Synchronous multifocal osteosarcoma: Results in twelve patients treated with neoadjuvant chemotherapy and simultaneous resection of all involved bones

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Summary

Background: Multifocal osteosarcoma is a rare type of tumor which is always excluded from therapy trials and is therefore rarely investigated for prognosis and treatment.

Patients and methods: Twelve patients with synchronous multifocal osteosarcoma underwent neoadjuvant chemotherapy and, when feasible, simultaneous resection of involved bones.

Results: Four patients were unsuitable for resection and died 5–13 months (average 9 months) later. In eight patients all lesions were resected simultaneously. Four patients are disease-free at 15, 20, 24, and 60 months (average 29 months), and four relapsed and died at 12, 24, 30 and 36 months (average 30.5 months).

Conclusions: Chemotherapy associated with aggressive surgery may be useful. The histological response of different lesions in the same patient are strongly correlated, confirming that synchronous multifocal osteosarcoma is not originally multicentric but unicentric with bone metastases.

Key words: bone sarcomas, chemotherapy, metastasis, multicentric, osteosarcoma, surgery

Introduction

Multifocal osteosarcoma is an aggressive, symptomatic bone tumor with multiple foci in the skeleton, usually without lung disease. When multiple bone lesions are simultaneously present at diagnosis it is a 'synchronous multifocal osteosarcoma', while when the bone lesions appear at different intervals it is a 'metachronous multifocal osteosarcoma'. Whether these tumors are multicentric in origin or are bone metastases is debatable [1].

In localized osteosarcoma [2-4] the association of chemotherapy-surgery has unquestionably improved prognosis. Since clinical trials exclude multicentric tumors, no homogeneous treatment was administered, and the role of multiagent chemotherapy coupled with aggressive surgery has been poorly investigated.

Reported here are twelve cases of synchronous multicentric osteosarcoma treated at our institution between January 1990 and December 1994 following the standardized scheme: primary chemotherapy – if feasible simultaneous resection of all neoplastic lesions – adjuvant chemotherapy.

Patients and methods

The eligibility criteria were:

1. typical histological and radiological features of primary central high-grade osteosarcoma

2. tumor affecting two or more bones, no visceral involvement

3. age under 50 years.

Of the 405 patients with osteosarcomas diagnosed during the cited period, 12 (4.9%) were eligible. A family history of cancer was recorded in 4 instances, with only one typical case of Li-Fraumeni syndrome. There were 2 bone lesions in five patients, 3 in three and 4 in four (Table 1). All sought medical advice for symptoms of single lesions while the other sites were discovered during staging. Whether multiple skeletal lesions represent true multicentric tumors or metastatic foci is unknown, but the symptomatic lesion is arbitrarily defined as 'primary tumor' and the others 'secondary lesions'. All primary lesions were in the extremities. The 20 secondary lesions were: 9 in appendicular bones, 4 in ribs, 4 in the spine, and 3 in the pelvis. All cases were diagnosed by open biopsy, and the histotype was osteoblastic in 10 cases and fibroblastic in 2 cases. The primary tumor was evaluated by plain roentgenograms, technetium-99 methylene diphosphonate bone scan, angiogram, CT scan and MRI. Radiographically, the lesions were sclerotic in 8 cases and mixed in 4 cases. Metastatic disease was investigated by total bone scan and lung CT.

Preoperative chemotherapy was administered according to Protocol OS/N5 (Figure 1), consisting of intravenous methotrexate (MTX), adriamycin (ADM), ifosfamide (IFO), and intra-arterial cisplatinum (CDP). Patients were restaged and, if feasible, both primary and metastatic lesions were excised simultaneously.

Surgery, resection or amputation, and reconstruction, prosthesis, allograft or vascularized graft, were chosen according to tumor site and extent, age and desired life style.

Tumor response to chemotherapy was defined as 'good' when necrosis was 90% or more, and 'poor' when it was lower than 90%.

