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The Management and Approach to Osteosarcoma in Children: A Mini-review Article

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Abstract
Osteosarcoma (OS) is the most common type of primary malignant bone tumor. The onset of OS is associated with local pain and swelling as well as joint dysfunction, occasionally. The most common location for OS is around the knee joint. These patients often tend to receive medical attention following physical exercise and trauma. The affected population is mainly teenagers, children, and young adults with age range of 10-30 years.
OS can be diagnosed via different approaches. The main serum markers for pediatric OS are insulin-like growth factor (IGF-1 and IGFBP-3), anti-ki57 antibody, tumor necrosis factor (TNF)-β and sTNF-R, T3, CD44, vascular endothelial growth factor, serum amyloid A, CXC chemokines, bone alkalin phosphatase, Interleukin (IL-2, IL-4, IL-8), interferon gamma (IFN-γ), TNF-α, and free polyamines.
Given that there is no comprehensive review literature regarding OS management in our country, this study aimed to assess a survey on the management and approach of OS in children. In this regard, we have discussed the epidemiology, etiology, type, clinical feature, diagnosis, and OS therapy.
Keywords: Childhood, Etiology, Malignancy, Osteosarcoma, Serum Marker

Introduction

Osteosarcoma (OS) accounts for 30%–80% of the primary skeletal sarcomas. The onset of OS is associated with local pain and swelling as well as joint dysfunction, occasionally (1). The prevalence of OS in metaphysis of long tubular bones is common, however rare in the pelvis, spine, and sacrum areas (2). The majority of individuals with OS demonstrated only a single lesion (1). The affected population is mainly teenagers, children, and young adults with age range of 10-30 years (3, 4). The most common location for OS is around the knee joint (5). In addition, the second most common location is the proximal tibia, followed by the proximal humerus and femur (5).

This review summarizes epidemiology, aetiology, type, and clinical features, diagnosis, and therapy of OS with focus on various procedures.

OS in children

OS is the most common solid cancer illness in children that occurs in approximately 6 children per million, annually (5). Bone tumors are rare in children with a range of 8.7/million in children less than 20 years (6). Furthermore, OS is more common in tall children (5). Limb-Salvage (LN) can be performed for up to 85% of children with OS. The principal surgical challenge in children after removal of the tumor is regarding how to reconstruct the limb (5).

Epidemiology of OS

The first peak of OS occurs during the second decade of life (16 and 18 years old in girls and boys, respectively). The second peak occurs in older adults. This frequency in boys was higher than girls in most series. In addition, the prevalence of OS in American-Africans is a little more than in Caucasians. The incidence of OS is extremely rare in children before 5 years old. About 15%–20% of patients at initial diagnosis show overt lung metastases, while 40% of individuals demonstrate metastases at a later stage.

This disease occurs in 42% of patients in the femur area, 19% occur in the tibia, and 10% in the humerus (3).

The Etiology of OS

Paget illness of bone (a metabolic illness) often occurs in old individuals and about 1% of individuals with this disease develop OS, suggesting that OS may be associated with anomalous bone remodeling, etiologically (7,8). In addition, OS is the second common tumor in individuals with retinoblastoma (9).

Insulin-like growth factors (IGF-I and IGF-II) are expressed by OS cells; its binding to ligands of the IGF receptor leads to stimulate the transduction pathways of the mitogen-activated protein kinase and phosphoinositide 3-kinases transduction pathways, causing cell proliferation of cells and prevention of apoptosis (10).

- **Genetic factor**

loss of chromosomes 9, 10, 13, and 17, loss of heterozygosity of 10q21.1, and amplification of chromosomes 6p21, 8q24, and 12q14, and to gain chromosome 1, are the common genomic changes and abnormalities which are related to osteosarcoma(11).

Many patients with OS have TP53 mutations (7).

- **Environmental factors**

Environmental factors, including viruses, trauma, ionizing radiation, and alkylating mediators affect the risk for osteosarcoma (7). Ionizing radiation is a risk factor for osteosarcoma (3%of cases).

Alkilating mediators, such as anthracyclines cyclophosphamide, nitrogen mustards, fosfamide and chemical agents containing methylcholanthren, beryllium oxide, zinc beryllium silicateaniline, and etc causes the progress of OS (7, 12). There is no confirmation regarding the incidence of OS via virus. But a viral source, including simian virus 40 (SV40) had been earlier proposed for OS (7).

Clinical Features of OS

Most individuals with OS demonstrate pain and swelling and often tend to receive medical attention following physical exercise and trauma. Generally, these symptoms last for several months (mean: 3–4 months). The pain is worsening over time.

If over the last few weeks, the pain is worsening, it is suspected to be OS. If the temperature of the body is normal, and the area is swollen, and warming, and larger diameter, indicating the tumor has grown significantly (3).

Types

According to WHO; the bone tumors are divided into central, surface, and intramedullary tumors with many subtypes in each group.

