

OSTEOSARCOMA IN THE PEDIATRIC AGE

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ARTICLE INFO

Article history:

Received 12 July 2018

Revised 30 September 2018

Accepted 28 October 2018

Keywords:

osteosarcoma, children, diagnosis, treatment.

ABSTRACT

Osteosarcoma is the most common form of malignant bone tumor; it is characterized by malignant mesenchymal cells producing osteoid or immature bone. The tumor predominantly involves children, teenagers and young adults with a peak of incidence in the second decade of life during the adolescent growth spurt, suggesting a correlation with rapid bone proliferation. Osteosarcoma originates more frequently in the metaphyseal region of long bones, with particular involvement of the distal femur (40%), proximal tibia (25%) and humerus (15%); 80% of osteosarcomas occur in the limbs, whereas 20% affect the axial skeletal and pelvis. Osteosarcoma arises from the medullary cavity and grows toward the cortex and adjacent soft tissue.

The osteosarcoma leads to death within a matter of months if left untreated. In the 1970s, the use of adjuvant chemotherapy in the treatment increased survival in patients with osteosarcoma. Pathological fractures and local diffusion of tumors are associated to a poor prognosis.

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1. Background

Malignant tumors that affect bone, cartilage, muscle and connective tissue are called sarcomas. The characteristics of sarcomas are the rarity in comparison with carcinomas, the involvement of all organs, and the highest incidence in younger individuals. The majority of primary tumors of the skeleton can be classified into three groups: fibrosarcomas arise from the fibrous matrix, chondrosarcomas from cartilage, and osteosarcoma from bone (1).

Osteosarcoma is the most common bone tumor in childhood, and is often fatal in both children and adults. The disease in adults has a worse prognosis than in children, especially with pathological fractures or a local diffusion of the tumor. The bone tumor is most likely derived from mesenchymal stem cells, but the exact origin is unknown. It usually involves long bones and metastasizes to the lung in approximately 80% of cases, and subsequent respiratory compromise is responsible for the death of patients.

Until 30 years ago, most patients died within 1 year of diagnosis; now, with neoadjuvant chemotherapy, a 5-year survival rate has reached 60% in patients with localized disease and 30% in patients with metastatic disease (2).

2. Epidemiology

Osteosarcoma is the third most common cancer in adolescence after lymphomas and brain tumors (3). The annual worldwide incidence of childhood cancer ranges from 75 to 150 per million children per year, with 1-3 cases of osteosarcoma per million people every year (4); males are affected more than females with a ratio of 1,6:1 (2). Osteosarcoma has a bimodal age distribution: the first peak incidence is in the second decade of life (11-20 years), and the second peak in older adults (> 65 years) (5). The disease is rare before the age of five (6,7). The peak in young age coincides precisely with the acceleration of growth, indeed in girls the onset of the disease is earlier than in men. The disease in children affects the para-articular areas of long bone, in adults the axial skeleton (1).

At diagnosis, 15-20% of patients show detectable metastases in the lungs or extrapulmonary locations, while 40% of metastases are found at a later stage (6-36 months later). It is presumed that most patients (60%) without lung metastasis have micrometastasis at initial diagnosis. Survival rates of patients without metastasis were 23% at 5 years and 0% at 4 years for pulmonary and bone metastases if the appropriate therapy is not performed (8,9).

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DOI: 10.3269/1970-5492.2018.13.29

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3. Type

The World Health Organization divides osteosarcoma into central and surface tumor, with a number of subtypes for each group (10). The evidence of bone or osteoid production is a requirement for histological diagnosis (11)

Central group includes conventional, telangiectatic, small-cell and low-grade osteosarcoma. Conventional is the most common type of osteosarcoma (80%) and can be divided into osteoblastic, chondroblastic, and fibroblastic depending on cell predominance; eighty percent of cases affect the metaphysis and diaphysis of long bones or the axial skeleton and have high-grade tumor cells (12). The telangiectatic form represents 4% of all osteosarcoma, is characterized by dilated blood-filled cavities and high-grade cells, mostly involves the metaphysis, and the prognosis is worse than the conventional type (13). It is very important to differentiate telangiectatic osteosarcoma from aneurysmal bone cysts on imaging because the two lesions appear radiographically similar; this form is often associated with pathological fractures because of the fragile nature of the tissue. The small-cell form, which constitutes 1-2% of all osteosarcoma, are characterized by small cells and have round hypochromatic nuclei with little nuclear polymorphism; this form of osteosarcoma must be differentiated from Ewing's sarcoma through the production of osteoid by tumor cells (14). Low-grade forms, which represent 1-2 % of all osteosarcoma, affects patients in the third or fourth decade of life, has a better prognosis, and in low grade cells may resemble a parosteal form (15).