Postoperative chemotherapy (Figure 1) was started two weeks after surgery.
### Table 1. Summary of the cases in the study.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/age</th>
<th>Bones involved</th>
<th>Surgery</th>
<th>Reconstruction</th>
<th>Necrosis (%)</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PE</td>
<td>M/12</td>
<td>Dist Femur L*</td>
<td>Resection</td>
<td>Prosthesis</td>
<td>98%</td>
<td>NED 60 mos</td>
</tr>
<tr>
<td>3. M.M.</td>
<td>M/11</td>
<td>Prox Tibia R*</td>
<td>Resection</td>
<td>Allograft</td>
<td>100%</td>
<td>Death 49 mos</td>
</tr>
<tr>
<td>4. C.S.</td>
<td>M/18</td>
<td>Dist Femur R*</td>
<td>Resection</td>
<td>Prosthesis</td>
<td>85%</td>
<td>Secondary lesions spine &amp; pelvis at 30 mos.</td>
</tr>
<tr>
<td>5. M.A.</td>
<td>F/11</td>
<td>Dist Femur L*</td>
<td>Resection</td>
<td>Prosthesis</td>
<td>30%</td>
<td>Death at 42 mos</td>
</tr>
<tr>
<td>6. B.F.</td>
<td>M/12</td>
<td>Dist Femur*</td>
<td>No surgery</td>
<td>Prosthesis</td>
<td>20%</td>
<td>Secondary lesions lung &amp; spine at 24 mos.</td>
</tr>
<tr>
<td>7. C.C.</td>
<td>M/24</td>
<td>Dist Femur*</td>
<td>Pelvis</td>
<td>Prosthesis</td>
<td></td>
<td>Death at 13 mos</td>
</tr>
<tr>
<td>8. C.F.</td>
<td>M/2</td>
<td>Dist Tibia R*</td>
<td>Rib, Spine</td>
<td>Prosthesis</td>
<td></td>
<td>Death at 6 mos</td>
</tr>
<tr>
<td>9. O.M.</td>
<td>F/17</td>
<td>Dist Femur R*</td>
<td>Pelvis, Spine</td>
<td>Prosthesis</td>
<td></td>
<td>Death at 12 mos</td>
</tr>
<tr>
<td>10. M.L.</td>
<td>M/7</td>
<td>Dist Femur L*</td>
<td>Prox Tibia L</td>
<td>Prosthesis</td>
<td>91%</td>
<td>NED at 24 mos</td>
</tr>
<tr>
<td>11. F.R.</td>
<td>F/29</td>
<td>Prox Femur L*</td>
<td>Rib</td>
<td>Resection</td>
<td>20%</td>
<td>NED at 20 mos</td>
</tr>
<tr>
<td>12 G.R.</td>
<td>M/18</td>
<td>Dist Femur R*</td>
<td>Prox Tibia R</td>
<td>Prosthesis</td>
<td>85%</td>
<td>NED at 15 mos</td>
</tr>
</tbody>
</table>

* Primary lesion.
NED = no evidence of disease.

| 0 | 1   | 4 | 5   | 8   | 12      | 16| 19| 22| 25| 26| 29| 32| 35| 36| 39| 42| 45|   |   |   |   |   |   |   |   |   |   |   |   |   |

**Figure 1.** Chemotherapy regimen OS/N5.
M = methotrexate 12 g/m² i.v., 4-hour infusion plus leucovorin rescue; P-A = cisplatin 40 mg/m² daily i.v., days 1–2–3, 72-hour continuous infusion adriamycin 60 mg/m² i.v., 8-hour infusion, day 3; I-P = ifosfamide 3 g/m² daily i.v., 1-hour infusion plus MESNA, days 1–2 cisplatin 40 mg/m² daily i.v., 72-hour continuous infusion, days 3–4–5; I-A = ifosfamide 3 g/m²/day i.v., 1-hour infusion plus MESNA, days 1–2 Adriamycin 60 mg/m² i.v., 8-hour infusion, day 3; A = Adriamycin 45 mg/m² daily i.v., 6-hour infusion, day 1–2; P = cisplatin 50 mg/m² daily i.v., 72-hour continuous infusion; days 1–2–3; I = Ifosfamide 2 g/m² daily i.v., 1-hour infusion plus MESNA; days 1–2–3–4–5.

