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European Journal of Cancer 41 (2005) 225–230

European Journal of Cancer

www.ejconline.com

Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: a European Osteosarcoma Intergroup Study

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Received 3 August 2004; accepted 10 August 2004
Available online 30 September 2004

Abstract

There are limited data that define the role of chemotherapy in the treatment of high-grade spindle cell sarcomas of bone, other than osteosarcoma or malignant fibrous histiocytoma (MFH-B). This prospective study evaluates the effect of doxorubicin and cisplatin on these tumours. Thirty-seven patients, age ⩽65 years, with spindle cell sarcoma of bone, except osteosarcoma or MFH-B, were included. Chemotherapy consisted of doxorubicin and cisplatin every 3 weeks for six cycles. Resection was performed after three cycles. In 15 patients with metastases, response assessment showed three complete responses (CR), four stable disease (SD), five progression; three were not evaluable. Median time to progression was 30 months (95% Confidence Interval (CI), 8–51 months) for the operable non-metastatic patients; median survival 41 months (95% CI, 16–82 months). Median time to progression in the metastatic group was 10 months (95% CI, 0–18 months) and median survival was 14 months (95% CI, 4–45 months). This study suggests a limited role for doxorubicin and cisplatin in metastatic high-grade spindle cell sarcoma of bone, other than osteosarcoma or MFH-B cases.

Keywords: Bone neoplasms; Chemotherapy; Mesenchymal chondrosarcoma; Radiation sarcoma; Leiomyosarcoma

1. Introduction

Primary high-grade spindle cell sarcomas of the bone are rare malignancies, accounting for less than 0.5% of all cancers. The most common high-grade sarcoma of bone is osteosarcoma. The prognosis of osteosarcoma patients has been substantially improved since the introduction of aggressive combination chemotherapy as part of multi-modality management. There is comprehensive data reported in the literature on every aspect of chemotherapy in osteosarcoma patients. The European Osteosarcoma Intergroup (EOI), which is a collaborating intergroup between the European Organisation for Research and Treatment of Cancer (EORTC)-Soft Tissue

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doi:10.1016/j.ejca.2004.08.026

and Bone Sarcoma group, Medical Research Council, United Kingdom Children's Cancer Study Group and the International Society of Paediatric Oncology (SIOP), has conducted large randomised trials aimed at determining optimal regimens [1,2]. In these trials, doxorubicin and cisplatin have been proven to be of similar efficacy to other combinations of chemotherapy.

Spindle cell tumours other than osteosarcoma are extremely rare. The best characterised is malignant fibrous histiocytoma of the bone (MFH-B) and a number of reports suggest a similar pattern of chemosensitivity to that of osteosarcoma [3–7]. Information about systemic treatment for other high-grade primary bone sarcomas [8,9], such as dedifferentiated chondrosarcoma, angiosarcoma, or leiomyosarcoma is sparse.

In 1987, the EOI started a phase II study to investigate the activity of the combination of cisplatin and doxorubicin in high-grade spindle cell sarcomas of the bone, other than osteosarcoma. The doxorubicin and cisplatin regimen was standard treatment for osteosarcoma in the EOI since 1983. This paper reports the study results for tumours other than MFH-B, the latter having been previously reported [3].

2. Patients and methods

2.1. Study population

Eligible patients were aged 65 years or younger, had high-grade spindle cell sarcoma of bone, other than MFH-B or osteosarcoma, and had not received chemotherapy previously. Patients could have localised or metastatic sarcoma, but in all cases evaluable and/or measurable disease was required.

In patients with resectable tumours, preoperative chemotherapy had to start within 42 days after biopsy. Adequate renal function (serum creatinine <150 μmol/l, hepatic function (serum bilirubin <20 μmol/l) and bone marrow reserve (white blood cells (WBC) $>4\times10^9$ cells/l, platelets $>100\times10^9$ cells/l) were required.

Informed consent was obtained according to the local policies.

Patients who had received previous chemotherapy or undergone immediate surgical resection were not eligible. Patients with a low performance status (World Health Organisation (WHO) >2) and concomitant disease, which prevented adequate chemotherapy, were also excluded.

