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Literature Review

Approach to Diagnosis and Management of Osteosarcoma

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Abstract

Osteosarcoma is a primary bone malignancy of mesenchymal origin. The prevalence of osteosarcoma in Indonesia is not known with certainty. Studies have shown that Paget disease, electrical burns, trauma, beryllium exposure, exposure to alkylating agents, FBJ virus, osteo-chondromatosis, enchondromatosis, fibrous dysplasia, orthopedic prostheses, and bone fractures have been associated with the occurrence of osteosarcoma. Survival rates are expected to improve with treatment consisting of a combination or one of recently developed surgical resection, chemotherapy, and targeted immunotherapy.

Introduction

In children and adolescents, osteosarcoma is a primary bone malignancy of mesenchymal origin. Osteosarcoma also occurs in an older age spectrum (>65 years) because of its association with abnormal bone growth as seen in Paget disease. At a younger age, the incidence of osteosarcoma is associated with rapid bone growth in adolescents. Although the pathophysiology is related to several factors, the exact cause is still unknown. Survival rates are expected to improve with treatment consisting of a combination or one of recently developed surgical resection, chemotherapy, and targeted immunotherapy. In this review article, we focus on the etiology and pathogenesis associated with the diagnosis and short-term and long-term management of osteosarcoma, including newly identified agents such as targeted immunotherapy.[1,2]

Epidemiology

The age distribution of osteosarcoma is bimodal. The first peak is in the 10 to 14 years age group, which corresponds to the pubertal growth spurt. This group accounts for the majority of primary osteosarcomas. In the age range 0-14 years, the incidence of osteosarcoma for all races and sexes is 4 cases per million people per year (3.5-4.6, confidence interval 95%). This number increases to 5 cases per million people per year (4.6-5.6, confidence interval 95%) in the age range 0-19 years. The next peak that can be observed is in adults aged 65 years and over, where the incidence of osteosarcoma is most likely secondary cancer due to malignant degeneration of the Paget disease, location of bone infarction, etc.

The prevalence of osteosarcoma in Indonesia is not known with certainty. The incidence of bone tumors at Cipto Mangunkusumo Hospital is 1.2%, with the incidence of malignant bone tumors being 1.3%. Based on hospital information system data in 2005, osteosarcoma is included in the top five cancer cases at the age of 1-17 years. In evaluating the profile of bone tumors in children at Cipto Mangunkusumo Hospital in 1995-2004, 73.7% of cases were osteosarcoma cases. In 1991-1995, at the RSUD Dr. Soetomo found 373 cases of malignant bone tumors, with 183 cases of primary malignant bone tumors. The ratio of male: to female is 1.4:1 and the number of primary cases is 44 cases per year, especially osteosarcoma which is 62.4% of cases.[4]

Etiology & Pathogenesis

Studies have shown that Paget disease, electrical burns, trauma, beryllium exposure, exposure to

alkylating agents, FBJ virus, osteochondromatosis, enchondromatosis, fibrous dysplasia, orthopedic prostheses, and bone fractures have been associated with the occurrence of osteosarcoma. An association with secondary osteosarcoma has been identified in patients with infarction and infection. In addition, osteosarcoma has been reported to be correlated with exposure to ionizing radiation, radium, and ancient contrast agents such as Trotrast.[3,6,7,8]

Other literature shows that the most common sites are the femur (42%, 75% tumors on the distal bone), tibia (19%, 80% tumors on the proximal bone), and humerus (10%, tumors on the proximal bone). 90% of bone proximal to bone). Other possible sites are the skull or jaw (8%) and pelvis (8%). Osteosarcoma can be divided into primary and secondary types. Primary tumors usually arise in the metaphysis of the long bones and tend to be more prominent in the knee, with nearly 60% occurring in these sites. Children and adolescents are the majority affected by this condition. Secondary tumors have a much wider distribution, reflecting the diverse nature of the underlying predisposing conditions. They most often appear in the adult population. The incidence is particularly high in the flat bones, especially in the pelvis (a commonplace Paget disease).[3]

Typical	Non-Typical
High-grade malignant tumor	Age >60 years
Mesenchymal cells producing osteoid and immature bone	41.3 % incidence of axial osteosarcoma in the elderly
Age 5-30 years, most often at the age of 10-20 years	High metastatic rates
Pain at night	Pathological fracture
History of minor trauma	Lymphadenopathy
Red Flag Sign • Significant weight loss • Loss of appetite • Pain at night • Worsening of pain on treatment • Abnormal Lump	
Local tenderness, mass, deformity	

