

# Progress in Metastasis and Treatment of Osteosarcoma

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**Abstract:** Osteosarcoma is a primary malignant tumor originating from mesenchymal tissue. It has the characteristics of high malignancy, easy metastasis (common lung metastasis) and poor prognosis. Metastasis is the main cause of treatment failure and poor prognosis. Although the treatment of osteosarcoma has made some progress in these decades, the 5-year survival rate of patients with metastasis has not increased much. This review explores the molecular mechanism of osteosarcoma metastasis, the current research progress of therapeutic drugs, immunotherapy and targeted therapy, and provides ideas for the treatment of osteosarcoma.

**Keywords:** Osteosarcoma; Metastasis; Immunotherapy; Targeted Therapy.

## 1. Introduction

Osteosarcoma is the most common primary malignant bone tumour in children, adolescents and the elderly. There are two peaks of incidence, the first in people aged 10-30 years, the first in people aged 15-19 years, and the second in people aged 60 years and over, with more men than women affected [1-2]. OS can be divided into three histological subtypes: intramedullary, superficial and extra-skeletal. The most common site is the distal femur or the proximal tibial epiphysis. The main treatment options for early OS are surgery, chemotherapy (drug therapy), radiotherapy and biologic therapy. Surgery is the mainstay of treatment, but unfortunately 80%-90% of patients treated with surgery or radiation have a recurrence and the five-year survival rate is about 70%, but it is worth noting that the five-year survival rate for patients with advanced OS is only 20% [3-5]. With advances in neoadjuvant chemotherapy, there has been some improvement in overall patient survival after treatment, but there has been no significant improvement in outcomes for patients with advanced OS with metastases [6]. The article will also discuss the metastasis of osteosarcoma, the immunological profile of OS, and the current status and development of treatment.

## 2. Metastasis of Osteosarcoma

The disease is characterized by high malignancy, poor prognosis and metastasis, with most osteosarcomas infiltrating surrounding tissues and even having lung metastases by the time they are detected. Lung metastasis is a major challenge in the management of osteosarcoma, and before the introduction of chemotherapy, over 90% of patients with osteosarcoma died from lung metastases. Since the 1970s, with the introduction and use of chemotherapy, the 5-year survival rate for osteosarcoma patients has increased to around 70%, but the 5-year survival rate following lung metastases is still only 0-30% [7-8]. The current main treatment modality is a combination of surgical resection and radiotherapy. Osteosarcoma is most likely to metastasise in the bloodstream and with it to distant organs in the body, such as the lungs, where the patient's respiratory system will suffer from chest tightness, chest pain and breathlessness, and the brain will suffer from motor deficits, aphasia and even unconsciousness. In addition, metastases to the liver and other

tissues or organs may also occur. Metastases from osteosarcoma should be treated with surgery, followed by chemotherapy and radiotherapy, and regular reviews. There are not many studies on osteosarcoma metastasis and treatment strategies. In order to illustrate the characteristics and biological behavior of metastatic osteosarcoma, the research ranges from conducting basic research to clinical studies, with the aim of early identification of targeted drug targets and promising treatment strategies to break the deadlock in clinical treatment of OS metastasis [9].

### 2.1. Modes of Metastasis in Osteosarcoma

#### 2.1.1. Blood Metastasis

Osteosarcoma is a common malignant bone tumor. As the disease develops, the cancer cells will spread to all parts of the body, invade the blood vessels and flow with the blood to distant organs of the body. The areas prone to metastasis include the internal organs, brain tissue and heart, etc. When the malignant tumour cells enter the lungs, the patient will experience chest tightness and chest pain, when they enter the brain tissue, the patient will experience cognitive and motor impairment, and when they invade the liver, the liver function will be damaged [10].

#### 2.1.2. Lymphatic Metastases

Osteosarcoma cells may also metastasize to other parts of the body through the lymphatic system, but lymphatic metastases are less common in clinical practice and patients with lymphatic metastases may experience swelling of the lymph. The cure rate for osteosarcoma in its early stages is relatively high. When the cancer cells have not spread and metastasized distally, the lesions can be removed surgically and treated with chemotherapy or radiotherapy. However, when the disease has reached an advanced stage, the cancer cells will spread to all parts of the body through metastasis and the chance of cure is extremely low [11].