2.2. Trial design

The primary objective was to assess the value of doxorubicin and cisplatin in patients with high-grade spindle cell sarcoma of the bone, other than osteosarcoma or MFH-B. For patients with resectable tumours, pathological response, time to progression and overall survival were studied.

For patients with metastatic disease, the effects of treatment were evaluated by clinical/radiological assessment after two, four and six cycles of doxorubicin and cisplatin according to the criteria of the International Union Against Cancer (UICC). Both the toxicity profile of the doxorubicin and cisplatin combination and the complications from the surgical procedures were investigated.

2.3. Therapeutic regimen

The regimen was similar to that used in previous EOI studies in osteosarcoma [1,2] and MFH-B [3] patients and was six cycles at 3 weekly intervals of doxorubicin 25 mg/m^2 days 1–3, given by intravenous (i.v.) bolus and cisplatin 100 mg/m^2 given by 4-h infusion on day 1. Hydration and electrolyte support were used and have been described previously [1–3].

2.4. Dose modifications

The doses of doxorubicin and cisplatin were reduced by 15% in patients with WHO grade 3 haematological toxicity and by 30% in cases of grade 4 toxicity and/or serious infection or bleeding. The doxorubicin dose was reduced by 20% in patients with grade 3 or 4 mucositis. Doses were not adjusted for reversible renal toxicity, but cisplatin was not given if the serum creatinine level remained above 150 μmol/l.

Chemotherapy was delayed until haematological recovery (WBC count of $>3\times10^9$ cells/l, granulocyte count of $>1.5\times10^9$ cells/l, and platelet count of $>100\times10^9$ cells/l), with repeated blood cell counts performed at weekly intervals and doses dictated by the nadir haematological values. Chemotherapy was discontinued if recovery was not apparent after 3 weeks.

2.5. Pretreatment and follow-up investigations

Initial patient evaluations comprised history taking and a physical exam, performance status, blood counts, liver and kidney function tests, chest radiograph and computed tomographs (CT) of the lungs, X-ray and magnetic resonance imaging (MRI) of the affected bone and bone scintigraphy.

In patients with resectable tumours, chest radiography, CT lung scans and MRI of the affected bone were repeated just before surgery. In patients with metastases, the appropriate radiological investigations were repeated after two, four and six cycles.

After completion of treatment, all patients were followed at 6 week intervals for 12 months, 2 month inter-

vals for 18 months and 3–4 month intervals for up to 5 years and thereafter at the investigator's discretion until death.

2.6. Central Pathology review

Central review for both biopsy material and operative specimens was performed by a member of the pathology subcommittee of the EOI, consisting of pathologists with specific experience in bone tumour pathology. The methodology has been described previously [1–3]. The tumour was resected longitudinally in a plane through its widest part. An entire slab of this cut surface was divided into individually labelled blocks, decalcified, cut, and stained for histological examination. A clear lead-acetate sheet with 2×2 mm squares was placed over the slides, and each square was assessed for tumour viability and tumour damage. The total number of squares in each category was then used to calculate the percentage of the specimen that contained viable and damaged tumour. A good response was defined as less than 10% viable tumour cells.

2.7. Response criteria

The response for patients with resectable disease was assessed by studying the percentage of viable cells in the specimens. For metastatic disease, response was assessed according to UICC criteria.

2.8. Statistical methods

2.8.1. Statistical design

This study was designed to estimate accurately the response of patients with high-grade spindle cell sarcomas of the bone to treatment with cisplatin and doxorubicin. Both MFH-B patients and non-MFH patients were recruited; the formal statistical design of the study for MFH-B patients is documented in a previous report [3].

Non-MFH patients are known to be less common than MFH-B patients, and have varying histologies. As recruitment could not accurately be predicted for these patients, and as the analysis would be stratified by metastatic status, no formal requirements for the sample size were stipulated for these patients.

2.9. Endpoints

Response to treatment was the primary endpoint.

In both groups, time to progression, overall survival and the patient's side-effect profile were secondary endpoints. Time to progression and overall survival were measured from the start of chemotherapy and estimated by the Kaplan–Meier method. In the evaluation of time to progression, patients who died without progression were censored at the time of their death.

