Osteosarcoma: An Updated Management

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Conventional or intramedullary (high-grade) osteosarcoma, except multiple myeloma, is the most common high-grade primary malignant bone tumor. It is defined as a highly malignant spindle cell sarcoma characterized by its production of osteoid matrix. The prevalence is found in 3 persons per 10,000 in the United States and accounts for 75 percent of all types of osteosarcoma. High-grade osteosarcoma should be considered a systemic disease manifested with micrometastatic disease of the lung or bone at the diagnosis. Approximately, 10 to 20 percent of patients have radiographic evidence of metastatic disease at the diagnosis. They are classified at having stage III disease, according to the Musculoskeletal Tumor Society (MSTS) staging system. Most patients (73 percent) present with stage IIB disease, and 12 percent of the patients present with metastases. The metastatic lesions are usually detected by computerized tomography (CT) scan of the chest or bone scan. Death from osteosarcoma is usually a result of progressive pulmonary metastasis with respiratory failure due to widespread disease.

Thirty years ago, osteosarcoma was determined an early fatal malignant bone tumor, with more than 80 percent of patients ultimately died of the disease within 2 years. The advancements of imaging, adjuvant chemotherapy and surgical techniques have led to a cure in approximately 70 percent of the patients who present with a non-metastatic extremity tumors. Osteosarcomas are classified into a number of subtypes based on their grade, number of sites, location in the bone, and cause. According to the WHO International Reference (IRC) for the Histological Definition and Classification of Bone Tumors, this malignant bone-forming tumor is commonly subclassified: firstly, by a decision whether it is a primary or secondary; and secondly, by the site of its origin, whether it is on the surface (juxtracortical) or within the bone (intramedullary). This paper only focuses on conventional high-grade osteosarcoma.

Current Concepts Regarding Etiology

The cause of osteosarcoma is still unknown like in most cases of bone tumors. Familial relation is described as a possible associated factor when members of the same family developed osteosarcoma. This is suggestive of a genetic predisposition. Patients with hereditary retinoblastoma and Li-Fraumeni syndrome are predisposed to developing osteosarcoma. Patients who have familial retinoblastoma have several hundred-fold of increased incidence of osteosarcoma. These patients have an inactive retinoblastoma gene, located on chromosome 13, which renders them susceptible to numerous malignancies, including osteosarcoma. Viral etiologies have been demonstrated to induce sarcoma in select animals by specific viruses. Trauma is thought to be a co-incidence that makes patients present to the doctors after an accident. Microfractures or gross fracture is not thought to be a causative factor, even though many investigators have tried to prove it out. Ionizing radiation is implicated as a direct cause of osteosarcoma and affected bone treated with irradiation is more susceptible than other tissues to secondary sarcoma development. Malignant change is being observed with great frequency as more patients survive other cancers treated by irradiation and alkylating agents, which may potentiate the radiation effect in the development of secondary osteosarcomas.

Clinical Aspects

Osteosarcomas generally occur in the metaphysis of long bones in adolescents and young adults. More than 75 percent occur in patients between 12 and 25 years of age. Osteosarcoma is exceedingly rare in children younger than 10 years or older than 60 years old. Older adults may also develop osteosarcoma, although many have predisposing factors such as Paget’s disease or prior radiation therapy. It is found more often in men. The most common locations are in the distal femur, proximal tibia, and proximal humerus. With 50 to 60 percent of tumors occur around the knee. Flat and axial skeletal bones are less commonly involved. In younger patients, osteosarcoma most commonly occurs around the knee. By contrast, older patients develop osteosarcomas more commonly in the flat bones.

Patients usually present with pain and soft-tissue mass. The clinical features of osteosarcoma can be highly variable. Symptoms may present for 3 or more months. A recent history of trauma is not uncommon, especially for tumors around the knee; however, it is more likely that a trauma merely directs attention to the existing tumor rather than causing it. The pain subsequently persists and worsens which is not specifically a related activity and present at rest or at night. There are usually no constitutional symptoms such as fever, weight loss, nausea or loss of appetite. The most important physical
finding is the presence of a mass. The size of the soft-tissue mass is variable and related to the duration time before the diagnosis and tender to palpation. (Fig 1) Patients often have painful or limited range of motion of the adjacent joint to the affected bone, or may have a sustained pathologic fracture. Certain laboratory studies are frequently high in alkaline phosphatase and lactic dehydrogenase (LDH). Abnormally high levels of lactic dehydrogenase have been shown to be associated with a poor prognosis.6,7

Imaging Studies

Plain radiographic features of osteosarcoma vary widely. The classic patterns on plain radiographs generally reveal an aggressive lesion in the metaphyseal part of long bones. A mixture of radiodense and radiolucent area with indistinct margins with no endosteal bone response is seen. Periosteal bone reaction with a Codman’s triangle over the corner lifting cortex and/or ‘sunburst’ appearance is seen.2,8 (Fig 2) Sometimes lamellar or ‘onion-skin’ periosteal reaction is found associated with previous findings. A soft-tissue density out of the cortex often occurs with variably ossified matrix, depending on the chondroblastic and osteoblastic areas. Radiographic features and clinical information help predict the histological diagnosis in most cases of osteosarcoma.

