The successful treatment of patients with osteosarcoma requires close cooperation within an experienced multidisciplinary team including pediatric or medical oncologists, surgeons, pathologists and radiologists. Therefore, therapy should be performed in specialized centers able to provide access to the full spectrum of care. As in other rare malignancies, treatment should be administered within prospective multicenter trials. Therapy must include complete surgical removal of all detectable tumor sites as well as multiagent chemotherapy. The chemotherapy regimen should include several or all of the following four drugs: doxorubicin, high-dose methotrexate with leucovorin-rescue, cisplatin and ifosfamide. Preoperative (neoadjuvant) plus postoperative (adjuvant) polychemotherapy should be preferred, because it allows preparation for safe surgery and preparation of the appropriate prosthesis for the individual patient. The choice of the postponed definitive surgical procedure should be influenced by the anatomical site of the primary tumor, its relationship to neighboring structures, such as vessels and nerves, age and growth potential of the patient, and probably also by the response of the tumor to preoperative chemotherapy. A major, as yet unsolved, problem is the dismal prognosis for patients with unresectable or relapsed osteosarcomas. Novel approaches are needed in order to improve their prognosis.

Key words: follow-up, limb salvage, multidisciplinary treatment, osteosarcoma, preoperative (neoadjuvant) chemotherapy, surgical techniques

introduction

Osteosarcomas are derived from primitive mesenchymal cells. They originate from bone and only rarely from soft tissue. Untreated, they run a dismal course with local and often metastatic disease progression. Before the introduction of polychemotherapy >90% of patients with osteosarcoma died from pulmonary metastases [1]

epidemiology

Osteosarcoma, the most frequent primary solid malignancy of bone, is defined by the presence of malignant mesenchymal cells which produce osteoid and/or immature bone [1–3]. The incidence of osteosarcoma in the general population is 2–3/million/year, but is higher in adolescence, in which the annual incidence peaks at 8–11/million/year at 15–19 years of age. Osteosarcomas account for 15% of all solid extracranial cancers in this age group. Males are affected 1.4 times more frequently than females [4, 5].

etiology and pathogenesis

In most patients, the etiology of osteosarcoma remains obscure. The predilection of osteosarcoma for the age of the pubertal growth spurt and the sites of maximum growth suggest a correlation with rapid bone proliferation. A minority of osteosarcomas are caused by radiation exposure. Exposure to alkylating agents may also contribute to osteosarcoma development. The incidence of osteosarcoma is increased in several well-defined hereditary disorders associated with germline alterations of tumor suppressor genes such as hereditary retinoblastoma [1] and the Li–Fraumeni cancer family syndrome [6].

diagnosis and staging

Local pain, followed by localized swelling and limitation of joint movement, are the typical signs and symptoms of osteosarcoma. In rare cases, particularly in patients with osteolytic tumors, a pathological fracture can be the first sign of disease. Approximately 15% of patients present with radiographic metastases, most commonly to the lung, but metastases can also develop in bone and rarely in lymph nodes [7].

Although osteosarcoma can occur in any bone, it is most common in the metaphyses of long bones. The most common primary sites are the distal femur, the proximal tibia, and the proximal humerus, with ~50% originating around the knee [3, 7, 8]. About 10% develop in the axial skeleton, most commonly the pelvis [9].

The evaluation of a patient with suspected osteosarcoma begins with a full history, physical examination, and plain radiographs [10]. Plain radiography is helpful to describe
osseous changes: osteosarcomas can present with osteoblastic, osteolytic or mixed appearance. They often have a soft tissue component in which patchy calcifications resulting from new bone formation or spiculae may be observed. A triangular area of periosteal calcification in the border region of tumor and healthy tissue is known as a Codman triangle, which is considered typical for osteosarcomas. Magnetic resonance imaging (MRI) is the best modality to assess the soft tissue component, its relationship to surrounding tissues, vessels and nerves, and its intramedullary extension, which is essential for safe definitive surgery. MRI has to include the whole involved bone as well as the neighboring joints, so as to not miss skip lesions, i.e. intramedullary tumor foci without direct contact with the primary lesion [11, 12].

