it was also for block 4 although at a lower level of significance (\( P = 0.07 \)).

Block 5 (HDC) was administered to 11 patients (10 with extremity tumours and one with a pelvic tumour). Nineteen patients (four patients with extremity and 15 patients with axial skeletal tumours) did not get HDC. The reasons for this omission included early progression in six patients, major unacceptable toxicity precluding the administration of HDC in eight patients, unresectability of the primary lesion in two patients and physician choice in three patients.

A total of 39 cycles were delayed for >1 but <2 weeks and seven cycles were delayed for >2 weeks. No difference was found between the two groups.

### Collection of PBSCs

A total of 22 patients underwent PBSC collection after block 2 (13/14 with extremity tumours and 9/16 patients with axial skeletal tumours). A total of 28 harvests were performed. All harvests were attempted between days 10 and 16 post-HDC (Table 2). The majority of patients (83%) were harvested between days 11 and 13. Six patients were harvested twice. The median number of WBCs on the day of harvest was \( 10.2 \times 10^9/l \) (range 3–57). The median CD34+ count was \( 3.8 \times 10^4/kg \) (range 0.6–15.8). Collections with an adequate CD34+ count were cultured, yielding a median granulocyte–macrophage colony-forming units of \( 5.5 \times 10^7/kg \) (range 10–346).

### Local treatment

**Surgery.** All patients with extremity osteosarcomas underwent resection of the primary tumour. The majority (13/14) underwent a limb salvage operation. In eight, three and two patients the resection was performed after block 4, 5 and 3, respectively. One patient with an extensive proximal femoral osteosarcoma underwent a hemi-pelvectomy before the institution of the chemotherapy protocol but was evaluable for pulmonary metastatic disease.

Nine patients (75%) with osteosarcoma of the pelvis underwent surgery (hemi-pelvectomy, hindquarter amputation or resection with fibula graft). One patient declined surgery, one

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Primary location</th>
<th>Limb</th>
<th>Axial</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
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<td>1</td>
</tr>
<tr>
<td>11–20</td>
<td>8</td>
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<td>21–30</td>
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<td>9</td>
</tr>
<tr>
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<td>7</td>
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<td>Tumour site</td>
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</tr>
<tr>
<td>Femur</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Tibial</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Humerus</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Fibula</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Pelvic tumours</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>Vertebral</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Sphenoid sinus</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Scapula</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Rib</td>
<td>–</td>
<td>1</td>
</tr>
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</tr>
<tr>
<td>Bone</td>
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</tr>
<tr>
<td>Both</td>
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<td>–</td>
</tr>
<tr>
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<tr>
<td>Osteoblastic</td>
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<tr>
<td>Chondroblastic</td>
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<td>3</td>
</tr>
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<td>Mixed</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MFH</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
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</tr>
<tr>
<td>No</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

MFH, Malignant fibrous histiocytoma.
had inoperable disease and in one case progressive disease was documented in the lungs. Among patients with other axial tumours one patient underwent a T12, L1, L2 vertebrectomy, one a forequarter amputation for an osteosarcoma of the scapula and one patient with osteosarcoma of the third and forth rib underwent a chest wall resection with gortex graft placement. One patient with osteosarcoma of the sphenoid sinus was inoperable and received local radiotherapy (50 Gy) to the involved site.

Metastasectomy. Surgery for pulmonary metastatic disease was performed in seven patients with extremity tumours and one patient with a pelvic tumour. Six thoracotomies were bilateral and two unilateral. One patient had simultaneous bilateral thoracotomies and the remaining five patients had sequential bilateral thoracotomies with an interval between procedures ranging from 3 weeks to 2 months.

Radiotherapy. Radiotherapy was delivered as an adjunct to the primary treatment or for palliation. Six patients received adjuvant radiotherapy to the primary site at a dose ranging between 50 and 60 Gy, one patient received whole lung irradiation after resection of metastatic disease (18 Gy in 12 fractions) and 16 patients received palliative radiotherapy which was to the primary site for control of local recurrence in 12.

Response. All patients were evaluable radiologically for response to treatment. Nine patients (30%) had a PR, five patients (17%) a mR, 14 patients (47%) had SD and two patients (6%) had PD while on treatment. Responses were higher among the patients with extremity tumours with a PR rate of 8/14 patients (57%).

A separate analysis of clinical response according to primary or metastatic disease was performed. Evaluation of clinical response of the primary site demonstrated a PR in four patients (13%), mR in six patients (20%), SD in 16 patients (54%) and PD in one patient (3%). Three patients (10%) were not assessed (one patient had immediate surgery, one presented initially with a pathological fracture of the primary and in one patient there was insufficient data from his records). Among 16 patients with metastatic disease (primarily in the form of pulmonary metastases) there was one CR (6%), seven PRs (44%), two mRs (13%) and six SDs (37%).