A radiological work-up usually includes CT scan or magnetic resonance imaging (MRI) of the primary to assess the extent of bone and soft-tissue involvement. Defining the local extent with CT or MRI has been shown to be an accurate predictor of tumor extent determined at the time of surgical resection.6,10 MRI is a sensitive and accurate imaging tool that can accurately demonstrate the introsseous extent of tumor and its relationship to muscle groups, subcutaneous fat, joints, major neurovascular structures and skip metastases, which occur in 5 to 10 percent. This modality has become standard in the work-up of osteosarcoma patients and has replaced CT to define local tumor extent.11 (Fig 3) MRI is also an important imaging that could give necessary information for classification of the stage of the disease that enable a decision making for surgical treatment.

In addition to imaging of the primary tumor, other various radiological studies help determine the extent of disease at presentation. These include a radionuclide bone scan with methylene diphenolphosphate labeled with technetium-99m (Tc⁹⁹m), which helps define the extent of the primary tumor, detection of skip lesions within the same bone and distant bone metastases.12 Postero-anterior and lateral radiographs of the chest allow detection of lung metastases in majority of the cases. However, chest CT is more sensitive in detecting pulmonary metastases and has become the imaging procedure of choice. There are false-positive results, particularly with smaller lesions, and biopsy confirmation of lung disease is usually required.13
The diagnosis of osteosarcoma can be predicted by radiographic appearance and location in about two-thirds of cases. However, a diagnosis should never be made from radiographs, and a biopsy for pathologic confirmation is mandatory.

**Histologic Features**

Osteosarcoma is classically defined as a tumor composed of a high-grade sarcomatous stroma with malignant osteoblasts that directly produce tumor osteoid or bone. The stromal cells of osteosarcoma show varying degrees of atypia, with pleomorphic nuclei and numerous mitotic figures. In some areas, osteoid is deposited in fine lace-like seams. (Fig 4-5) Osteosarcoma has been divided into several histologic subtypes based on the predominant type of matrix and stromal cells present in the lesion. These subtypes include osteoblastic, chondroblastic and fibroblastic. The osteoblastic subtype is the most common, accounting for about half of the tumors. Recent studies suggest no specific treatment or prognostic significance of these histologic subtypes.

**Staging**

The staging work-up for osteosarcoma is the same as that for any high grade sarcoma. A thorough history and physical examination are taken. Blood tests, including LDH and alkaline phosphatase levels, are obtained. In addition to plain radiographs of the involved bone and chest, a whole-body bone scan, a chest CT, and an MRI study of the entire bone are necessary before histologic confirmation is obtained.

The most widely used staging system is the one developed by Enneking and associates based on a retrospective review of cases of primary malignant bone tumors treated by primary resection. This system categorizes localized malignant bone tumors by grade (low grade: stage I; high grade: stage II) and by local anatomic extent (A: intracompartmental; B: extracompartmental). The compartmental status is determined by whether or not the tumor extends through the cortex. Patients with skip lesion, lymphatic and distant metastases are stage III. In the younger age groups, the vast majority of osteosarcomas are high-grade lesions; hence, virtually all patients are stage IIB or III distinguished by the presence or absence of detectable metastatic disease.

**Treatment**

The treatment of patients with osteosarcoma includes wide resection or amputation of the primary and adjuvant chemotherapy. Since this tumor is relatively radioresistant, radiation therapy is not included in adjuvant treatment. However, a recent study suggests that patients with microscopically positive margins following resection or those unable to undergo surgical resection may benefit from the use of high-dose radiation therapy, as evidenced by a superior outcome in that series for patients given radiation therapy compared with patients who did not receive radiation therapy (p = 0.0033). The outcome of patients with osteosarcoma has improved significantly as a result of the administration of adjuvant systemic chemotherapy. Protocols that include doxorubicin, high-dose methotrexate, cisplatin and other drugs have shown improvement of disease-free survival of 50-60 percent in most studies compared with disease-free survival of 10-20 percent without chemotherapy.