### 2.2. Signalling Pathways Involved in the Metastatic Process of Osteosarcoma

#### 2.2.1. PI3K/Akt Signalling Pathway

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway is one of the important intracellular signalling pathways that regulate tumour cell differentiation, migration and infiltration [12]. It is the signalling pathway most closely associated with tumours [13]. Activation of

PI3K/ Akt/ mTOR signalling pathway in primary osteosarcoma cases is strongly associated with poor patient prognosis [14], and osteosarcoma patients carrying Akt genotype AA have a higher risk of metastasis in Chinese patients [15]. Epithelial-to-mesenchymal transition (EMT) is highly correlated with invasion and distant metastasis in osteosarcoma [15], with epithelial cells possessing a high migration and infiltration capacity and a mesenchymal cell phenotype that uses the EMT process to break down the extracellular matrix. Upregulation of matrix metalloproteinases (MMPs) can degrade the extracellular matrix and basement membrane, thus participating in and facilitating the EMT process [16-17]. In the range of 0-50 µg/mL, MMP-2 and MMP-9 expression was reduced by the inhibition of Akt phosphorylation, and showed similar anti-osteosarcoma metastatic effects as PI3K inhibitors in U2OS cells in a dose-dependent manner. Bitter coumarin was able to down-regulate the phosphorylation level of Akt and PI3K expression, inhibit the activity of PI3K / Akt signaling pathway, down-regulate the activity of MMP-9. the activity of PI3K / Akt signaling pathway, down-regulate MMP-2 and MMP-9, and inhibit the migration and invasion of osteosarcoma cells. Osteosarcoma tumour stem cells have a higher tumorigenic rate and greater metastatic capacity, and play an important role in the development and metastasis of osteosarcoma [ 18-21]. Studies have shown that the PI3K/Akt signaling pathway is involved in the stemness regulation of osteosarcoma cells [ 22]. Andrographolide was able to reduce the expression of MMP-2 and the stem cell marker CD133 in U2OS and MG63 cells, and in vivo experiments confirmed that andrographolide was effective in reducing the number of osteosarcoma lung metastases, and that these effects were mediated by the effects on These effects were achieved through the regulation of the PI3K/Akt signalling pathway [23]. In addition, there are various active ingredients of Chinese herbal medicine, such as euphorbol, isoglycyrrhizin and lupinol, which can reduce the expression levels of MMP-2 and MMP-9 through PI3K/Akt/mTOR signaling pathway and inhibit osteosarcoma metastasis.

### 3. Treatment of Osteosarcoma

#### 3.1. Surgical Treatment

Surgical treatment is based on a combination of advances in surgery, imaging, chemotherapy and radiotherapy, and is a collaborative effort to save lives and protect the patient's function to the greatest extent possible. The first step in surgical treatment is to standardise the process of individualised neo-adjuvant chemotherapy and then to perform surgery (limb-sparing surgery) on the basis of the effectiveness of chemotherapy. The key to surgical treatment is the need to remove the tumour at the optimal surgical margin and to develop an individualised functional reconstruction plan. [1]. The assessment of patients with suspected osteosarcoma begins with a complete history, physical examination and plain radiographs. x-ray diagnosis is based primarily on the fact that if there is both new bone formation and bone damage within the bone tissue, when the epithelium of the bone ruptures, the cancerous cells will overtop the periosteum, resulting in the characteristic Codman's triangle (a triangular area of periosteal calcification in the area bordering the tumour and healthy tissue called the Codman the triangle is considered to be a typical feature of osteosarcoma). There is a large amount of neoplastic bone

formation. (1) There is a large amount of cloudy, patchy tumour bone within the bone with a high-density factor and, at its most intense, a large ivory change. (2) The soft tissue masses also contain a greater amount of tumour bone. (3) Bone destruction is generally less marked. (4) Periosteal hyperplasia is generally more pronounced. 2. Osteolytic type. (1) Sieve-like, worm-like, large lamellar bone damage. (2) Pathological fracture easily caused. (3) A small amount of tuberos bone and periosteal hyperplasia is usually still visible (if the tuberos bone is not obvious, it is difficult to confirm the diagnosis on X-ray). Mixed type. The two types, sclerotic and osteolytic, are present together. The more differentiated osteoblasts produce ivory-like osteoblasts, while poorly differentiated osteoblasts produce immature bone and bone-like tissue in the form of cotton wool; and needle-like osteoblasts produce needle-like bone perpendicular to the osteocortex after the cancer cells have broken through the osteocortex [24-26]. MRI (Magnetic Resonance Imaging) is currently the most effective imaging test for assessing the relationship between adjacent tissues, blood vessels and nerves and the tumour lesion (which should extend more than 3cm beyond the boundary of the osteosarcoma lesion), so MRI can also be used clinically to examine all parts of the body [27-28].

#### 3.1.1. Surgical Approach

Surgery is also a crucial part of the treatment of osteosarcoma, as it is essential to restore the patient's limb function at an early stage by completely removing the malignant tumour, so that the patient can achieve a high quality of life during the survival period. Surgical options include amputation and limb-sparing surgery. Limb-sparing surgery is currently the most common surgical procedure for osteosarcoma of the limb. However, a rigorous assessment of the patient's physical condition and lesions is required before limb-sparing surgery can be performed to determine whether the patient is ready for limb-sparing surgery [29-30].

These include.

