OSTEOSARCOMA

Executive Summary

Osteosarcoma is the most common primary malignant bone tumor in children and young adults and accounts for 5% of all pediatric malignancies. It is a very aggressive type of cancer, but the majority of patients can be cured with a combination of chemotherapy and surgery. The standard regimen of chemotherapy is a combination of doxorubicin, cisplatin, and methotrexate. In limited resource settings, a combination of doxorubicin, carboplatin and ifosfamide may be considered. In addition, complete surgical resection of the primary bone tumor and all detectable metastatic lesions should be pursued. Radiation therapy does not have a role in the primary treatment of conventional osteosarcoma. The overall survival for children with localized disease is approximately 70%, while those with metastatic disease have an outcome close to 20%.

Public Health Relevance

While osteosarcoma is a relatively rare cancer, it is the eighth most common cancer in children and adolescents and it is the most common of the bone cancer (1). In 2009, a US-based study used data collected in several countries from 1968-1997 to determine the global incidence and distribution of osteosarcoma in children. These data estimated the global incidence rate to be between 3 to 4.5 cases per 1 million children, adolescents, and young adults (0-24 years of age) per year (2). The incidence rates were estimated to be relatively consistent throughout the world, with Italy, parts of Latin America, Sudan, and Uganda reporting slightly higher rates than in other regions. In those aged 0 to 24, osteosarcoma affects males at a rate of 3–5 per million and females at a rate of 2-4 per million (2). The onset of osteosarcoma tends to occur at younger ages in females than in males around the world. The incidence in the US in 2009 was found to be highest among Asian and Pacific Islander ethnic groups, suggesting that these groups are more susceptible to the disease (2). A possible risk factor is rapid bone growth, which suggests a link between adolescent growth spurts and the onset of the disease (1).

Requirements for diagnosis, treatment, and monitoring

**Diagnostics:** Histologic analysis of tumor tissue obtained by biopsy is required for diagnosis. Biopsy should be undertaken by an orthopedic surgeon experienced in orthopedic oncology, and who will likely perform the definitive surgery. Core needle biopsy by an interventional radiologist may be performed after discussion with the orthopedic surgeon about the appropriate biopsy tract.

**Testing:** Plain radiographs of the primary site are the initial investigation of choice in a patient with symptoms suggestive of a bone tumor. Once osteosarcoma is suspected, a contrast enhanced MRI of the entire length of the involved bone should be obtained (3). There are no specific blood
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tests for osteosarcoma, but lactate dehydrogenase and alkaline phosphatase levels may serve as a surrogate to track tumor burden. Additional imaging studies should be obtained at diagnosis to assess the extent of primary tumor and for the presence of metastatic disease. Computed tomography scan of the chest and radionuclide bone scan are used to detect lung (most common) and bone metastases, respectively (4,5). Organ function measurements prior to starting chemotherapy include complete blood counts, liver function tests, renal function tests, evaluation of hearing capacity (audiogram) and cardiac function (commonly by echocardiogram to estimate ejection and shortening fractions).

**Administration and Care of Patients:** Chemotherapy should be administered in a cancer center with capacity for intravenous chemotherapy infusion and monitoring. Cisplatin can cause severe nausea and vomiting and requires administration of prophylactic anti-emetics. It is preferable to administer chemotherapy using a centrally placed intravenous catheter. Doxorubicin extravasation can lead to local tissue injury and necrosis. Methotrexate-containing regimens require frequent monitoring of methotrexate levels, intravenous hydration, urinary alkalinization and folic acid rescue. Due to the high cumulative dose of doxorubicin in osteosarcoma treatment regimens and the subsequent risk of cardiac toxicity, co-administration of dexrazoxane should be strongly considered (when available). Supportive care with G-CSF administration may be required to ensure timely therapy, especially towards the end of treatment.