**Results**

After preoperative chemotherapy one patient had radiological progression with increased tumor volume, new bone lesions and lung metastases (case 8), and three (cases 6, 7, 9) remained unchanged. These four cases, judged unsuitable for resection of the secondary lesions, were treated with palliative radiotherapy. The remaining eight patients showed a clinical and radiological response. Pain when present decreased or disappeared. The 'primary tumor' when palpable decreased in size, serum alkaline phosphatase regressed to normal, and an increased density was radiographically seen in the tumor.

These 8 patients underwent simultaneous surgery of the primary and secondary lesions. Surgery of the primary tumor was limb salvage in 7 and amputation in 1. The 11 secondary lesions were all resected but one. In 14 cases reconstruction was necessary (12 prostheses and 2 allografts).

The histological response of the primary tumor to chemotherapy was good in 5 cases and poor in 3, while in the 11 secondary lesions the response was good in 5 lesions and poor in 6. Although CDP was delivered...
intra-arterially, there was a surprising concordance between the histological response of the different lesions in the same patient. All three cases with poor response of the primary tumor had the same poor response in the 4 secondary lesions. Three of the 5 patients with a good response of the primary tumor, also had good necrosis in the secondary lesions. Of the remaining 2 patients one had a poor necrosis in the secondary lesion and 2 in the other were good and 1 poor.

As of March 1996, with 15 to 74 months of follow-up (average 38.5 months), the four unoperated patients had died at 5, 6, 12 and 13 months. Four of the 8 patients simultaneously resected for neoplastic foci, were disease-free 18, 20, 24 and 60 months after the beginning of treatment. Four relapsed, one with new lesions in uninvolved bones, two with lung and bone metastases and one with lung metastases. The average time to relapse was 25 months (range 12-49 months). These four patients had not received uniform treatments and died 6, 6, 12 and 13 months after relapse.

Conclusion

In unicentric osteosarcoma without detectable metastases at diagnosis the chemotherapy-surgery association has been thoroughly studied and shown to improve the cure rate by 60%-70% compared to 10%-20% after local treatment alone [2-4]. In patients with pulmonary metastases at presentation [5-7] as in those with localized disease who relapse after adjuvant or neoadjuvant treatment [8] aggressive resection of pulmonary metastases has lengthened survival, probably increasing the cure rate. The role of chemotherapy combined with aggressive surgery has not been investigated in patients with synchronous multifocal osteosarcoma which is considered a fatal disease within a year. The results reported in this study seem to demonstrate that the chemotherapy-surgery combination may be effective. In fact, 8 of 12 patients were apparently rendered disease-free and of these 4 are still disease-free 18 to 60 months after the beginning of treatment. The histological response to chemotherapy of the different lesions simultaneously resected was evaluated. Although a preoperative drug (CDP) was delivered intra-arterially, the comparison showed a surprising concordance in 6 of the 8 evaluable cases. This finding warrants comment. In the neoadjuvant treatment of unifocal osteosarcoma without detectable metastases at presentation, the primary tumor's histologic response to chemotherapy is strictly correlated to prognosis [2, 4]. This means that both the primary tumor and the micrometastases, which are the targets of chemotherapy, have the same chemosensitivity. This assumption seems confirmed by a previous study [6] in which there was a strong correlation between the histologic response of the primary and secondary tumors in 7 of 9 patients with unifocal osteosarcoma with lung metastases at presentation who were treated with primary chemotherapy followed by simultaneous resection of all detectable lesions. Meyers et al. [7] likewise found an apparent correlation between the response of the primary and secondary tumors in 13 of 14 patients with metastatic osteosarcoma at presentation who were treated by chemotherapy followed by subsequent resection of all detectable lesions. This supports the theory that the bone lesions are not multicentric but are probably bone metastases of a unicentric tumor.

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References

3. Bacci G, Picci P, Ferrari S et al. Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 144 patients preoperatively treated with high-dose methotrexate (i.v.) followed by cisplatinum (i.a.) and adriamycin (i.v.). Cancer 1993; 72: 3227-38.

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