Table 1. Typical versus atypical osteosarcoma

Diagnosis

National Comprehensive Cancer Network`s 2020 Guidelines for Initial Evaluation of Osteosarcoma (Version 1.2020)

a. Clinical History and Physical Examination

Osteosarcoma symptoms can appear for a long time, sometimes weeks or months, before the patient requests an evaluation. The most common symptom is bone pain, especially with exertion. Parents often worry that their child has sprained sprain, arthritis

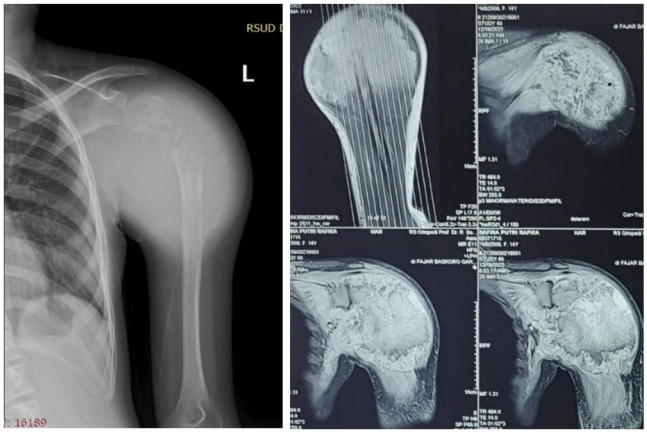

Figure 1. X-Ray and MRI findings in osteosarcoma of the proximal humerus

1. OS Central	a. Conventional i. Osteoblastic ii. From the chondraoblast iii. Fibroblastic b. Epithelioid c. Giant cell-rich d. Osteoblastoma-like e. Small cell f. Telangiectatic g. Low-grade central
2. Multifocal	
3. Gnathic	
4. OS Surface	a. Periosteal b. Parosteal c. High-grade surface d. Intracortical
5. OS Seconds	

Table 2. Types of Osteosarcoma

or growth pain/growing pains. There may or may not be a history of traumatic musculoskeletal injury reported. Swelling or a lump may or may not be reported, depending on the size and location of the tumor. Systemic symptoms, such as those seen in lymphoma (fever, night sweats, etc.), are rare. Respiratory symptoms are rare and, if present, indicate extensive pulmonary involvement. Additional symptoms are unusual because metastases to other sites are very rare.[9]

Physical examination findings are usually focused around the site of the primary tumor and may include: a palpable mass that may be tender and warm with or without overlying throbbing or bruits, although these signs are nonspecific; decreased joint involvement range of motion; local or regional lymphadenopathy (uncommon); and respiratory findings with the metastatic form.[9]

b. Laboratory Analysis

Biochemical markers such as serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) are assessed at baseline because they provide

evidence for diagnosis and prognosis. ALP levels will be high because of the increased osteoblastic activity associated with osteosarcoma. Very high levels have been associated with a heavy tumor burden and are generally considered a poor prognostic indicator. It is also important to assess the end of the course of treatment because biomarker levels can decrease with successful treatment and can increase with residual disease or relapse.[10,11] ALP is increased when there is active bone formation because ALP is a by-product of osteoblast activity. Osteosarcoma is characterized by the production of immature osteoid tissue or bone so that serum ALP levels are high in osteosarcoma patients.

c. Diagnostic Imaging of Primary Tumors

1. Radiography

although MRI is the gold standard for diagnostic imaging of osteosarcoma, radiography is generally the first study obtained when a potential bone mass is identified on physical examination. Conventional radiographs of osteosarcoma may show damage to medullary bone and cortical, permeative, or cortical cortex moth-eaten, configuration "Sunburst" (due to aggressive periostitis), configuration "Codman triangle" (due to elevation of the periosteum away from the bone), bone lesion "fluffy" or "cloud-like" undefined, soft tissue mass, calcified osteoid matrix produced by the tumor.[10]

2. Computed Tomography

the main role of CT is primarily to assist with biopsy planning and disease staging. Unless the bone lesion is predominantly lytic in nature, CT may not make a significant contribution to direct tumor assessment after X-ray and MRI. For lytic lesions, small amounts of mineral material may not be observable on either plain film or MRI. However, chest CT is the modality of choice for evaluating metastases.[10]