Early results treatment with either surgery and/or radiation therapy provided 2-year survival rates of 15-20 percent. A poor prognosis of the patients with this treatment is caused by microscopic metastases at the time of diagnosis, as evidenced by the fact that 80-90 percent develop metastatic recurrence if treated with surgical resection and/or radiation therapy. Since the era of advances of imaging, systemic chemotherapy and surgical techniques, most of the patients with non-metastatic osteosarcoma of the extremity can have a long-term survival rate with remained useful limbs.

Two different studies definitely proved the need for adjuvant chemotherapy to improve the outcome of patients with localized extremity osteosarcoma. Link et
al. developed a randomized study of observation and adjuvant chemotherapy. Patients who were treated with surgery alone had a 2-year relapse-free survival (RFS), a probability of 17 percent, versus 66 percent for those who received adjuvant chemotherapy. With longer follow-up, the 6-year-RFS rate for the observation group was 11 percent, while for those who received adjuvant therapy remained at 66 percent. Eiber et al. reported similar outcomes, definitively proving that adjuvant chemotherapy produced higher disease-free survival rates for patients with non-metastatic osteosarcoma.

A recent interest, introduced by Rosen et al., focuses on the use of preoperative chemotherapy (neoadjuvant chemotherapy) before resection of the primary tumor. This approach has several advantages such as developing a custom endoprosthesis for limb-salvage procedures, defining prognostic groups based on the observed histologic response to the chemotherapy, facilitating resection by reducing the size of the tumor and increasing tumor necrosis, and possibly making limb salvage "safer," in the minds of surgeons. A strong correlation between the degree of necrosis (Huvos grade) and subsequent disease-free survival (DFS) was observed and has been confirmed in a number of subsequent clinical trials. A theoretical concern with this approach is that the delay in removal of the bulk tumor could lead to the emergence of chemotherapy resistance. However, a prospective Pediatric Oncology Group trial demonstrated no difference between the treatment that used immediate definitive surgery and that with neoadjuvant chemotherapy followed by definitive surgery.

Specific roles of various chemotherapeutic agents in the treatment of osteosarcoma have been subjects of many studies. For example, the role of high-dose methotrexate remains controversial, with a few randomized studies reported that it was not an important component of therapy. The European Osteosarcoma Intergroup (EOI) has continued to the two-drug combination of cisplatin and doxorubicin, since there was no survival advantage to the use of more complex regimens observed in their studies. Since 1991, both Siriraj Hospital and Ramathibodi Hospital have used the Mahidol regimen protocol for the management of osteosarcoma, which includes a combination of 2 drugs as in the EOI protocol. This project was sponsored by the Mahidol Cancer Committee Network. Since then the survival rate of patients with osteosarcoma has improved. Patients with non-metastatic osteosarcoma survive longer than in the past. Additionally, although the use of bleomycin, cyclophosphamide, and actinomycin D was common in osteosarcoma, subsequent studies have demonstrated the combination to be ineffective. These drugs are no longer included in the treatment of osteosarcoma.

The different chemotherapy administration techniques both intra-arterial and intra-venous route have been studied in term of effect to patients’ prognosis. Intra-arterial administration of chemotherapy offers theoretical advantages of maximizing drug delivery to the tumor vasculature and pharmokinetic studies demonstrate high local drug concentrations with dramatic clinical responses. Although theoretically appealing, and effective including responses, the use of this approach in the context of multiagent chemotherapy does not appear to offer a significant advantage over intra-venous chemotherapy.

Recent investigations have identified some mechanisms by which tumors become resistant to a seemingly effective therapy. One of the major causes of failure is drug resistance, i.e., failure of the tumor cells to respond to the chemotherapeutic agents administered. Multidrug resistance in osteosarcoma occurs by a number of mechanisms, one of which is P-glycoprotein. P-glycoprotein is a membrane-bound glycoprotein pump encoded by the MDR-1 (multidrug resistance) gene which is expressed in various tumors and normal tissues. It has been hypothesized that a major reason for poor chemotherapy responses is the presence of P-glycoprotein, but sufficient data have not been accrued to allow P-glycoprotein expression as a prognostic factor.

**Prognosis**

The outcome of osteosarcoma treatment depends on several factors. The most consistent prognostic factor at diagnosis is the presence of clinically metastatic disease, which confers an unfavorable prognosis. Patients who present with metastases have a much worse prognosis, and if they cannot be rendered surgically free of disease, most of them could not survive. Patients with metastatic disease at diagnosis, the number of pulmonary nodules, their laterality, the ability to do a complete resection, and the response to preoperative therapy appear to be of prognostic significance. Patients who present with metastatic disease in the chest alone have a better prognosis than do those with bony metastases. An initial aggressive treatment to patients who present with metastatic disease is warranted; doing so has improved their prognosis. Management of relapsed disease includes aggressive resection of pulmonary metastases, if possible, and alternative chemotherapy protocols. Radiation therapy is also appropriate for metastatic lesions.