Surface tumors are parosteal, periosteal and high-grade osteosarcoma. Parosteal osteosarcoma is a low-grade tumor that originates from the periosteum, accounts for 4-6% of all osteosarcoma, and commonly affects the distal femur. In radiographs it is observed as a densely ossified and lobulated mass while the medullary cavities are spared (11). Periosteal form is less common than parosteal, has a cartilaginous matrix component and intermediate-grade tumor cells. The tumor originates between the cortex and the cambium layer of the periosteum with an associated periosteal reaction (16). High-grade surface osteosarcoma represents less than 1% of all osteosarcoma and has high-grade tumor cells; radiographically, this form shows a surface lesion with partial mineralization that invades the cortex and surrounding soft tissues (11).

Osteosarcomas in children are almost always of the conventional type, while in adult parosteal or extraskeletal types are more frequent (1).

4. Etiology

The etiology of osteosarcoma remains obscure and controversial, but the higher incidence in pubertal age suggests a correlation with rapid bone proliferation. Multiple associations have been made between osteosarcoma and race, age, gender, genomic alterations, radiation exposure, without detection of a specific cause (8).

The majority of osteosarcomas in childhood occur without a familial predisposition or a long exposure to radiation, while radiation-induced osteosarcoma is frequent of adult age (10-20 years after receiving radiotherapy). Osteosarcoma in pediatric age is associated with several rare diseases like Bloom syndrome, Rothmund-Thomson syndrome, Li-Fraumeni syndrome and Retinoblastoma (2). A variety of serological

markers have been associated with osteosarcoma, and these markers play an important role in angiogenesis, cell adhesions, cell cycle, apoptosis, cell differentiation, and dissemination of metastases (17,18). Nowadays, no specific markers for osteosarcoma have been identified.

Osteosarcoma is associated with several chromosomal abnormality in 70% of tumor specimens, with particular involvement of tumor-suppressor genes or DNA helicases (3). The retinoblastoma tumor suppressor gene (RB) produces a nuclear protein that exerts a growth-suppressive effect on the cell cycle and is altered in patients with osteosarcoma. Mutations of p53 tumor suppressor gene, that produces a transcription factor, have been involved in osteosarcoma oncogenesis (19); amplification or over expression of MDM2 and CDK4 gene, or involvement of transcriptional factors C-myc and C-fos have been observed in osteosarcoma cells. Other genetic mutations and expression profiles that have been identified are ErbB-2, cathepsin D, FBX 7, miR-421, and HMGB1 (8). Matrix-Gla protein expression play a role in facilitating the tumor to spread to the lungs (20).

5. Diagnosis

The diagnosis of osteosarcoma is difficult and late due to lack of specific signs, and requires a multidisciplinary approach. Patients have symptoms for several months (3-6 months) before the diagnosis is made. Pain is the most clinical sign observed in children, but very often it is referred to a trauma and further exams are not performed. Also the pain is treated for several months like growing pains, tendinitis, or muscle fatigue; therefore the clinical identification of the tumor is delayed by pediatricians and orthopedics (1). The suspicion of Osteosarcoma arises when the tumor mass becomes palpable or the disease appears on an MRI performed in the course of investigating pain. Swelling appears later with a hard consistency mass. Limping and limitation of joint movement can be observed when the patient walks. The lung is the most common site of metastases; mediastinal lymph nodes are very rarely involved; skip metastases can be observed in less than 10%, and are often in the same bone and adjacent joint (21). In rare cases, a pathological fracture can be the first sign of the disease (22).

The diagnosis is based on diagnostic images and laboratory tests and confirmed by a biopsy and histological study of tissues.

An imaging study consists of an x-ray of the area affected by tumor and adjacent joint to evaluate the macroscopic extension in the bone, osteoblastic and/or osteolytic aspect, periosteal reaction, and to identify pathological fractures (3). Where the tumor breaks the cortex, a triangle of immature bone can be observed (Codman's sign) due to a reaction of periosteum. CT scan is useful to quantify the exact size and extension of the tumor, cortical irregularities or fractures, mineralization, and neurovascular involvement; also a CT scan of the lungs should be performed routinely to evaluate the existence of metastatic dissemination at this site (23). It is reasonable to repeat a CT scan 6-12 weeks following the first in order to identify micrometastasis. MRI requires immobilization of patients for a long period of time and assistance of an anesthesiologist for sedation; this exam provides better information on the involvement of adjacent muscle structures, soft tissue and vascular-nervous bundle, and allows to confirm skip lesions extending into the joint (24). CT scan and MRI are indispensable for planning and surgical treatment. The bone scintigraphy

with Tc⁹⁹ and positron emission tomography (PET) provides fixation of the drug in the primary tumor and also detects any lesions in other bones, or pulmonary metastasis that are not evaluable by other exams (1). PET is useful to assess the response to chemotherapy and to predict progression-free survival (23).