3. Magnetic Resonance Imaging

after identifying a suspicious lesion on radiography, MRI may be required for further characterization. MRI is an indispensable tool for determining the extent of tumors inside and outside the bone. All bones involved, as well as one joint above and one joint below the tumor, should be included in the study so skip lesions not missed. MRI can accurately and precisely delineate tumor grade in adjacent soft tissues, joint involvement, whether or not the tumor traverses the physis, and proximity to the neurovascular bundle closest. Nearly every aspect of treatment can be assessed by MRI, from pre-surgical assessment of limb resection to chemotherapy response rates in the form of tumor necrosis, shrinkage, and better capsulation.[10] Sequences traditionally obtained in an osteosarcoma MRI may show the following:[10]

- T1 Weighted Images: Non-ossifying soft tissue component: signal intensity intermediate; Osteoid component: low signal intensity; Peritumoral edema: signal intensity intermediate; and Scattered hemorrhage foci: variable signal intensity based on chronicity.
- T2 Weighted Images: Components of soft tissue non-ossified: high signal intensity; Osteoid component: low signal intensity; and Peritumoral edema: high signal intensity.

4. Diffusion Weighted Imaging (DWI) - MRI

The most common primary malignant bone tumor is intramedullary osteosarcoma. Yakushiji et al. found that DWI may be more effective than gadolinium-enhanced MRI in differentiating chondroblastic osteosarcoma from other osteosarcomas. This is important because the large chondroid component can make it difficult to biopsy areas containing malignant tumor cells. Missing chondroblastic osteosarcoma is detrimental not only to patient management but also to the final clinical outcome. Patients with chondrosarcoma have a 5-year survival rate of 72.6% when they receive appropriate treatment whereas the 5-year survival rate for chondroblastic osteosarcoma is around 60%.[12]

5. Positron Emission Tomography

PET is a nuclear medicine imaging technique that detects severe metabolic lesions. It is an important tool for determining tumor extent and locating subtle lesions after initial imaging has identified a suspicious mass. Later in treatment, PET can help detect relapse.

Therefore, apart from conventional, well-standard anatomical imaging procedures, metabolic PET imaging is an ongoing focus of research assessing its potential usefulness in sarcoma patients, for example, to determine the metabolic rate of osteosarcoma, monitor response to neoadjuvant therapy, and differentiate sarcomas that are viable of post-treatment changes. PET scan the most widely used for osteosarcoma is 18F-FDG.PET scan Other clinical studies with reported utility for imaging osteosarcoma in patients are 18F-fluoride (18F) ion, whereas 18F-labeled monoclonal antibodies, 18F-fluoromisonidazole, RGD-labeled glycopeptides 18F, 3H-thymidine, 13N-methionine, and PET of transcriptional activity p53 in osteosarcoma has only been used in animal studies.[13]

Because of the reported overlap of 18F-FDG uptake values between different tumor grades, it is usually not possible to differentiate low-grade and occasionally high-grade osteosarcoma from benign 18F-FDG-avid lesions, such as giant cell tumors or osteomyelitis. Thus, the results made it impossible to

avoid a biopsy. PET 18F-FDG is, however, very helpful for targeting biopsies in large and heterogeneous tumors to achieve representative tumor specimens because the highest-grade area determines the histological grade and subsequent biologic behavior. This information about tumor biology cannot be provided by other radiological imaging tools. Another topic of interest that should be further evaluated in clinical studies is tumors that are highly metabolically active but histologically low-grade tumors. Within the tumor subset, histological grade did not predict the outcome. Moreover, high initial 18F-FDG uptake is predictive of poor overall and event-free survival. Clinical follow-up studies in these patients will clarify whether 18F-FDG PET is more accurate for outcome prediction than conventional clinical tumor assessment.[13]