Histological response and completeness of resection was assessed in 23/26 patients who underwent surgery. One patient had his primary operation before the initiation of chemotherapy and therefore was not assessable for histological response. One patient died during the operation and the specimen was not evaluated and in one case the resected tumour-bearing bone was irradiated ex vivo and re-implanted. Seven patients (30%) had a good response (>90% necrosis) (95% CI 10% to 50%). Nine primary tumours (39%) were completely resected, eight (35%) were marginally resected and in six tumour specimens (three of each group) the margins contained viable tumour. Among the seven patients with a good response to chemotherapy, four had a complete resection, two had marginal resections and one an incomplete resection.

Histological response was assessed in eight cases of pulmonary metastatectomy. In five cases there was viable tumour in the resected specimen. All these cases coincided with viable tumour in the resected primary too. In two cases the tumour was found to be necrotic and in one case no tumour cells were found.

Toxicity. Table 3 summarises the cumulative toxicity for all patients for blocks 1–4. Grade 3 or 4 neutropenia was observed in 98 cycles (49%). Significant renal impairment (with corrected GFR values <60 ml/min/1.73 m²) occurred in seven patients (six with axial skeletal and one with extremity tumours). Hypokalaemia developed in 30% and hypomagnesaemia in 28% of cycles of ifosfamide administration but was easily manageable with potassium and magnesium supplementation and was never symptomatic. Ten patients developed signs of encephalopathy during ifosfamide administration, which in three cases was severe enough to warrant discontinuing treatment early. Ninety-one cycles (42%) required subsequent admission of the patient for supportive management. The majority of these admissions (70%) were for intravenous antibiotic therapy because of febrile neutropenia, and 15% for platelet transfusions. There was no statistically significant difference recorded between patients with extremity primaries and those with axial skeletal primaries.

### Table 2. Mobilization details

<table>
<thead>
<tr>
<th>Harvest day</th>
<th>No. of patients</th>
<th>Median WBC count ($\times 10^9/l$)</th>
<th>Median CD34 cell count ($\times 10^6/kg$)</th>
<th>Median CFU-GM ($\times 10^4/kg$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>13</td>
<td>6.1</td>
<td>6.4</td>
<td>69.9</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>7.2</td>
<td>1.9</td>
<td>15.6</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>28.5</td>
<td>2</td>
<td>52.1</td>
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<tr>
<td>14</td>
<td>1</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
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<td>–</td>
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</tr>
</tbody>
</table>

CFU-GM, granulocyte–macrophage colony-forming units; WBC, white blood cell.
The 11 patients who received HDC were evaluable for toxicity. Six patients received G-CSF post-HDC and five patients did not. The median number of days in hospital for HDC was 23 days (range 15–29). The most serious grade 3/4 side effects were as follows: stomatitis, five patients (45%); nausea with vomiting, seven patients (64%); febrile neutropenia requiring intravenous antibiotics, 11 patients (100%) and hypotension, one patient. The median number of days requiring intravenous antibiotic therapy was 11 days (range 4–13). The median time to recovery of WBC to $>1.0 \times 10^9/l$ was 9 days (range 6–13) and the median time to recovery of platelets to $>25 \times 10^9/l$ was 6 days (range 2–14).

There were two treatment-related deaths: one from neutropenic sepsis on day 13 post-HDC and one from massive blood loss and hypotension during surgical removal of the primary tumour (T12, L1, L2 vertebrectomy).

**Local recurrence pattern.** Of 26 patients (12 with extremity and 12 with axial skeletal osteosarcomas) who underwent resection of their primary tumour, 14 recurred locally. The median time to recurrence was 9 months (range 2–50). The local recurrence pattern was significantly higher among those patients with axial skeletal tumours (75%) compared with patients with extremity tumours (42%).

**Survival.** After a median follow up of 29 months or to death (range 12–57 months), 22 patients have died. Ninety per cent of patients have been followed for >2 years and 80% for >3 years. Figures 2 and 3 detail the Kaplan–Meier analysis of overall survival for the whole group and each subgroup according to age, site and histological response and completeness of resection in patients with poor prognosis osteosarcoma. The median survival time for the whole group was 16 months from commencement of the regimen with 95% confidence intervals ranging from 13 to 19 months. The median survival for extremity osteosarcoma was 22 months (range 7–55) and for axial skeletal osteosarcoma 13 months (range 7–57). The 2- and 3-year survival rates for the whole group of patients was 33% and 17%, respectively. Two- and 3-year survival rates were 50% and 21% for the group of patients with extremity tumours and 19% and 13% for those with axial skeletal tumours.