There isn't a laboratory test that is diagnostic for Osteosarcoma; laboratory values are generally normal with the exceptions of increase of alkaline phosphatase or LDH based on the increase in osteoblastic or osteoclastic activity, respectively; an elevation of both have been associated with inferior outcomes (22). The C-reactive protein (CRP) has worse prognostic value in osteosarcoma in patients with preoperative value greater than 1.0mg/dl (25). Mild anemia may also be present at diagnosis and erythrocyte sedimentation rate increases in the presence of relapse (8).

A biopsy allows the histological identification of a bone tumor; it can be open/incisional or needle/closed; in the last procedure, the technique involves a bone needle with the tip in correspondence with the center of the lesion under radioscopic guidance or with imaging assistance. Open biopsy was considered the gold standard for its accuracy rate of 98%, but is associated with complications; the need to perform an open biopsy is rare, due to the presence of a soft tissue mass together with the bone, and should be performed by the same surgeon who will treat the bone tumor. Percutaneous biopsy with core needle is preferred because there is less risk of contamination and complications, and shows a sensitivity of 82% (26). The biopsy must avoid pathological fracture of bone and local dissemination of the tumor with blood. Multiple biopsies that cause a pathological fracture can end in amputation making it impossible to salvage the limb (1). Infection after biopsy can condition the entire course of treatment. Tumor resection must include the biopsy tract due to contamination of neighboring tissues. The microscopic diagnosis of osteosarcoma is based on the identification of the osteoid matrix by the tumor cells.

Bone disease to be included in differential diagnosis are Ewing's sarcoma, fibrosarcoma, aneurysmal bone cyst, and myositis ossificans.

6. Treatment

The treatments for Osteosarcoma consist of a combination of chemotherapy and surgery.

Surgical treatment has the purpose to remove the tumor through wide excision; treatment options are limb salvage and amputation. The type of surgical procedure depends on the tumor stage, response to chemotherapy, patient's age, general condition and life expectancy (27).

Limb salvage techniques allow the treatment of 80% of patients with osteosarcoma and consist of two steps: resection and reconstruction (28). Resection allows the elimination of disease and should include excision of previous biopsy sites and tracts, removal of tumor mass with margins of at least 6-7 cm. When surgical margins are inadequate, the risk of local recurrence is very high. Preoperative CT scans may determine the quantity of bone to be osteotomized during surgery. The invasion of the tumor through the growth plate or joint is a contraindication for limb salvage and an indication for amputation. Reconstruction is the next step in limb salvage and is utilized in weight-bearing bones; it can be divided in endoprosthetic replacement and biological reconstruction. The first

treatment has been reported to have good functional outcomes and it involves the use of modular, custom-made or growing implants for the skeletally immature. Titanium alloy is used more than cobalt-chrome because it is associated with a lower rate of infection (29). Ahlmann found a survivorship rate of 78% at five years and 60% at fifteen years after surgery, respectively (30). More operations in young patients are needed for lengthening and for management of complications (wear, infection, fracture, loosening); the use of closed expandable prosthesis allows lengthening without undergoing further interventions and to reduce complications. Biological replacements consist of allograft, autograft, and allograft prosthetic composite (APC) reconstructions. Allograft is at risk for non union and infection, and is regarded as an effective treatment of tumor reconstruction. APC combines the effects of biological graft (consolidation to host bone, reinsertion of the soft tissues) with the stability of the prosthesis (few complications). The most used autograft is the fibula, that can be vascularized or not; the blood supply in the graft reduces the time of union with the healthy bone. The advantages of autograft are the preservation of anatomy and bone-inductive activity, while complications are bone absorption, fracture and pseudoarthrosis. (31). To circumvent these complications massive bone allografts have been supplemented with an intramedullary vascularized free fibula (Capanna technique). The combination of the osteogenic potential of the vascularized free fibula and the structural support of the cortical allograft represent an attractive treatment in the reconstruction of bone defects. Reports of the Capanna technique in the pediatric age are limited.