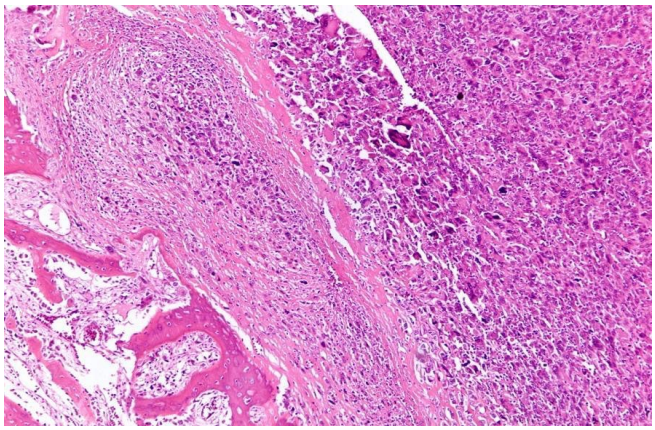

Figure 2. Medium-magnification micrograph of osteosarcoma (middle and right of image) adjacent to non-malignant bone (bottom-left of image): Top right of the image has a poorly differentiated tumor. Osteoid with a high density of malignant cells is seen between non-malignant bone and a poorly differentiated tumor (H&E stain).

d. Biopsy

A biopsy is necessary after a physical examination, laboratory analysis, and imaging studies confirm a lesion consistent with osteosarcoma. Definitive surgical intervention must include an excision biopsy tract. To avoid recurrence due to possible colonization of cancer cells on the biopsy tract. In this case, a tattoo should be done so that it can be easily identified. Ideally, the surgeon performing the biopsy should be the same surgeon who performed the resection, so they know the path and extent of the biopsy. Open-access biopsy previously considered the best choice because of its high accuracy. However, recent studies have found that open access is correlated with an increased risk of complications such as infection, improper wound healing, and colonization of the site by tumor cells, as previously discussed. Thus, the core biopsy has been replaced traditional open approach, not only because of the reduced risk of contamination operating room bed with tumor cells but also because of their lower cost and shorter recovery time. This is especially important for patients who are aware of potency limb-sparing surgery, whereas many local networks as possible need to be securely maintained. A core needle biopsy was performed with a single deep needle puncture through the trocar across a plane of tissue at the site included in the final resection. Multiple nuclei are needed from the representative area of the mass – the area of soft tissue around the lesion. The necrotic central region produces little viable tissue, whereas the 'Codman triangle' produces only reactive bone. Importantly, recent studies have shown that fine needle aspiration is not an effective approach for biopsy because sufficient tissue samples are not obtained for an accurate diagnosis. After the biopsy, the tissue sample must be analyzed by a pathologist in a biopsy format or frozen for definitive diagnosis, assessment, and histological subtype. All of these influence medical and surgical treatment strategies.[14]

e. Immunohistochemistry and Tumor Marker

Kaseta et al. (2007) analyzed the expression of the bax, caspase-8, and cytochrome c genes in subjects with osteosarcoma. They performed immunohistochemical analysis of 35 patients treated surgically with primary OS and 18 tissue specimens from non-malignant bone lesions. The authors suggested that neither gene had a predictive role in survival, but decreased 4-year disease-free survival in the control group, confirming that more intensive adjuvant treatment may reduce disease relapse rates.[15] Contrary to previous hypotheses about c-erbB-2 and its potential role as a prognostic biologic marker, c-erbB-2 expression is not associated with metastatic risk.[16]

Zhao et al. (2008) assessed the distribution of ribonucleoprotein hnRNP A2/B1 in the nuclear matrix of human MG-63 osteosarcoma cells, suggesting that this nuclear matrix protein has an important role in the regulation of cell differentiation.[17] Luo et al. (2008) studied the role of osteoblasts in the development of osteosarcoma. The authors confirmed that alkaline phosphatase (ALP), Runx2, OSX, and osteopontin (OPN) levels were low in the OS line because most OS cells fail to complete terminal differentiation. The results suggest that changes in the osteoprogenitor can interfere with the pathways of osteogenic differentiation. Thus, identifying potential differentiation defects in OS tumors will make it possible to reconstruct tumorigenic events in osteoprogenitors and develop rational differentiation therapies for clinical OS management.[18]

Staging

OS is classified based on its location, the type of cells involved, and the tumor grade. Most of the OS is located in the long medullary cavity. OS also includes preexisting periosteal, cortical, soft tissue, or bony lesions. All OS contain varying amounts of osteoid, mostly composed of cartilage and fibrous tissue. If one cell type accounts for 50% of the malignancy, the tumor is considered osteoblastic, chondroblastic, or fibroblastic, depending on its type. The prevalence of these three cell types is 50–80%, 5–25%, and 7–25%. In addition, the histological grades are low (grade 1), medium (grade 2), and high (grade 3 or 4), which are the tumor regions with the highest degeneration rates and the highest mitotic rates. Table 1 shows the different types of operating systems. In addition, it has been reported that 30% of well-differentiated chondroblasts or osteoblasts and OS usually respond poorly to chemotherapy. In addition, several studies have reported reduced metastasis-free survival in tumors with chondrocyte subtypes. It has also been reported that survival in high-grade OS is independent of the predominant cell type.[27,29]