3. Results

Between April 1988 and October 1997, 37 patients with bone sarcomas, other than osteosarcoma or MFH-B, were entered in this EOI study.

3.1. Patient's characteristics

A variety of histological tumour types were encountered (Table 1). Twenty one patients had resectable localised tumours whereas 15 had detectable metastases and 1 an irresectable local recurrence. Twenty-five male and 12 female patients were included. The median age for the non-metastatic patients with resectable tumours was 38 years (17–60 years). In the group with metastases, the median age was 45 years (16–65 years). Performance status was WHO 0 in 12, WHO 1 in 18 patients, WHO 2 in 7 patients. Many of the tumours were localised outside of the limbs (Table 2). Sites of metastases, which were predominantly in the lung, are summarised in Table 3.

3.2. Toxicity of the chemotherapy

The regimen had substantial toxic effects; granulocytopenia and thrombocytopenia were frequent events

Table 1
Histopathological type of tumours included in the study

Cell type	Resectable non-metastatic	Other	Total
Dedifferentiated chondrosarcoma	2	7	9
Mesenchymal chondrosarcoma	2	5	7
High-grade spindle cell sarcoma NOS	5	1	6
Dedifferentiated parosteal osteosarcoma	1	0	1
Malignant peripheral nerve sheath tumour of bone	1	0	1
Leiomysarcoma	3	0	3
Radiation sarcoma	4	0	4
Paget's sarcoma	1	2	3
Fibrosarcoma	2	1	3
Total	21	16	37

NOS, not otherwise specified.

Table 2
Localisation of primary tumour

	Resectable non-metastatic	Other	Total
Femur	6	3	9
Tibia	6	–	6
Humerus	2	1	3
Ulna	1	–	1
Other	6[a]	12[b]	18
Total	21	16	37

[a] Pelvis, acetabulum, metatarsal, ilium, sacrum, sternal manubrium.
[b] Acetabulum, sacrum, chest wall, pelvis, mandible, rib, iliac crest, ischium.

Table 3
Pattern of metastases

Lung	12
Bone	2
Liver	2
Nodes	1
Unspecified	1

(Table 4). No patients had severe renal and/or hepatic impairment. There were no toxic deaths.

3.3. Surgery

Surgery was performed in nineteen of the twenty-one patients with tumours that were initially resectable. In eighteen patients, surgery took place after three cycles, in one patient after two cycles. The type of surgery is shown in Table 5. One patient refused surgery, one showed such progression of disease that surgery became impossible. Surgical resection was performed in one patient with metastatic disease. There were only a few postoperative complications (Table 6).

Table 4
Maximal toxicity occuring during chemotherapy per cycle

Who toxicity grade	3	4
Leucopenia	12	12
Thrombocytopenia	4	5
Granulocytopenia	6	24
Nausea/vomiting	16	3
Oral	7	0
Diarrhoea	3	0
Renal	0	0
Liver	0	0
Skin	0	0
Neurotoxiciy	0	0
Ototoxicity	2	0
Pulmonary	0	0
Alopecia	25	0
Cardiac	1	0
Infection	4	0
Other	6	1

Table 5
Type of surgery

Amputation	4
Conservative surgery and bone graft	4
Conservative surgery and prosthesis	7
Conservative surgery without reconstruction	1
Conservative surgery + bone graft + prosthesis	2
Subtotal sacral resection	1

Table 6
Post-operative complications

Deep infection (at surgical site)	1
Vascular	1
Neurological	2
Skin necrosis	1
Other	2 (*)

(*) Luxation prosthesis, titanium cyst.

3.4. Histopathological and radiological response to chemotherapy

All of the 20 resected specimens were available for assessment of the histological tumour response. Two specimens showed less than 10% morphological viable cells; in the remaining 18, more than 10% morphological viable remnant tumour could be seen. In patients with metastatic disease, radiological assessment showed three CR, no PR, four SD and five PD; three patients were not evaluable for response (Table 7).

3.5. Compliance with the protocol

Nineteen of the 37 patients received six cycles of chemotherapy. All but seven patients completed at least three cycles. The principal reason for early discontinuation was disease progression.