- **Central**
  - **Conventional OS**

The most common class of OS is conventional OS and shows that about 80% of OS cases influence patients in the first and second decades of life. This is subdivided into chondroblastic, osteoblastic, and fibroblastic groups regarding its dependence on the predominant characteristics of the cells; but no significant difference is seen in clinical outcomes among these groups (13, 14).

- **Telangiectatic osteosarcoma (TO)**

TO accounts for approximately 4% of OS (15). Radiographically, TO is metaphyseal, with geographic patterns of bone destruction (13). The prognosis of TO is worse than the conventional type, but no difference is seen between the two types (16, 17).

- **Low-grade osteosarcoma(LGO)**

LGO accounts for 1–2% of all OS and affects individuals in the third or fourth decade of life (18). The recognition of low-grade OS is difficult due to low grade, and may be similar to fibrous dysplasia, parosteal OS or desmoplastic fibroma.

Small-cell osteosarcoma

Small-cell osteosarcoma accounts for 1–2% of all OS. Its histological characteristics are round hypochromatic nuclei cells, small cells and little nuclear polymorphism (13).

- **Surface**
  - **Parosteal osteosarcoma**

It is an OS with a low grade originated from the periosteum. Parosteal OS shows 4-6% of OS and occurs in other sites such as the proximal tibia and humerus (13, 19). Histologically, Parosteal OS demonstrates streams of bone trabeculae which exhibit a high degree of parallel orientation (20).

- **Periosteal osteosarcoma (PO)**

PO has a matrix gradient which is less common than parosteal and has mainly cartilaginous characteristics (13).

- **High-grade surface osteosarcoma**

This type of OS forms less than 1% of all OS and demonstrates a surface lesion with a high grade. This type of OS is characterized by a superficial lesion with mineralization and may occur in the surrounding soft tissues (13).

Diagnosis

- **Magnetic resonance imaging (MRI)**

MRI evaluates the invasion of lesion into the soft tissue, neurovascular structures, skip lesions, level of bone marrow replacement, and extension into the bordering joint(21,22).

- **Computed tomography (CT) scan**

CT scan is useful to see the extent of inside, and outside invasion and to detect micromineralized bone-like formation of tumors that are not diagnosed by X-rays (1).

- **Positron emission tomography (PET) scans**

PET scan is applied to evaluate primary lesions and detect metastatic lesions in other bones and lungs. PET scan evaluates the histologic answer of the illness to chemotherapy and predicts progression-free survival (7, 13)

- **X-ray**

X-ray with high spatial resolution demonstrates the size and location of the tumor and the extent of bone destruction (1).

The radiation dose received by individuals during an X-ray examination is small and leads to minimal damage to the body. Furthermore, because it is relatively cost-effective for most patients, it is the preferred technique for early lesion screening and diagnosis (1).

Although X-ray examination is associated with various advantages, it has some shortcomings, including low-density resolution; thus it does not show tiny bone injuries and soft tissue masses, tumor invasion of the bone marrow and callus, the surrounding structures soft tissue masses (1)

- **Biopsy**

Biopsy is necessary for the correct diagnosis of OS (1, 23).

Tissue biopsy is associated with many advantages (1, 24): 1): enables visual lesion tissues, 2): permits more precise

information regarding the development of lesions, 3): helps the understanding the body's capability to resist disease.
The routine biopsy procedure includes incisional biopsy and needle aspiration biopsy. Performing the second technique is easy, however it occasionally leads to material acquisitions; and unfavorable punctures. But tumor tissues are not strongly obtained for the diagnosis through this procedure (25).

- **Serum markers**

There is no reliable laboratory test for the diagnosis of OS. Various serum markers have been assessed regarding their usefulness in progression, diagnosis, and recurrence. The most important serum biomarkers are discussed as follows.
Alkaline phosphatase and lactate dehydrogenase are worth serum markers and the diagnostic importance of alkaline phosphatase is high in OS (26).There is significant association between alkaline phosphatase (ALP) with tumor volume (26). Higher levels of lactate dehydrogenase (LDH) were the most predictive factor for patients with poorer prognosis (27).
The use of ALP and lactate dehydrogenase may be valuable in the initial stages of OS. The combination of ALP and LDH may be valuable with other diagnostic methods (27).
Furthermore, the increased level of miR-194 can serve as a new and promising biomarker for prognosis and detection of OS (28).
Antiangiogenic proteins**,** including pigment epithelial-derived factor**,** troponin I, TGF-*β*, and troponin are reduced in OS (26).
In OS, matrix metalloproteinases degrade extracellular collagens, allowing tumor and endothelial cell invasion. Matrix metalloproteinases are involved in angiogenesis and vessel wall remodeling and enhance vascular leakage (7).
Cathepsin K which is produced by osteoclasts for breaking osteopontin, osteonectin, and collagen I helps invasion (29).

8. Serum markers for pediatric OS

The candidate list of the most serum markers for pediatric OS is shown as follows.