Patients should be monitored for treatment response and adverse effects of therapy. Disease evaluation scans should be performed pre-surgery and at approximately every 3 months. Patients should be monitored regularly for bone marrow suppression with blood counts, hearing loss with audiological examination, cardiac dysfunction with echocardiogram, and for liver and renal toxicity.

**Overview of Regimens**

The following tables include basic information on administration and dosing for MAP and OS99, and exclude ancillary medications pertaining to the management of side effects.

**Standard Regimens (of equivalent efficacy)**

**MAP: 6 cycles**

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
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<th>5</th>
<th>6</th>
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<td>M</td>
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**Surgery**

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<th>16</th>
<th>17</th>
<th>20</th>
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Anthracycline cumulative dose: 450 mg/m²
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**OS99: 12 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Dosage Details</th>
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<tbody>
<tr>
<td>Doxorubicin (D)</td>
<td>Intravenous infusion</td>
<td>25 mg/m² days 1,2,3 or days 1,2 (see below)</td>
</tr>
<tr>
<td>Carboplatin (C)</td>
<td>Intravenous infusion</td>
<td>See dose calculation below</td>
</tr>
<tr>
<td>Ifosfamide* (I)</td>
<td>Intravenous infusion</td>
<td>2.65 g/m² days 1,2,3</td>
</tr>
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<table>
<thead>
<tr>
<th>Week 0</th>
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<th>6</th>
<th>9</th>
<th>14</th>
<th>17</th>
<th>20</th>
<th>23</th>
<th>26</th>
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<tr>
<td>Chemo</td>
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Anthracycline cumulative dose: 375 mg/m² (25 mg/m² days 1,2,3 in one cycle prior to surgery and 25 mg/m² days 1,2 in six cycles after surgery)

Carboplatin dose is calculated using the formula: dose (mg/m²) = 8 × [(0.93 × GFR in ml/min/m²) + 15]

*Administration of ifosfamide requires the accompanying drug, mesna.

In addition to chemotherapy described above, patients who present with metastatic disease in the lungs should undergo surgical resection of all pulmonary nodules if possible. This procedure is usually performed after administration of neoadjuvant chemotherapy.

**Review of Benefits and Harms**

**Benefits**

Osteosarcoma occurs in adolescents and young adults, and as such curative regimens may result in many life years gained. Before the use of chemotherapy, surgical resection resulted in only 20% survival (6). Even after complete surgical resection by amputation in localized disease, the majority of patients developed clinically detectable pulmonary lesions and died. This indicated that microscopic lung disease was present in most patients at diagnosis. The utility of chemotherapy was proven conclusively when a randomized controlled trial showed 17% event free survival (EFS) in the surgery-only arm and 66% EFS in the adjuvant chemotherapy arm (7). The MAP regimen remains the standard of care for localized osteosarcoma (6). OS99 regimen was designed to simplify the management of osteosarcoma in developing countries and did not include high dose methotrexate or cisplatin (9). The survival outcomes were comparable to the MAP regimen. The addition of the immunomodulatory agent muramyl tripeptide (MTP) to the MAP regimen was investigated by the Children’s Oncology Group (10). The 6-year overall survival for localized osteosarcoma patients was 78% in the MTP arm compared to 70% in the MAP only arm. Based on this study, MTP is approved for use in combination with chemotherapy for upfront treatment of localized osteosarcoma in Europe and other countries (but was rejected by the FDA in the United States, thus it has not be recommended by the UICC review). In contrast, the prognosis for metastatic osteosarcoma remains dismal with overall survival between
20% -30%. In addition to chemotherapy, complete surgical resection is critical for survival benefit. In one study, patients who underwent complete surgical resection had an overall survival of 65% compared to 15% for those who underwent incomplete resection (11). Survival is highly dependent on the amount of tumor necrosis following neo-adjuvant chemotherapy, as determined by comprehensive histological analysis of the resected tumor.