Although a recent report suggests that primary site, tumor size, pathologic fracture, response to chemotherapy, and surgical remission are important prognostic factors, only the presence of metastases is sufficiently predictive to allow treatment satisfaction. Patients with osteosarcoma axial lesion have inferior prognosis outcome than those with appendicular lesion. Both LDH and alkaline phosphatase levels may correlate with outcome by many studies. Histologic evaluation of the percent of necrosis from tumor response to induction chemotherapy is also a consistent prognostic factor but it cannot be assessed at the time of diagnosis. Unfavorable responders (usually defined as patients with less than 95 percent necrosis) are more likely to develop distant metastases than patients with more than 95 percent necrosis, despite continuation of adjuvant chemotherapy after surgery. Histologic grading of response offers one means of identifying patients at high risk for the development of recurrent disease early in their management. The initial hope that poor responders could be added new agents, which is an area of continued investigation.

**Future directions**

Despite improvements from the use of chemotherapy and appropriate surgery, 20 to 40 percent of patients ultimately die of osteosarcoma with metastases. Future needs and directions to study the molecular pathology of osteosarcoma include: incorporating the current lists of genetic alterations into functionally related groups of genetic alterations (hyperproliferative, cell cycle control, apoptosis, DNA damage response); gaining a better
understanding of the timing and relationship of common oncogenic events; developing a comprehensive analysis of the p53 and RB pathways in a large set of osteosarcoma samples; gaining a better understanding of different "equivalent" oncogenic events (preferential 1q21 amplification in low-grade/surface osteosarcoma, preferential p53 missense mutation in adult osteosarcoma); gaining a better understanding of the paradox of carcinoma-type cytogenetics in the setting of a younger age range; and defining the biologic/genetic subsets of osteosarcoma according to karyotypic complexity.

Increasing the understanding of the basic biology of osteosarcoma has been a high priority in recent years. P-glycoprotein expression, DNA ploidy, human epidermal growth factor receptor 2 overexpression, cDNA expression profiling, and comparative genomic hybridization. Many genes, protein expressions and molecular markers are also currently under study, and may soon provide customized information on tumor prognosis and metastatic potential as well as indications of possible tumor targets for selective therapy.

Another area of active research has been the use of radiographic studies as predictors of chemotherapy response at surgical resection. Assessments by conventional radiographs, CT scan, and MRI show definite changes in response to presurgical chemotherapy, but the changes do not correlate reliably with histologic response. Various studies suggest that three-phase bone scans, Tc 99m MIBI scintigraphy, thallium scintigraphy, dynamic MRI and positron emission spectroscopy may predict histologic tumor response and have promising predict the outcome of the treatment. If radiographic studies are effective at determining the degree of necrosis at surgical resection, then these studies could serve as a prognostic factor or a determinant of therapeutic efficacy.

There is a clear need for latest effective agents for patients with osteosarcoma, especially those who present with metastatic disease or develop tumor recurrence. Many novel agents that have been studied in the clinical trials such as monoclonal antibodies, transstuzumab (Hercetpin; Genetech, Inc.; South San Francisco, CA), inhaled GM-CSF and interferon-γ, adeno viral gene therapy, trimetrexate (Neurexin; MedImmune, Inc.; Gaithersburg, MD) and imatinib (Gleevec; Novartis Pharmaceuticals Corporation; East Hanover, NJ) are also in active area of research in osteosarcoma. For patients presenting with localized osteosarcoma, increasing the dose intensity may increase the efficacy of currently available agents.

REFERENCES

1. What is the following disease associated with high incidence of osteosarcoma?
   A. Albright-McCune-Sternberg syndrome
   B. Retinoblastoma
   C. Gardner’s syndrome
   D. Maffucci’s syndrome
   E. Breast cancer

2. What is the most common location for osteosarcoma?
   A. Shoulder
   B. Spine
   C. Pelvis
   D. Hip
   E. Knee

3. What is the most important imaging that can clearly demonstrate the local extent of osteosarcoma?
   A. Plain radiograph
   B. Bone scan
   C. CT scan
   D. MRI
   E. PET scan

4. What is the most appropriate treatment for a non-metastatic osteosarcoma of the extremity?
   A. Surgery
   B. Chemotherapy
   C. Radiation therapy
   D. Surgery and chemotherapy
   E. Surgery, chemotherapy and radiation therapy

5. Regarding to prognostic factors for osteosarcoma, the most important factor is.............