Houdek (32) used the Capanna technique for limb salvage in eighteen pediatric patients (nine boys and nine girls) with a mean age of 11 years (range 5-18 years); the overall limb salvage rate was 94%, although fourteen patients underwent an additional surgical procedure at a mean of fifteen months from the graft implant; the author only reports one failure secondary to tumor recurrence resulting in amputation. The Capanna technique has a high incidence of complications as a result of the avascular nature of the allograft: non union occurred in six patients, seven patients sustained an allograft fracture, no case of infections. The average limb length discrepancies were less than 2 cm at last follow-up, and corrective procedures have been performed, including lengthening in four patients and growth modulation in six patients (32). All surviving patients were able to return to their previous sport activity after limb salvage. The Capanna technique should be considered in pediatric cases of large, segmental defects of the lower extremity.

The limb can be saved when resection can be achieved with a 5-cm margin and vascular and nerve structures allow the viability of the limb. Complications associated with limb salvage are infections, compartmental syndromes, ruptures of the extensor apparatus, material breakage, homograft fracture, and dislocations of implants.

Amputation is reserved to the non-resectable tumor with soft tissue contamination, tumors infiltrated in the main neurovascular bundles, local recurrence, or when the removal of the tumor causes loss of functionality to the limb. Some studies have reported comparable survival rates between limb salvage and amputation (3). A particular type of amputation for tumors around the knee is the rotationplasty, that was first described in 1930 Borggreve and is the treatment of choice in patients under seven years; it consists of the resection of the distal femur followed by rotation of the tibia and foot and reattachment to the remaining portion of the femur (33).

The surgery is carried out 15 weeks after chemotherapy and appropriate planning of the intervention is required to be performed.

A multidisciplinary approach is essential to decide on amputation or limb-salvaging surgery.

Micrometastasis requires the incorporation of chemotherapy to the treatment of osteosarcoma (1). Chemotherapy allows to treat disseminated osteosarcoma when the tumor volume is still microscopic. The chemotherapy is performed in association with surgery, but the composition and the best timing for its application continue to be subject to debate. The standard of care for osteosarcoma with metastasis is neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. The aim of this sequence is to control the micrometastasis, which already spread at the time of diagnosis and was not initially detectable, reduce the volume of the tumor, and evaluate the effectiveness of chemotherapy in specimens derived from resection or amputation. The four agents used are methotrexate, doxorubicin, cisplatin and ifosfamide. Patients with metastases are treated with etoposide (3). The degree of necrosis observed in the surgical specimen is an important prognostic factor for osteosarcoma: a 5-year survival rate of more than 80% is observed in patients who present a complete response to the chemotherapy, while less than 90% of patients who didn't present histological response or necrosis have a 5-year mortality rate of more than 60% (1). Iphosphamide and etoposide are used for improving the prognosis of unresponsive patients (34). Chemotherapy could cause early and late toxicity; early toxicity consists of alteration of laboratory exams (granulocytopenia), acute liver, and kidney failure; while late toxicity consists of cardiac failure, sterility, second tumor, and neurological disorders (2). A disadvantage of preoperative chemotherapy is the risk of a pathological fracture, while a disadvantage of postoperative chemotherapy is the risk of infection of reconstructions (1). The total duration of chemotherapy is usually 6-8 months (22,35).

Osteosarcoma is quite resistant to radiotherapy (2). Radiotherapy is useful to prolong survival and to control pain in patients with multifocal osteosarcoma or when the surgery is not feasible. Machak observed that chemotherapy and radiotherapy allow a 5-years survival rate of 56% (36). High doses (> 80 Gy) are required to achieve tumor kill (5). Extracorporeal irradiation is an effective treatment and consists of removal of the tumor, irradiation, and reimplantation back in the body (5). Radiation treatment has a controversial role due to its effectiveness and risk of infection, and its definition would require further evaluation in controlled clinical trials (3).

In most studies, a follow-up is recommended every 6 weeks until 2 years after diagnosis, every 2-5 months until 4 years, every 6 months until 10 years, and every 6-12 months thereafter (3)

7. Conclusions

Osteosarcoma is a rare bone tumor found in areas of rapid bone turnover, particularly the distal femur and proximal tibia of young patients. It is a highly aggressive tumor that metastasizes primarily to the lungs. Chemotherapy development and surgery improvement have allowed a revised treatment of osteosarcoma in recent years. A multi-disciplinary approach has increased the number of conservative procedures (85%). Advances in treatment is based on immune therapy and targeted chemotherapy, showing encouraging results.

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