3.6. Survival

Median time to progression was 30 months (95% Confidence Interval (CI), 8–51 months) for the operable non-metastatic patients, with a median survival of 41 months (95% CI, 16–82 months). The 5-year survival rate for this group was 41%. Median time to progression in the inoperable and metastatic group was 10 months (95% CI, 0–18 months); median survival in this group was 14 months (95% CI, 4–45 months).

4. Discussion

Determining the optimal treatment for very rare tumours is difficult, even with the resources of a large co-operative group. Despite the heterogeneity within

Table 7
Chemotherapy effect (histopathology and radiology)

Histology	Response of primary tumour	Response of metastases
Dediff. chondrosarcoma	>10% v.c.	n.a.
Dediff. chondrosarcoma	>10% v.c.	n.a.
Dediff. chondrosarcoma	n.a.	n.a.
Dediff. chondrosarcoma	n.a.	Not evaluable
Dediff. chondrosarcoma	n.a.	SD
Dediff. chondrosarcoma	0–10% v.c	CR
Dediff. chondrosarcoma	n.a.	CR
Dediff. chondrosarcoma	n.a.	PD
Dediff. chondrosarcoma	n.a.	Not evaluable
Dediff. parosteal osteosarcoma	>10% v.c.	n.a.
Fibrosarcoma	>10% v.c.	n.a.
Fibrosarcoma	>10% v.c.	n.a.
Fibrosarcoma	n.a.	CR
Leiomyosarcoma	>10% v.c.	n.a.
Leiomyosarcoma	>10% v.c.	n.a.
Leiomyosarcoma	Local recurrence, progression	n.a.
Mesenchymal chondrosarcoma	>10% v.c.	n.a.
Mesenchymal chondrosarcoma	0–10% v.c.	n.a.
Mesenchymal chondrosarcoma	n.a.	PD
Mesenchymal chondrosarcoma	n.a.	SD
Mesenchymal chondrosarcoma	n.a.	PD
Mesenchymal chondrosarcoma	n.a.	SD
Mesenchymal chondrosarcoma	n.a.	PD
Neurosarcoma	>10% v.c.	n.a.
Paget's sarcoma	>10% v.c.	n.a.
Paget's sarcoma	n.a.	Not evaluable
Paget's sarcoma	n.a.	SD
Radiation sarcoma	>10% v.c.	n.a.
Radiation sarcoma	>10% v.c.	n.a.
Radiation sarcoma	>10% v.c.	n.a.
Radiation sarcoma	n.a.	n.a.
High-grade spindle cell sarcoma	>10% v.c.	n.a.
High-grade spindle cell sarcoma	>10% v.c.	n.a.
High-grade spindle cell sarcoma	>10% v.c.	n.a.
High-grade spindle cell sarcoma	>10% v.c.	n.a.
High-grade spindle cell sarcoma	n.a.	PD
High-grade spindle cell sarcoma	>10% v.c.	n.a.

n.a., not applicable; SD, stable disease; PD, progression; v.c., viable cells. Dediff., dedifferentiated, CR, complete response.

this series relating to the histological type, primary site, resectability and stage, a number of conclusions can be drawn. First, the rarity of spindle cell tumours of the bone, other than osteosarcoma and MFH-B, is demonstrated: over the study period, 52 MFH-B were entered in the same protocol and the Group was accruing 60 patients each year with operable osteosarcoma in neoadjuvant trials. Secondly, survival in those with localised tumours, while considerably better than those with metastatic disease, is unsatisfactory. Thirdly, chemotherapy had little impact on the outcome of those patients with metastases.

This EOI study was initiated to determine the value of doxorubicin and cisplatin in the treatment of spindle cell tumours of the bone, other than osteosarcoma or MFH-B. The results reported elsewhere for these drugs in the treatment of osteosarcoma [1,2] and MFH-B [3] are encouraging and most investigators accept the role of (neo) adjuvant chemotherapy in general in these histological subtypes [1–3].