**Harms and Toxicity Considerations**

Nausea, vomiting, myelosuppression, alopecia and mucositis are common to all chemotherapy regimens for osteosarcoma (12). Sepsis is the most serious acute complication that may lead to death. Cisplatin can cause ototoxicity and nephrotoxicity. Cisplatin exposure may also lead to infertility. The cumulative doxorubicin dose is relatively high in most regimens and may result in cardiac dysfunction in up to 4% of study subjects (13). Inability to adequately excrete high dose methotrexate may result in acute renal failure and severe mucositis (14). Ifosfamide administration may result in acute neurotoxicity, which may manifest as weakness, altered mental status and seizures (15). The cumulative incidence of second malignant neoplasm in osteosarcoma survivors at 25 years was 5.4% (16).

**Systematic Reviews**

The following reviews and analyses summarize the literature supporting the use of MAP, OS99 and MAP + MTP regimens for osteosarcoma.


**Abstract:** We conducted a randomized controlled trial to determine whether intensive multi-agent adjuvant chemotherapy improves the chances of relapse-free survival in patients with non-metastatic high-grade osteosarcoma of the extremity, as compared with concurrent controls. After undergoing definitive surgery, 36 patients were randomly assigned to adjuvant chemotherapy or to observation without adjuvant treatment. At two years the actuarial relapse-free survival was 17 percent in the control group, similar to that found in studies before 1970, and 66 percent in the adjuvant-chemotherapy group (P less than 0.001). Similar results were observed among 77 additional patients who declined to undergo randomization but who elected observation or chemotherapy. We conclude that the natural history of osteosarcoma of the extremity has remained stable over the past two decades, that adjuvant chemotherapy increases the chances of relapse-free survival of patients with high-grade osteosarcoma, and that it should be given to all such patients.


**Abstract:** PURPOSE: To compare three-drug chemotherapy with cisplatin, doxorubicin, and methotrexate with four-drug chemotherapy with cisplatin, doxorubicin, methotrexate,
and ifosfamide for the treatment of osteosarcoma. To determine whether the addition of muramyl tripeptide (MTP) to chemotherapy enhances event-free survival (EFS) and overall survival in newly diagnosed patients with osteosarcoma. PATIENTS AND METHODS: Six hundred sixty-two patients with osteosarcoma without clinically detectable metastatic disease and whose disease was considered resectable received one of four prospectively randomized treatments. All patients received identical cumulative doses of cisplatin, doxorubicin, and methotrexate and underwent definitive surgical resection of primary tumor. Patients were randomly assigned to receive or not to receive ifosfamide and/or MTP in a 2 x 2 factorial design. The primary end points for analysis were EFS and overall survival. RESULTS: In the current analysis, there was no evidence of interaction, and we were able to examine each intervention separately. The chemotherapy regimens resulted in similar EFS and overall survival. There was a trend toward better EFS with the addition of MTP (P = .08). The addition of MTP to chemotherapy improved 6-year overall survival from 70% to 78% (P = .03). The hazard ratio for overall survival with the addition of MTP was 0.71 (95% CI, 0.52 to 0.96). CONCLUSION: The addition of ifosfamide to cisplatin, doxorubicin, and methotrexate did not enhance EFS or overall survival for patients with osteosarcoma. The addition of MTP to chemotherapy resulted in a statistically significant improvement in overall survival and a trend toward better EFS.