Cancer staging help determines the extent or likelihood of the tumor spreading throughout the body. It also provides a means of predicting the likely prognosis. As explained by Enneking, a good staging system should enable the physician to communicate the patient's condition, suggest a prognosis, guide surgical management, and suggest appropriate additional treatment.[15] The two most commonly used surgical staging systems today for OS and malignant OS are the Enneking/MSTS system (Table 2) and AJCC (Table 3). Although there are slight differences between these two systems, most of the basic concepts are the same as they depend on tumor grade, size, and metastases.[30]

Treatment

Local Control

1. **Surgery - Limb-Sparing Procedure**

   Onco-surgery, which removes large areas of the tumor, is aimed at achieving complete resection of the disease. In this case, surgery can be done in two ways: limb-sparing and amputation. Amputation is an important therapeutic approach for cases of early OS. After ineffective adjuvant therapy, amputation is considered a necessary and effective alternative treatment for malignant bone tumors that can cause extensive cellular damage. For amputations, the osteotomy level should have a tumor-free margin of at least 5 cm. Most doctors consider the safety plane for an osteotomy to be 5 cm beyond the plane of the tumor. However, a reliable dimensional basis is required for determination based on X-ray, CT, and MRI.[33]

   The goals of surgical treatment of OS have evolved from saving lives to maximizing the function of the affected limb. Limb-sparing is a surgical intervention to restore bone and joint function after extensive resection of malignant bone tumors of the extremities. The key to surgery is the selection of the right border. With the latest popularity of therapy limb-sparing comprehensive treatment combined with neoadjuvant chemotherapy, surgery limb-sparing is more widely used in clinical applications. 80-95% of patients with soft tissue sarcomas of the bones and extremities can undergo surgery limb-sparing.[33,34]

   Computer-assisted once-surgery are becoming increasingly important in the treatment of OS. Currently, there is no commercial platform that meets all the software and hardware requirements related to OS operation.[38]

2. **Radiotherapy**

   Local radiation therapy has been shown to have some benefit in patients who cannot be resected surgically or whose tumors remain at the edges of surgery and in patients with OS whose tumors are less responsive to chemotherapy. Preliminary results confirm that external beam radiation combined with systemic therapy may be an effective approach for local control and palliation. Following the use of effective induction chemotherapy in non-metastatic limb OS, Machak et al. regard radiation therapy as a reliable method of controlling localized disease and maintaining limb function.[33]

   A recent study confirmed that the combined application of ginseng polysaccharide (GPS) and ionizing radiation (IR) made OS cells sensitive to IR [85]. Although sensitizers may represent a breakthrough in radiotherapy, advances and improvements in radiotherapy technology and equipment are increasing long-term cancer survival. In the future, radiotherapy for OS is based on radiotherapy sensitization research combined with advanced techniques such as stereotactic radiosurgery, proton therapy heavy ion radiotherapy, and surgical treatment. and chemotherapy organically combined to achieve better treatment. Low dosage and high precision effect. Its role in comprehensive adjunctive limb-sparing therapy cannot be overlooked.[33]

3. **Cryosurgery**

   The use of liquid nitrogen as cryosurgery for osteosarcoma has been reported in previous studies. However, the use of cryosurgery as a method of reconstructive osteosarcoma in very young children has not been reported in previous studies. Cryosurgery is explained by applying liquid nitrogen into the tumor cavity or immersing the resected segment in liquid nitrogen. In this case,

curettage and drilling into the base and walls of the bone are performed to maximize contact between the liquid nitrogen and the deepest layers of the bone. Adequate contact with the tumor margins is important to ensure the delivery of extreme temperatures that destroy malignant cells. The efficacy of cryosurgery has been reported in 10 patients without local or systemic recurrence in all subjects and a functional score of 82.4%. Another study by Tsuchiya et al. with similar cryosurgery techniques showed excellent limb function in the majority of subjects and high rates of bone fusion. In this case, we found a radiology unit at 6 months follow-up with a musculoskeletal community tumor score of 76.6%. However, complications were reported in 25% of subjects with infection (10.5%), fracture (7.5%), and local recurrence (7.5%). Apart from the complications mentioned, cryosurgery can be an option for the biological reconstruction of osteosarcoma.[39]