A metastatic work-up is essential at presentation and includes a (spiral) CT scan of the thorax and a 99mTc bone scan (Table 1). Osteosarcomas lack specific tumor markers; however, an elevation of lactate dehydrogenase or, more frequently, alkaline phosphatase levels in serum is found in some patients. Both have been associated with inferior outcomes. Since polychemotherapy for osteosarcoma can result in cardiac and auditory dysfunction and significant kidney and liver toxicity, patients should have baseline assessments including echocardiography, an audiogram, and liver and kidney function test (Table 1).

**histopathology**

The diagnosis of osteosarcoma must always be verified histologically. Because of the broad spectrum of histological appearances and the rarity of the tumor, it is strongly recommended that biopsies should be performed in specialized centers, so that appropriate biopsy techniques and appropriate histological examination of the obtained material are guaranteed, including genetic evaluation where necessary. Open biopsy is considered the most suitable technique to obtain sufficient material for histological evaluation and additional studies. True-cut needle biopsy may also be used, provided that sufficient material can be obtained, while fine-needle biopsies are not appropriate.

The biopsy specimen should be forwarded to the specialized pathologist without prior fixation. The hallmark of diagnosis is the proliferation of malignant mesenchymal tumor cells and the production of osteoid and/or bone by these tumor cells. The amount of osteoid and/or bone production varies greatly between tumors and within an individual tumor. Thus, identification of diagnostic osteoid may require extensive sampling. Chondroid and fibrous matrix may also be present, reflecting the mesenchymal origin of the malignant cells. The current World Health Organization (WHO) classification [1] recognizes three major subtypes of conventional osteosarcoma: osteoblastic, chondroblastic and fibroblastic, reflecting the predominant type of matrix within the tumor. In addition to classical osteosarcoma, the WHO classification recognizes additional histological variants, including telangiectatic osteosarcoma, small cell osteosarcoma, parosteal and periosteal osteosarcomas, as well as low grade central and high grade surface osteosarcomas [1]. The classical central subtypes are nearly always WHO grade III high malignant tumors, whereas surface osteosarcomas are mostly low grade I or intermediate grade II tumors. The current TNM (tumor–node–metastasis) classification of osteosarcomas is shown in Table 2.

**Table 1.** Recommended diagnostic work-up for osteosarcoma patients

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>X-ray</th>
<th>Tumor localization in two planes</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray</td>
<td></td>
<td>Whole extremity p/a</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td></td>
<td>Whole extremity/tumor region</td>
</tr>
<tr>
<td>Metastases 99mTc bone scan</td>
<td></td>
<td>Whole skeleton</td>
</tr>
<tr>
<td>Computed tomography</td>
<td></td>
<td>Chest</td>
</tr>
<tr>
<td>Organ function</td>
<td>Heart</td>
<td>Echocardiogram, electrocardiogram</td>
</tr>
<tr>
<td>Organ function</td>
<td>Hearing</td>
<td>Audiogram</td>
</tr>
<tr>
<td>Kidney</td>
<td>Creatinine (including estimated clearance)</td>
<td>Tubular function tests</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>Other laboratory</td>
<td>Alkaline phosphatase i.S.</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase i.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase i.S.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

i.S., in serum.

**Table 2.** TNM classification of bone sarcoma [2]

| T0 | No evidence of primary tumor |
| T1 | Tumor 5.8 cm in greatest dimension |
| T2 | Tumor >8 cm in greatest dimension |
| T3 | Discontinuous tumors in the primary bone site |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| M0 | No distant metastases |
| M1 | Distant metastases |

| Stage IIA | T1 N0 M0 (low grade) |
| Stage IIA | T1 N0 M0 (low grade) |
| Stage IIB | T2 N0 M0 (high grade) |
| Stage III | T3 N0 M0 (high grade) |
| Stage IVA | Any T N0 M1a (any grade) |
| Stage IVB | Any T N1 Any M (any grade) |

| Stage IVB | Any T Any N M1b (any grade) |
rationale for a multidisciplinary treatment approach

Local therapy alone is insufficient, as 80–90% of all patients with seemingly localized disease will develop metastases, mostly in the lungs, and will die if chemotherapy is not included as part of the multidisciplinary treatment [3]. Early studies describing the efficacy of multiagent chemotherapy included those by Rosen et al. in North America [13] and by Winkler et al. in Europe [14]. Two randomized trials in North America proved the efficacy of chemotherapy [15, 16]. Current treatment regimens encompassing primary (preoperative; neoadjuvant) induction chemotherapy, followed by definite surgery and then postoperative (adjuvant) chemotherapy lead to cure in approximately two-thirds of patients with seemingly localized disease [3, 8]. The total duration of chemotherapy is usually at least 6–8 months.

