Osteosarcoma – EMLc

The application sought the addition of doxorubicin, cisplatin, methotrexate, carboplatin and ifosfamide to the core list of Essential Medicines for Children for the treatment of osteosarcoma.

The Committee noted that doxorubicin and methotrexate are currently included on the complementary list of the EMLc for other indications.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Osteosarcoma is the most common primary malignant bone tumour in children and young adults and accounts for 3–5% of all paediatric malignancies. It is a very aggressive type of cancer, but most 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 tumour and all detectable metastatic lesions should be pursued. Radiation therapy does not have a role in the primary treatment of conventional osteosarcoma. The 5-year survival rate for children with localized disease is 60–80%; while for those with metastatic disease the 5-year survival rate is about 15% to 30% *(1)*. In metastatic disease, survival is about 40% if the cancer has spread only to the lungs, or if all of the metastases and primary tumour can be surgically removed.

Public health relevance

While osteosarcoma is relatively rare, it is the eighth most common cancer in children and adolescents and the most common bone cancer *(2)*. A 2009 study used data collected on five continents to determine the global incidence and distribution of osteosarcoma in children. Annual global incidence was estimated to be 3–5 cases per 1 million children, adolescents and young adults (0–24 years of age) *(3)*. Incidence was relatively consistent throughout the world, with Italy, parts of Latin America, Sudan, and Uganda reporting slightly higher rates than other regions. Among those aged 0 to 24 years, osteosarcoma affects males at a rate of 3–5 per million and females at 2–4 per million *(3)*. Peak incidence (about 8.5 cases per million per year) occurs in young men aged 15–19 years. The onset of osteosarcoma tends to occur at younger ages in females than in males. A possible risk factor is rapid bone growth, which suggests a link between adolescent growth spurts and disease onset *(2)*.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Histological analysis of tumour tissue obtained by biopsy is required for diagnosis. Biopsy should be undertaken by an orthopaedic surgeon experienced in orthopaedic oncology, who will probably also perform the definitive surgery. Core needle biopsy by an interventional radiologist may be performed after discussion with the orthopaedic 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 tumour. Once osteosarcoma is suspected, contrast-enhanced magnetic resonance imaging of the entire length of the involved bone should be performed *(4)*. There are no specific blood tests for osteosarcoma, but lactate dehydrogenase and alkaline phosphatase levels may serve as a surrogate to track tumour burden. Additional imaging studies should be carried out at diagnosis to assess the extent of the primary tumour and the presence of metastatic disease; computerized tomography scan of the chest and radionuclide bone scan are used to detect lung and bone metastases, respectively *(5, 6)*. Organ function measurements before the start of chemotherapy include complete blood counts, liver function tests, renal function tests, evaluation of hearing capacity and cardiac function.

Administration and care of patients

Chemotherapy should be administered in a cancer centre with capacity for intravenous chemotherapy infusion and monitoring. Cisplatin can cause severe nausea and vomiting and requires administration of prophylactic antiemetics. 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 folinic acid rescue. Supportive care with administration of granulocyte colony-stimulating factor 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 preoperatively and then approximately every 3 months. Patients should be monitored regularly for bone marrow suppression with blood counts, for hearing loss with audiological examination, for cardiac dysfunction with echocardiogram, and for liver and renal toxicity.

Overview of regimens

The following sections include basic information on administration and dosing for MAP (high-dose methotrexate (HDMTX), cisplatin, and doxorubicin) and OS99 (carboplatin, ifosfamide, and doxorubicin) chemotherapy regimens; no details are given of ancillary medications pertaining to the management of adverse events.

Standard regimens

- **MAP (6 cycles)**
  - doxorubicin (A) 37.5 mg/m^2 IV infusion on days 1 and 2 of weeks specified below (cumulative anthracycline dose 450 mg/m^2)
  - cisplatin (P) 60 mg/m^2 IV infusion on days 1 and 2 of weeks specified below
  - methotrexate (M) 12 g/m^2 IV infusion given over 4 hours in weeks specified below

Week	1	4	5	6	9	10		12	15	16	17	20	21	22	24	25	26	28	29
Chemo	A P	M	M	A P	M	M	**Surgery**	A P	M	M	A P	M	M	A	M	M	A	M	M

- **OS99 (12 cycles)**
  - doxorubicin (D) 25 mg/m^2 IV infusion on days 1, 2 and 3 in one cycle before surgery and on days 1 and 2 in six cycles after surgery of weeks specified below (cumulative anthracycline dose: 375 mg/m^2)
  - carboplatin (C) IV infusion on day 1 of weeks specified below (dose calculated using the formula: 8× [(0.93 × glomerular filtration rate in ml/min per m^2) +15]
  - ifosfamide[1] (I) 2.65 g/m^2 IV infusion on days 1, 2 and 3 of weeks specified below

Week	**0**	**3**	**6**	**9**		**14**	**17**	**20**	**23**	**26**	**29**	**32**	**35**
Chemo	C I	C I	C I	D	**Surgery**	I D	C I	C D	I D	C I	C D	I D	C D

In addition to the 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.

[1] Administration of ifosfamide requires the accompanying drug, mesna. The Committee noted that mesna is currently included on the EMLc as an adjuvant medicine.