Abstract: PURPOSE: To determine whether the addition of ifosfamide and/or muramyl tripeptide (MTP) encapsulated in liposomes to cisplatin, doxorubicin, and high-dose methotrexate (HDMTX) could improve the probability for event-free survival (EFS) in newly diagnosed patients with osteosarcoma (OS). PATIENTS AND METHODS: Six hundred seventy-seven patients with OS without clinically detectable metastatic disease were treated with one of four prospectively randomized treatments. All patients received identical cumulative doses of cisplatin, doxorubicin, and HDMTX and underwent definitive surgical resection of the primary tumor. Patients were randomly assigned to receive or not to receive ifosfamide and/or MTP in a 2 double dagger 2 factorial design. The primary end point for analysis was EFS. RESULTS: Patients treated with the standard arm of therapy had a 3-year EFS of 71%. We could not analyze the results by factorial design because we observed an interaction between the addition of ifosfamide and the addition of MTP. The addition of MTP to standard chemotherapy achieved a 3-year EFS rate of 68%. The addition of ifosfamide to standard chemotherapy achieved a 3-year EFS rate of 61%. The addition of both ifosfamide and MTP resulted in a 3-year EFS rate of 78%. CONCLUSION: The addition of ifosfamide in this dose schedule to standard chemotherapy did not enhance EFS. The addition of MTP to chemotherapy might improve EFS, but additional clinical and laboratory investigation will be necessary to explain the interaction between ifosfamide and MTP.

**Abstract:** BACKGROUND: The standard treatment of osteosarcoma includes cisplatin and high-dose methotrexate (HDMTX); both agents exert significant toxicity, and HDMTX requires complex pharmacokinetic monitoring and leucovorin rescue. In the previous OS91 trial, the treatment of localized disease with carboplatin, ifosfamide, doxorubicin, and HDMTX yielded outcomes comparable to those of cisplatin-based regimens and caused less toxicity. To build on this experience, the authors conducted a multi-institutional trial (OS99) that evaluated the efficacy of carboplatin, ifosfamide, and doxorubicin without HDMTX in patients with newly diagnosed, localized, resectable osteosarcoma. METHODS: Treatment was comprised of 12 cycles of chemotherapy administered over 35 weeks: 3 cycles of carboplatin (dose targeted to area under the concentration-time curve of 8 mg/mL × min on Day 1) and ifosfamide (at a dose of 2.65 g/m(2) daily ×3 days) and 1 cycle of doxorubicin (at a dose of 25 mg/m(2) daily ×3 days) before surgical resection, followed by 2 additional cycles of the combination of carboplatin and ifosfamide and 3 cycles each of doxorubicin (25 mg/m(2) daily ×2 days) combined with ifosfamide or carboplatin. RESULTS: A total of 72 eligible patients (median age, 13.4 years) were enrolled between May 1999 and May 2006. Forty of the 66 (60.6%) evaluable patients had good histologic responses (>90% tumor necrosis) to preoperative chemotherapy. The estimated 5-year event-free survival rate was 66.7% ± 7.0% for the OS99 trial compared with 66.0% ± 6.8% for the OS91 trial (P = .98). The estimated 5-year survival rate was 78.9% ± 6.3% for the OS99 trial and 74.5% ± 6.3% for the OS91 trial (P = .40). CONCLUSIONS: The regimen used in the OS99 trial was found to produce outcomes comparable to those of cisplatin-containing or HDMTX-containing regimens. This therapy offers a good alternative for patients, particularly those who demonstrate an intolerance of HDMTX, and for institutions that cannot provide pharmacokinetic monitoring for MTX.


**Abstract:** PURPOSE: Successful therapeutic interventions to prevent disease progression in patients with non-metastatic osteosarcoma have included surgery with adjuvant chemotherapy. Presurgical chemotherapy has been advocated for these patients because of putative improvement in event-free survival (EFS). The advantages of presurgical chemotherapy include early administration of systemic chemotherapy, shrinkage of primary tumor, and pathologic identification of risk groups. The theoretic disadvantage is that it exposes a large tumor burden to marginally effective chemotherapy. The contribution of chemotherapy and surgery timing has not been tested rigorously. **PATIENTS AND METHODS:** Between 1986 and 1993, we conducted a prospective trial in patients with non-metastatic osteosarcoma who were assigned randomly to immediate surgery or presurgical chemotherapy. Except for the timing of surgery (week 0 or 10), patients received 44 weeks of identical combination chemotherapy that included high-dose methotrexate with leucovorin rescue, doxorubicin, cisplatin, bleomycin,
cyclophosphamide, and dactinomycin. RESULTS: One hundred six patients were enrolled onto this study. Six were excluded from analysis. Of the remaining 100 patients, 45 were randomly assigned to immediate chemotherapy, and 55 were randomly assigned to immediate surgery. Sixty-seven patients remain disease-free. At 5 years, the projected EFS +/- SE is 65% +/- 6% (69% +/- 8% for immediate surgery and 61% +/- 8% for presurgical chemotherapy; P = .8). The treatment arms had similar incidence of limb salvage (55% for immediate surgery and 50% for presurgical chemotherapy).