treatment surgery

The goal of osteosarcoma surgery must always be complete tumor removal. Margins should be at least wide according to Enneking’s definition [17] (Table 3), meaning that the tumor including the biopsy scar has to be removed surrounded by an inviolated cuff of healthy tissue. Advances in imaging techniques and in biomedical engineering as well as positive effects of preoperative chemotherapy have led to a major shift away from amputation towards limb-salvage surgery [3, 6, 8, 18, 19]. Options for reconstruction after limb-sparing tumor resections are manifold and include endoprosthetic devices [18–20], biological reconstruction, or a combination of both. Rotation-plasty, another well-established biological reconstruction method for tumors around the knee, can result in functional and psychological outcomes equal or even superior to endoprosthetic reconstruction [21], but is cosmetically challenging.

Surgery of sarcomas of the axial skeleton remains particularly challenging, both because local recurrence poses a great hazard and because complications after reconstruction are frequent [19, 22, 23]. It is essential that surgeons are aware of all surgical techniques and implement the most appropriate one for each individual patient after consultation within the multidisciplinary osteosarcoma team. More recent advances include total en bloc spondylectomy for vertebral tumors [23] and hip transposition for pelvic sarcomas [24].

radiotherapy

Osteosarcoma was long considered a radioresistant tumor, thus the experience with radiotherapy in local treatment of osteosarcomas is limited [25]. However, recent data suggest that the administration of radiotherapy may be useful in patients treated with multiagent chemotherapy who are unable to undergo complete resection or who have microscopic residual tumor foci following attempted resection [22]. The use of targeted radiotherapy with Samarium-153-ethylidenediametetramethylene phosphate may also be considered in selected situations, although the role of this treatment modality is not well defined and its definition would require further evaluation in controlled clinical trials [26, 27].

systemic therapy

polychemotherapy. Currently, doxorubicin [28], cisplatin [29], high-dose methotrexate with leucovorin-rescue [30] and ifosfamide [31] are considered the most active agents against osteosarcoma, but the ideal combination remains to be defined. Most current protocols include a period of preoperative (neoadjuvant) chemotherapy, even though this has not proved to add a survival benefit over postoperative (adjuvant) chemotherapy alone [32]. The extent of histological response to preoperative chemotherapy [33], however, offers important prognostic information. Current prospective trials evaluate whether altering postoperative chemotherapy in poor responders improves outcomes. The use of high-dose chemotherapy followed by retransfusion of autologous hematological stem cells has not led to improved outcomes [34].

immunomodulation. An early, uncontrolled Swedish series of single-agent treatment with α-interferon reported promising results [35]. The current EURAMOS 1 Intergroup Study is evaluating α-interferon maintenance after completion of chemotherapy in a randomized study [36]. Addition of the immunomodulator liposomal muramyl tripeptide phosphatidyl ethanolamine (MTP) to postoperative chemotherapy was reported to correlate with a statistically significant advantage in overall survival and a non-significant trend in event-free survival in a follow-up report of a recent randomized trial [37]. The study’s design and associated statistical limitations have been criticized, leading several authors to recommend that the exact role, if any, of this new immunomodulatory treatment remains to be proven in further studies [38, 39].

supportive care

Together with the therapeutic advances in osteosarcoma management with polychemotherapy, a number of agents have been developed to help reduce the chemotherapy-related toxicity. The introduction of serotonin antagonists [40] has dramatically reduced chemotherapy-induced emesis. Such agents alone or in combination with dexamethasone have become the standard of care with the use of highly emetogenic chemotherapy, especially cisplatin. Other agents used in...
supportive care of osteosarcoma patients include opioids for tumor pain control and hematopoietic growth factors to decrease the incidence and duration of chemotherapy-induced severe granulocytopenia. The addition of granulocyte colony-stimulating factor (G-CSF) to chemotherapy led to increased dose density of treatment and improved histologic response, but not to improved survival rates in a randomized trial by the European Osteosarcoma Intergroup [41].

**treatment of metastatic disease and relapse**

Curative treatment for primary metastatic osteosarcoma is identical to that of localized disease, with the mandatory addition of surgical removal of all known metastatic foci, usually by exploratory thoracotomy including palpation of the whole lung [42]. Approximately 30% of all patients with primary metastatic osteosarcoma and >40% of those who achieve a complete surgical remission can become long-term survivors [42].