Review of benefits and harms

Benefits

Because osteosarcoma occurs in adolescents and young adults, curative regimens may result in many life-years gained. Before the use of chemotherapy, surgical resection resulted in only 20% survival *(7)*. 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 value of chemotherapy was supported by the results of the Multi-Institutional Osteosarcoma Study, a randomized controlled trial of 36 patients with non-metastatic high-grade osteosarcoma of the extremity *(8)*. This trial showed 17% event-free survival (EFS) in the surgery-only arm and 66% EFS in the adjuvant chemotherapy arm.

The MAP regimen of high-dose methotrexate, doxorubicin and cisplatin has become the standard of care for localized osteosarcoma *(9)*. The ISG/OS-1 trial compared the efficacy and toxicity of two MAP-based chemotherapy regimens, with or without ifosfamide, in 246 patients with non-metastatic osteosarcoma of the extremity. The two treatment arms (A and B) received the same cumulative doses of MAP. Patients in treatment arm A received postoperative ifosfamide only if they had a poor histological response to chemotherapy. Patients in treatment arm B were given ifosfamide with MAP in the primary phase of chemotherapy. No statistically significant differences were observed between arms A and B in the 5-year rates of overall survival (OS) (73% and 74%, respectively) or EFS (64% and 55%, respectively). Patients in treatment arm B experienced a greater incidence of grade 4 haematological toxicity (leukopenia, thrombocytopenia, febrile neutropenia).

Intergroup Study 0133 was a prospective, randomized, phase III trial of 662 patients with newly diagnosed osteosarcoma without clinically detectable metastatic disease. The study compared four prospectively randomized treatments in a 2 × 2 factorial design: MAP chemotherapy and MAP plus ifosfamide, with or without addition of muramyl tripeptide (MTP), a synthetic lipophilic glycopeptide capable of activating monocytes and macrophages to a tumoricidal state *(10)*. The primary end-points for analysis were EFS and OS. Patients in the MAP-only treatment arm had a 6-year EFS of 64% compared with 58% for patients in the MAP-plus-ifosfamide arm. Six-year OS rates were similar in the two groups (71% and 70%, respectively). The addition of MTP to chemotherapy improved 6-year OS from 70% to 78% ($P = 0.03$). The hazard ratio for OS with the addition of MTP was 0.71 (95% CI: 0.52–0.96). The role of MTP has been disputed, as a possible interaction between MTP and ifosfamide is suspected, calling for prudent interpretation of the role of MTP *(11)*. Immunotherapy with MTP might offer additional marginal benefit but the potential role of MTP in combination with chemotherapy remains to be confirmed. The application did not propose inclusion of MTP in the EMLc.

The OS99 regimen (doxorubicin, carboplatin and ifosfamide) has been proposed as an alternative to MAP to simplify the management of osteosarcoma in settings unable to provide the required monitoring for methotrexate and for patients unable to tolerate high-

dose methotrexate *(12)*. The results of the phase II OS99 trial of 72 patients found that this regimen was associated with survival outcomes comparable to those seen with regimens containing cisplatin or high-dose methotrexate, with 5-year EFS and OS of 66.7% and 78.9%, respectively *(12)*.

In contrast to localized disease, the prognosis for metastatic, relapsed or recurrent osteosarcoma remains poor, with 5-year OS less than 30% *(1)*. 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 with 15% for those who underwent incomplete resection *(13)*. Survival is highly dependent on the amount of tumour necrosis following neoadjuvant chemotherapy, as determined by comprehensive histological analysis of the resected tumour.

Harms and toxicity considerations

Nausea, vomiting, myelosuppression, alopecia and mucositis are common to all chemotherapy regimens for osteosarcoma *(14)*. Sepsis is the most serious acute complication that may lead to death. Cisplatin can cause ototoxicity and nephrotoxicity and 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 patients *(15)*. Inability to excrete high-dose methotrexate adequately may result in acute renal failure and severe mucositis *(16)*. Ifosfamide administration may result in acute neurotoxicity, which may manifest as weakness, altered mental status and seizures *(17)*. The cumulative incidence of second malignant neoplasm in osteosarcoma survivors at 25 years was 5.4% *(18)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended the addition of doxorubicin, cisplatin (1 mg/mL, 50-mL and 100-mL vials), methotrexate, carboplatin and ifosfamide to the complementary list of the EMLc for the treatment of osteosarcoma. The Committee considered that the results of the trials supported the use of the MAP regimen as standard therapy for osteosarcoma as it was associated with clinically relevant improvements in EFS and OS. Although OS99 chemotherapy has not been widely adopted, the Committee noted that this chemotherapy was associated with similar benefits to MAP in terms of EFS and OS, and it may be a treatment option in some settings.

The Committee also recommended that these medicines be included on the complementary list of Essential Medicines for adults, noting that the peak incidence of osteosarcoma is in the second decade of life and the EMLc is intended for use only for children up to the age of 12 years.

Given the requirement for treatment with high-dose methotrexate to be accompanied by calcium folinate (leucovorin/folinic acid) rescue, the Committee also recommended inclusion of calcium folinate on the complementary lists (both EMLc and EML) for this indication. Similarly, given the requirement for treatment with ifosfamide to be

accompanied by mesna, the Committee recommended inclusion of mesna on the complementary lists (both EMLc and EML) for this indication.

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