Ten patients have survived in excess of 2 years, of whom five have subsequently died of their disease. Of the remaining five patients, four had an extremity osteosarcoma with pulmonary metastases at initial presentation and received HDC and one patient had a pelvic tumour which was completely excised and had a good response to chemotherapy (without HDC). Four patients are currently disease-free and one has pulmonary metastatic disease.

**Discussion**

With the introduction of CT scanning, the number of patients with osteosarcoma who have detectable lung metastases at
first presentation has, predictably, increased. Currently, as many as 20% of patients with osteosarcoma have lung metastases at diagnosis [7, 16] compared with only 10% previously reported [17]. Pelvic osteosarcoma constitutes another 4–10% of osteosarcomas of all sites [18, 19] while patients with tumours located in the axial skeleton (including the pelvis) account for 27% of all osteosarcoma patients in some series [20]. Therefore poor risk osteosarcoma—a heterogeneous group of tumours in terms of location but with similarly dismal prognostic features—comprises a significant proportion (up to 47%) of patients with osteosarcoma at initial presentation.

While treatment policies in patients with non-metastatic osteosarcoma are shifting towards less toxic, shorter-duration regimens [21], those with poor prognosis disease respond poorly to conventional first-line treatment. The prognosis for this group of patients, even if surgical elimination of all macroscopic tumour is accomplished, is dismal, providing ample justification for the use of novel therapies even at initial diagnosis [16, 22, 23]. However, no active new agents have been identified for this disease; hence, the attempt in this study to maximise advantage from the judicious use of established agents.

In this pilot study from two collaborating centers, 30 patients were accrued within a reasonable time period (4 years). The group of patients was reasonably uniform in terms of management and the reported survival rates suggest that they were correctly selected as a ‘poor risk’ category. A significant caveat of the study was the inclusion of two heterogeneous groups of patients by location site e.g. those with extremity tumours and pulmonary metastases and those with tumours located in the axial skeleton. The relative preponderance of patients with pelvic tumours, along with the fact that most of them were older and debilitated, accounts in part for the low survival rates of the whole group.

The poor outcome for this group reflects both accurate selection of patients with poor prognosis and a failure to deliver effective therapy. This was despite patients being treated in a centre with extensive experience in the delivery of intensive chemotherapy and in the management of bone tumours. Delivery of chemotherapy at the planned doses was compromised in many, and wide surgical excision was only achieved in a minority.

The chemotherapy strategy was to use the most active drugs in maximum doses over a relatively short period. Renal impairment, mainly in those with tumours of the axial skeleton, often developed early, particularly effecting the delivery of ifosfamide and methotrexate.

In the present protocol ifosfamide was administered at a considerably higher dose and a more protracted schedule compared with other studies in similar groups of patients. Michelagnoli et al. [24] used ifosfamide at a total dose of 7.5 g/m² for 3 consecutive days, while Voûte et al. [25] used ifosfamide at a dose of 6 g/m² for 2 days. This dose escalation was based on evidence suggesting a positive dose–response curve for ifosfamide in soft tissue sarcomas and osteosarcomas [26, 27]. However, this high-dose schedule was not feasible, especially in patients with axial skeletal tumours, principally because of non-hematological toxicity. A signific-
ant reduction of GFR during therapy was recorded among patients with axial skeletal tumours (38% of patients) versus 8% of patients with extremity tumours. Other significant toxicities included reversible, severe hypokalaemia, hypomagnesaemia and encephalopathy (19% of courses) necessitating early discontinuation of treatment in three cases.

When clinical response was assessed separately between primary and metastatic disease the overall response rate recorded was 33% and 63%, respectively. The higher overall response rate documented in patients with metastatic disease (which is mostly soft tissue disease) reflects our inability to accurately assess the primary site by conventional radiological methods or by clinical examination as a consequence of the production of osteoid and new bone.

In our study the overall good histological response rate was disappointingly low at 30%. Responses among patients with extremity tumours were higher [5/14 patients (36%)]. Bacci et al. [16] reported a complete histological response rate of 24% and a good histological response rate of 48% in patients with extremity tumours with pulmonary metastases. In another study with a similarly heterogeneous cohort of patients, Voûte et al. [25] reported a category 1 response rate of 33%. The majority of patients, however, had extremity tumours (metastatic and non-metastatic), while a separate analysis of the group with pelvic and axial tumours demonstrated no good histological responses.

The 2- and 3-year survival rates of 50% and 21% for patients with metastatic disease at diagnosis are consistent with other reports in the literature. In a series of 23 patients with metastatic extremity tumours, Bacci et al. [28] reported a 2-year survival rate of 41%. In the series by Meyers et al. [7] (62 patients), the 3-year survival was 20% and in the series reported by Marina et al. [8] (18 patients), the 3-year survival was 30%. In a study by Michelagnoli et al. [24], in 15 relapsed or metastatic patients the 2- and 3-year survival rates were both 50%. However, in all of the above mentioned studies, except for the study by Bacci et al. [28], the primary site was not specified. In a recently published phase II study of the European Osteosarcoma Intergroup (45 patients), the 3-year survival rate for metastatic limb tumours was 30% [25].