Systemic Control

1. Chemotherapy

Research on the effects of chemotherapy on OS began in the 1970s. At that time, chemotherapy was used as an adjunctive therapy after surgery to eliminate the formation of lesions and metastases that could not be removed completely by surgery alone. In the late 1970s, innovative preoperative chemotherapy was boldly and successfully applied in the clinic to eliminate tumor asymptomaticity before surgery, reduce the reaction zone around it, and create conditions suitable for limb-sparing surgery. This approach has become known as neoadjuvant chemotherapy.[40]

The importance of neoadjuvant chemotherapy is to allow early systemic treatment that eliminates potential micro-metastases. Preoperative chemotherapy can be evaluated and postoperative chemotherapy can be guided based on the degree of tumor necrosis. Reduce tumor edema bands. Increase the limb salvage rate. This reduces the recurrence rate.[41] This concept is widely accepted and widely used in clinical practice, with the gradual establishment of comprehensive limb-sparing therapy complementing neoadjuvant chemotherapy, limb-sparing surgery being the mainstay of OS, and OS leading to a significant 5-year survival rate.[42]

2. Targeted Therapy

Given that genetic mutations are the most fundamental cause of OS, it is important to involve genetic research in OS prevention and treatment strategies. Gene therapy involves the introduction of normal or therapeutic genes into human target cells via vectors to correct genetic defects or provide a therapeutic effect sufficient to achieve a therapeutic outcome. This is a medical method.[33]

OS mainly focuses on tumor suppressor genes, suicide genes, combination gene therapy, antisense genes, immune genes, and anti-angiogenic genes. The p53, p16, p21, and Rb tumor suppressor genes are currently being tested for therapy. Of these, p53 has been studied in detail. These studies show that patients with OS frequently have mutations in p53.[33] Wu et al. noted that p53-expressed protein may be a prognostic biomarker for predicting overall survival from OS, further enhancing the status of p53 as an entry point for gene therapy in OS. I pay attention. leaves et al.[29] reported that overexpression of wild-type p53 sensitizes a multidrug-resistant OS cell line to chemotherapy, which may provide new clues for the resolution of chemotherapy resistance. I have. For suicide gene therapy, the thymidine kinase (TK)/propoxyguanosine (GCV) system is preferred. Zhang et al.[44]

Based on combination gene therapy, the effect of other combination therapies is more significant, not only by creating a synergistic effect but also by reducing the side effects caused by the use of a single drug. Combining gene therapy with other therapies to treat OS patients is expected to be recognized as a useful approach for gene therapy in the future[46], especially genetically modified T-cell therapy. This has shown promise in preclinical studies. Gene therapy has made great strides in recent years and offers valuable prospects, but it is still in the experimental stage and far from having a true clinical application.

3. Immunotherapy

Immunotherapy is carried out to modulate the body's immune function which allows, among other things, the killing tumor cells, regulating and balancing the body's immune function, as well as differentiation and suppression of tumor growth. This therapeutic approach is important in adjuvant oncology because it provides specific and effective outcomes for cancer patients, especially by providing novel and effective treatments for sex enhancement of advanced, metastatic, and recurrent OS. As the most basic components of immunotherapy, cytokines regulate the activation, proliferation, and functional activity of immune cells.[33]

Checkpoint inhibitors are also an interesting area of research. However, an increased understanding of tumor immunity has confirmed that tumor cells are poorly immunogenic and cannot be expressed strongly in the immune system. Therefore, the introduction and expression of immunogen-related molecules into tumor cells enhances the immunogenicity of tumor cells and provides strong immune stimulation of the immune system. This

line of thinking has led to the new topic of tumor immunotherapy. There is still a lot of work to be done, but it is hoped that immunotherapy will provide a breakthrough and revolutionize the treatment of OS.[17]

Conclusion

Osteosarcoma is a malignant tumor that arises in mesenchymal tissue. Advances in chemotherapy and surgery have made it possible to transform OS from a nearly universally fatal disease to one in which the majority of patients survive. Accurate and effective diagnosis, preoperative chemotherapy, surgical resection, postoperative chemotherapy, and lifelong surveillance are key components in the successful management of this complex and potentially fatal disease.

Acknowledgment

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