The impact of chemotherapy on other histological entities is more difficult to determine. In the treatment of osteosarcoma, histologically judged response to preoperative chemotherapy has been widely validated as a prognostic indicator. It may be reasonable to extrapolate this to other tumour types, but there are no data which actively supports this proposal. Furthermore, in both osteosarcoma and Ewing's sarcoma, an excellent histological response does not confer absolute protection from relapse, and the converse, that a poor response may still be associated with long-term survival, is also true. Thus, despite the absence of histological response rates of >90%, a lack of benefit of chemotherapy for the patients reported here can only be suspected rather than proven. Nevertheless, the achievement of high rates of tumour damage may still be a useful surrogate of efficacy in testing new chemotherapy regimens in such rare diseases, where randomised studies are not practical.

Spindle cell sarcomas of the bone, other than osteosarcoma, occur in an older age group than osteosarcomas. The difficulties of delivering dose-intensive chemotherapy in adults compared with children is well recognised, but in this study most patients with operable tumours were able to receive at least three cycles of preoperative chemotherapy, suggesting that the poor outcome is due to primary tumour resistance rather than due to a failure to deliver the chemotherapy.

No advantage for any one of the histological subtypes studied could be determined because of the very small number of cases in each category. The literature contains occasional reports of responses to chemotherapy in mesenchymal chondrosarcoma [8] and dedifferentiated chondrosarcoma [9,10]. However, such reports have included only a few patients and the methods of response assessment vary. Our series has the advantage of uniform therapy and outcome measured by histological response, time to progression and overall survival. For those with localised resectable tumours, the time to progression was over 2 years, but survival after relapse was short. This may indicate both a particularly aggressive disease and ineffective treatment for recurrence. Although not statistically significant, the inferior median survival of 14 months for patients with unresectable or metastatic disease should be noted.

The choice of doxorubicin and cisplatin as chemotherapy was based on the activity of this combination in osteosarcoma, and preliminary reports of activity in MFH-B. Whether other agents would be more effective remains to be explored; the activity of drugs such as ifosfamide and methotrexate has not been determined, but will be the subject of future EOI studies.

Conflict of interest statement

All authors report no financial and personal relationship with other people or organisations that could influence this work.

References

1. Bramwell VHC, Burgers M, Sneath R, *et al*. A comparison of two short intensive chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol* 1992, **10**, 1579–1591.
2. Souhami RL, Craft AW, Eijken JW v/d, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997, **350**, 911–917.
3. Bramwell VHC, Steward WP, Nooij M, *et al*. Neoadjuvant chemotherapy with doxorubicin and cisplatin in malignant fibrous histiocytoma of bone: a European Osteosarcoma Intergroup study. *J Clin Oncol* 1999, **17**, 3260–3269.
4. Bacci G, Cervellati C, Picci P, *et al*. Adjuvant chemotherapy for localized malignant fibrous histiocytoma (MFH) of bone. Preliminary results. *Chem Oncol* 1981, **V**, 59–65.
5. Weiner M, Sedlis M, Johnston AD, *et al*. Adjuvant chemotherapy of malignant fibrous histiocytoma of bone. *Cancer* 1983, **51**, 25–29.
6. Urban C, Rosen G, Huvos AG, *et al*. Chemotherapy of malignant histiocytoma of bone. A report of five cases. *Cancer* 1983, **51**, 795–802.
7. Chawla SP, Benjamin RS, Abdul-Karim F, *et al*. Adjuvant chemotherapy of primary malignant fibrous histiocytoma of bone – prolongation of disease-free and overall survival. *Adjuv Ther Cancer* 1984, **IV**, 621–629.
8. Huvos AG, Rosen G, Dabska M, *et al*. Mesenchymal chondrosarcoma. A clinicopathological analysis of 35 patients with emphasis on treatment. *Cancer* 1983, **51**, 1230–1237.
9. Van Oosterom AT, Dirix LY. Chondrosarcoma and other rare bone sarcomas. *Curr Opin Oncol* 1990, **2**, 495–499.
10. Mitchell AD, Ayoub K, Mangham DC, Frimer RJ, Carter SR, Tillman RM. Experience in the treatment of dedifferentiated chondrosarcoma. *J Bone Joint Surg B* 2000, **82**, 55–61.