Survival rates for patients with axial skeletal tumours were disappointing with a median survival of 13 months and 2- and 3-year survival rates of 19% and 13%, respectively. However, these did not differ from other recently reported studies. Voûte et al. [25] reported a median survival of 2 years and a 5-year survival rate of 41% in a similar group treated with cisplatin, ifosfamide and doxorubicin. Grimer et al. [29] reported a 5-year survival rate of 18% with a median survival of ~1 year in 36 patients with osteosarcoma of the pelvis. Finally, the Cooperative Osteosarcoma Study (COSS) Group reported a 5-year survival rate in a similar group of patients of 14% [11]. These data confirm that patients with pelvic tumours form a distinct group with a worse prognosis compared with patients with metastatic osteosarcoma of the extremities. They are usually older, and although many may undergo surgery to the primary site, they do not fare well, as reflected in the poor rates of local tumour control.

In our study, neither age nor site of the primary tumour were found to be important predictors of outcome. The log rank tests used to compare different age groups, and the extremity versus axial skeletal groups showed no evidence of a statistically significant difference ($P = 0.15$ and $P = 0.7$, respectively). In the study by Meyers et al. [7], age was a good predictor of outcome with older patients being more likely to survive. The results in that study, however, were not controlled for the primary site and, in addition, the distribution of the primary site according to age was not specified. In the study by Grimer et al. [29] of patients with pelvic osteosarcomas, those <20 years of age had a better 5-year survival when compared with the whole group of patients (33% versus 18%).

There is a strong correlation between degree of necrosis following preoperative chemotherapy and survival in non-metastatic osteosarcoma of the extremities [30]. A similar correlation, however, has not been extensively reported for the poor prognosis osteosarcoma group. In the present study, despite the small number of patients, there was evidence to suggest that a good histological response of the primary site, coupled with adequate excision margins, is associated with a superior survival outcome ($P = 0.03$).

The local recurrence pattern reported in this study was significantly higher among patients with axial skeletal tumours compared with those with extremity tumours (75% versus 42%). Although a separate analysis of survival according to the local recurrence pattern was not deemed necessary, it is evident from these results that the higher local recurrence pattern among patients with axial skeletal tumours may have contributed to the inferior survival rates recorded among this group.

The role of HDC in metastatic osteosarcoma patients and its impact on survival has not yet been fully explored. This approach deserves to be investigated in this group of patients where novel therapies are needed. The number of reported studies that have incorporated consolidation with high-dose therapy and stem-cell support for patients with metastatic, recurrent or refractory osteosarcoma is very limited [31–35]. The small number of studies may be the result of the increased difficulty of identifying agents that have activity against osteosarcoma and which can be intensified with the aid of stem-cell support. Both ifosfamide and doxorubicin, which are known to be active in osteosarcoma, have non-haematopoietic dose-limiting toxicities precluding them from any HDC protocols. In the present study, high-dose chemotherapy, although feasible in the group of patients with limb osteosarcoma, does not appear to be associated with a survival advantage when compared with other similar groups treated with conventional chemotherapy. The group of patients with axial skeletal tumours did not receive the intended megatherapy. A number of reasons accounted for this, such as early disease progression, unacceptable toxicity, poor performance status and
physician choice. Whether advancing the HDC schedule to an earlier stage of their treatment—before disease progression, or intolerable toxicity from conventional chemotherapy, or a further decline in their performance status occurs—would have a different impact on outcome is not known. However, the toxicity seen at the early stages of therapy suggests that this approach is not going to be an effective one.

Our results are in accordance with other studies which suggest that the prognosis of patients with metastatic and axial skeletal osteosarcoma is extremely poor. One of the primary endpoints of the study—to assess the feasibility of HDC—was accomplished. It is evident, however, that this approach is not obviously superior to other standard conventional chemotherapy regimens.

In conclusion, better therapeutic strategies are needed for the heterogeneous group of poor prognosis osteosarcoma. A better selection of patients (e.g. those with operable primaries and potentially resectable metastatic disease versus those with inoperable primary tumours and widespread metastatic disease) and tailoring therapy according to their performance status and disease extent might yield superior results. A greater understanding of the biological properties which distinguish these groups of osteosarcoma may provide additional information in the future. Finally, earlier detection, especially of pelvic tumours which tend to present at a late and unfortunately inoperable stage, as well as management in specialist centres with all necessary resources will hopefully have a positive impact on their survival.

References
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