Treatment for relapse, either locally or within the lungs, is primarily surgical. The prognosis is poor, with long-term post-relapse survival in <20%. Complete removal of all metastasis must be attempted, as the disease is otherwise almost universally fatal. In contrast, more than a third of the patients with a second surgical remission survive 5 years or more. Even patients with multiple recurrences may be cured as long as recurrences are resectable, and repeated thoracotomies are often warranted [43–45]. Overall, CT scans tend to underestimate the number of pulmonary metastases and may also fail to detect contralateral involvement in patients with seemingly unilateral pulmonary metastasis [46]. Thus, bilateral exploration by open thoracotomy including palpation of both lungs is recommended.

The role of second-line chemotherapy for recurrent osteosarcoma is much less well defined than that of surgery, and there is no accepted standard regime. Choice may take into account the prior free interval and disease resectability, and often includes ifosfamide, etoposide and/or carboplatin [43–46].

**follow-up and late effects of treatment**

Follow-up intervals recommended in most trials are every 6 weeks to 3 months in years 1 and 2 after diagnosis, every 2–4 months in years 3 and 4, every 6 months in years 5–10 and every 6–12 months thereafter. Each visit should include a history and physical examination, and a chest X-ray (Table 4). Since late metastases may occur >10 years after diagnosis, there is no universally accepted stopping point for tumor surveillance. As in other childhood cancers, cured patients need lifelong follow-up [47].

Polychemotherapy of osteosarcoma may be associated with permanent alterations of cardiac [48], renal [49], auditory and reproductive function, orthopedic problems and other late effects including secondary malignancies [50]. Thus appropriate investigations to detect these late effects as early as possible should be included during regular follow-up (Table 4).

<table>
<thead>
<tr>
<th>Time</th>
<th>Tumor directed</th>
<th>Late effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>X-ray chest and CT</td>
<td>Echocardiogram, audiogram, liver and kidney function, hepatitis B/C and HIV serology</td>
</tr>
<tr>
<td></td>
<td>X-ray and (CT)/MRI primary site</td>
<td></td>
</tr>
<tr>
<td>Years 1 and 2</td>
<td>X-ray chest every 6–12 weeks</td>
<td>Echocardiogram every 1–2 years, audiogram*, liver* and kidney function</td>
</tr>
<tr>
<td></td>
<td>X-ray primary site every 4 months</td>
<td></td>
</tr>
<tr>
<td>Years 3 and 4</td>
<td>X-ray chest every 6 months</td>
<td>Echocardiogram every 1–2 years</td>
</tr>
<tr>
<td></td>
<td>X-ray primary site every 4 months</td>
<td></td>
</tr>
<tr>
<td>Years 5–10</td>
<td>X-ray chest every 6 months</td>
<td>Echocardiogram every 2–4 years</td>
</tr>
<tr>
<td>Thereafter</td>
<td>(Few) relapses reported as late as two decades after treatment. Discuss with patient whether to continue chest X-ray every 6–12 months</td>
<td>Echocardiogram every 2–4 years</td>
</tr>
</tbody>
</table>

Every visit should include detailed history and physical. Many institutions will add complete blood counts. Evaluate any site with unexplained pain or swelling. Chest CT scan is optional, but should always be performed if chest X-ray shows metastasis or is inconclusive. Add consultation with orthopedic surgery and physical therapy as indicated. Offer fertility testing for males. Additional investigations may be indicated.

*Need not be repeated if normal at 1 year.

*Some groups recommend annual radiographs of the primary site until year 10.

CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging.

**outlook**

While surgical reconstruction techniques have improved considerably over the past decades, allowing limb salvage in most patients, chemotherapy still relies on the same drugs as in the early 1980s, and survival rates have not improved since then. Translational research is required to identify targets for novel treatment modalities. Due to the rarity of disease, pivotal trials evaluating the addition of innovative therapies to conventional regimens will require multicenter, multinational, often intergroup collaboration. The activation of any clinical trial in a rare disease at centers which may see a patient a year or less—as is the case for most medical oncology institutions treating osteosarcoma—is cumbersome and associated with little or no financial incentive. This should not deter us from trying to include as many young adults as possible in interdisciplinary trials of this cancer which so typically occurs at the pediatric–adult interface.
disclosures

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references