CONCLUSION: Chemotherapy was effective in both treatment groups. There was no advantage in EFS for patients given presurgical chemotherapy.


Abstract: PURPOSE: We compared two chemotherapy regimens that included methotrexate (MTX), cisplatin (CDP), and doxorubicin (ADM) with or without ifosfamide (IFO) in patients with non-metastatic osteosarcoma of the extremity.

PATIENTS AND METHODS: Patients age ≤ 40 years randomly received regimens with the same cumulative doses of drugs (ADM 420 mg/m(2), MTX 120 g/m(2), CDP 600 mg/m(2), and IFO 30 g/m(2)) but with different durations (arm A, 44 weeks; arm B, 34 weeks). IFO was given postoperatively when pathologic response to MTX-CDP-ADM was poor (arm A) or given in the primary phase of chemotherapy with MTX-CDP-ADM (arm B). End points of the study included pathologic response to preoperative chemotherapy, toxicity, and survival. Given the feasibility of accrual, the statistical plan only permitted detection of a 15% difference in 5-year overall survival (OS).

RESULTS: From April 2001 to December 2006, 246 patients were enrolled. Two hundred thirty patients (94%) underwent limb salvage surgery (arm A, 92%; arm B, 96%; P = .5). Chemotherapy-induced necrosis was good in 45% of patients (48% in arm A, 42% in arm B; P = .3). Four patients died of treatment-related toxicity (arm A, n = 1; arm B, n = 3). A significantly higher incidence of hematologic toxicity was reported in arm B. With a median follow-up of 66 months (range, 1 to 104 months), 5-year OS and event-free survival (EFS) rates were not significantly different between arm A and arm B, with OS being 73% (95% CI, 65% to 81%) in arm A and 74% (95% CI, 66% to 82%) in arm B and EFS being 64% (95% CI, 56% to 73%) in arm A and 55% (95% CI, 46% to 64%) in arm B. CONCLUSION: IFO added to MTX, CDP, and ADM from the preoperative phase does not improve the good responder rate and increases hematologic toxicity. IFO should only be considered in patients who have a poor histologic response to MTX, CDP, and ADM.


Abstract: Long-term outcome for patients with high-grade osteosarcoma has improved with the addition of systemic chemotherapy, but subsequent progress has been less marked. Modern, multiagent, dose-intensive chemotherapy in conjunction with surgery achieves a 5-year event-free survival of 60-70% in extremity localized, non-metastatic
disease. A major, as yet unsolved, problem is the poor prognosis for metastatic relapse or recurrence, and for patients with axial disease. This article reviews the current state of the art of systemic osteosarcoma therapy by focusing on the experiences of cooperative osteosarcoma groups. Also, we shed light on questions and challenges posed by the aggressiveness of the tumor, and we consider potential future directions that may be critical to progress in the prognosis of high-grade osteosarcoma.

**Recommendations**

The reviewers recommend the incorporation of osteosarcoma treatment options into the WHO Model List of Essential Medicines, and recommend specifically that carboplatin, cisplatin, and ifosfamide be added for pediatric indications to the core Essential Medicines List.

**Medicines proposed for Section 8.2 of the Child EML**

Carboplatin  
Cisplatin  
Ifosfamide
References