- Insulin-like growth factor (IGF-1 and IGFBP-3**)**
- Anti-ki57 antibody
- Tumor necrosis factor (TNF)-β and sTNF-R
- T3
- CD44
- Vascular endothelial growth factor
- Serum amyloid A
- Bone alkaline phosphatase
- CXC chemokines
- Interleukin (IL-2, IL-4, IL-8), IFN-γ, TNF-α
- Free polyamines (3).

Treatment

There are many treatments for OS. Following the most important treatment methods is explained.

- **Surgery**

Tumor surgery is performed with the aim of achieving complete removal of the disease. In the surgery of OS, the lesion should completely be removed to avoid distant metastasis and local recurrence. If the lesion cannot be completely removed by surgery, the local recurrence rate can be as high as 25% (30).
The performing surgery in this case has two types, including LN and amputation (31).
LN surgery is a surgical method for restoration of bone and joint function after removing many bone tumors (1). LN surgery is the desired selection for some patients (32). LN is specially selected over amputation. More than 85% of patients apply this method (7).

- **Chemotherapy**

Chemotherapy is applied as an adjuvant therapy after surgery to remove the organization of lesions and metastasis which cannot be completely eliminated by surgery alone (33). For deleting the pre-operative subclinical nature of tumors, for reducing the surrounding reaction zone, and developing an appropriate situation for LN surgery, new preoperative chemotherapy was used, leading to neoadjuvant chemotherapy (NC) (1).

The importance of NC is due to early systematic therapy for eliminating potential micrometastases, allowing the assessment of preoperative chemotherapy according to tumor necrosis rate for guiding postoperative chemotherapy, decreasing tumor edema bands, increasing the LN rates, and decreasing the recurrence rates (34).

Adjuvant MAP chemotherapy which is composed of the combination of HDMTX, ADM, DDP is a cornerstone of therapy (35). Most clinics conduct 2-6 courses of chemotherapy before surgery for 6–18 weeks, worldwide (1)The side effects and toxic effects of chemotherapy drug; including liver and renal function damage, neurotoxicity, bone marrow suppression and gastrointestinal reactions can be considered (36). In addition, high frequency of hearing loss was seen in 11% of patients undergoing cisplatin (37).

- **Radiotherapy**

Chemotherapy is especially effective in patients who cannot be surgically resected or in patients whose tumors stay at the resection margin or in OS patients with poor response to chemotherapy (38, 39).

Another study revealed that radiotherapy is a valid procedure to protect limb functions and control local diseases (1).

Ciernik et al. showed that in proton therapy procedure, a high dose of radiation therapy is provided for local therapy in individuals with unresectable or incompletely removed OS. But OS is not sensitive to the technique of radiotherapy. Recent studies have shown that the combined use of ionizing radiation and ginseng polysaccharide enhances the sensitivity of OS cells to ionizing radiation (1). Radiotherapy for OS in the future will be done according to the combination of radiotherapy sensitization with progressive procedures, including stereotactic radiotherapy (40), heavy ion radiotherapy (1), and proton radiotherapy (41) to achieve better therapy effect with low dose and high precision

- **Gene therapy**

Gene therapy in the 1990s provided novel insight for OS therapy (1). In gene therapy, genes with therapeutic effects or normal genes were introduced into human target cells via vectors for correcting the gene defects or exerting therapeutic effects to obtain the results (42). The treatment of OS genes is mainly concentrated on tumor suppressor genes; antisense genes combined gene therapy, anti-angiogenic gene, suicide genes, and immune genes (43). The tumor suppressor genes including p16, p53, p21, and Rb have been evaluated for therapy (44). Meanwhile, p53 has been deeply studied. According to these studies, patients with osteosarcoma have a p53 mutation (36). Other studies demonstrated that p53-expressing protein may be a prognostic biomarker to predict the overall survival of OS. Ye and colleagues revealed that overexpression of p53 enhances the sensitivity of chemotherapy to multidrug-resistant OS in cell lines (46).

- **Immunotherapy**

This procedure is done to regulate the immune function by the possible killing of tumor cells, differentiating, and preventing tumor growth, and regulating the body's immune function (1). This therapy approach is important in the adjuvant therapy of tumors, due to its specific outcomes for patients with cancer, particularly via providing effective and

new therapy procedures for recurrent and advanced, metastatic OC(47,48).

OS immunotherapy includes specific and non-specific immunotherapy**,** immuno-guided therapy and adoptive immunotherapy. Interleukin-2 is applied for postoperative therapy of OS to yield clinical effect. This component activates the T cell effector and increases the action of natural killer cells (1).

Conclusion

The affected population of OS is mainly teenagers, children, and young adults. The advances in the treatment of OS are slowly made as more is being perceived regarding the illness pathophysiology. Immunotherapy, NC, surgery, radiotherapy, and gene therapy are the most important treatment methods in these individuals. Immunotherapy, and new drug delivery systems are developed and the old principles considering NC and surgical resection are being challenged.

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