##### (1) Allogeneic or autologous bone grafting

Allogeneic or autologous bone grafting is used. The autologous bone, mainly fibula, can be replaced by a complete free graft or an anastomotic vascular graft to reconstruct the function of the joint with internal or external fixation. The advantages of this method are no rejection, fast healing and low cost. However, if the size and shape of the lesion is different from that of the resected bone segment, the reconstruction result will not be satisfactory, and infection, fracture, bone discontinuity and other adverse consequences may occur [31].

##### (2) Artificial prosthesis replacement

This procedure involves the osteotomy of the tumour site, the insertion of an artificial prosthesis and the reconstruction of the surrounding defective soft cells. For the safety of the procedure, an individualised prosthesis is designed to treat the patient with a preserved limb based on the efficacy of the chemotherapy and MRI examination. With a prosthesis, 80-90% of patients can regain joint function, and some patients can use the prosthesis for more than 20 years, but the exact duration of use needs to be considered in the context of the prosthesis itself and whether the patient suffers from infection, loosening, recurrence or other complications after surgery [32].

##### (3) Rotational amputation

Mostly used in patients under 10 years of age with malignant tumours, this involves replacing the ankle joint

with a knee joint and converting from an above-knee to a below-knee amputation. The advantages of this treatment are: it is a definitive procedure that can be used for a long time without prolonging the life of the limb and rarely requires reoperation; it is a quick healing procedure with few complications and good preservation of limb function, the patient has a normal gait and can exercise; although there is no knee extension device, there is still a functional knee joint; the resection border is basically comparable to AKA; the disadvantages are: the appearance is unacceptable and the patient needs some time to adjust psychologically; it is not easy to accept. It requires a special prosthesis and is more expensive; there are certain complications such as osseous discontinuity, vascular events, pain in the affected limb and early ankle OA [33].

#### (4) Bone removal surgery

This is performed on the basis of adequate chemotherapy, using the principle of distraction osteogenesis, using a specially designed external fixation brace to the proximal and distal ends of the bone defect. This is then held together and the free fragmented bone ends are transported to the bone defect. During the course of the osteogenic transport, new bone tissue grows at the joint. This is achieved by providing support (fixation) to the defective limb with the aid of an external fixation frame and finally by artificially cutting off the normal bone at the upper or lower end of the main segment of the bone defect, or by fixing removable pins or truncated blocks of normal active bone to a fixation brace. The truncated bone block is moved artificially (approx. 1 mm) in a defined direction, at a suitable speed and frequency, so that the bone block is moved in a gradual manner. The repair is carried out by gradually aligning the bone defect with the broken end of the corresponding bone defect [34].

#### (5) Amputation surgery

This procedure is a salvage procedure for the treatment of osteosarcoma and is mainly used in patients with OS who have failed limb preservation surgery and in patients whose tumour has invaded a vascular nerve. The procedure involves transosseous amputation and joint dissection. Amputation is relatively simple and does not require special techniques or equipment, and chemotherapy can be started after early post-operative recovery [35].

### 3.2. Radiation Therapy

Radiotherapy is the local treatment of radiation to destroy and eradicate the primary or metastatic foci of a local tumour. Osteosarcoma is also a type of malignancy that is less sensitive to radiotherapy. The overall local control rate after high dose irradiation is low and most patients still have clear tumour residuals, so it is not advisable to treat osteosarcoma with radiotherapy alone. In this case, the current standard of care for osteosarcoma of the limb requires a combination of neoadjuvant chemotherapy and surgery, with radiotherapy as an adjuvant or palliative treatment. For lesions that cannot be removed surgically in the pelvis, skull base, head and neck and spine, and where tumour remains in the margins after excision, local radiotherapy can be effective in these cases [39-40].

### 3.3. Chemotherapy

Chemotherapy can significantly reduce the proliferation of malignant tumours or kill cancer cells by administering chemically synthesised drugs systemically or locally to the patient. This method affects both tumour cells and normal

cells in the body, and the drugs used in the treatment are toxic to a certain extent, which can damage normal cells and tumour cells indiscriminately and can easily cause a variety of adverse reactions and side effects. However, chemotherapy is still irreplaceable in tumor treatment, and the current combination of targeted drugs and chemotherapy is more effective than chemotherapy alone and is more easily accepted by patients to reduce the damage to the body [41].

#### 3.3.1. Common Chemotherapeutic Agents

The following drugs are commonly used in chemotherapy today:

##### (1) Paclitaxel

Paclitaxel, a natural anti-cancer drug, has also been widely used clinically in the treatment of breast cancer, ovarian cancer and some head and neck cancers and lung cancer. The most commonly used paclitaxel chemotherapy drugs in the market are paclitaxel, paclitaxel albicans and paclitaxel polyene. After treatment with paclitaxel, some patients may develop symptoms of bone marrow suppression, clinically manifested as leukopenia or thrombocytopenia or infection, and may also develop numbness in the ends of the hands and feet; mild or severe hair loss; and impairment of liver and kidney function [42].

##### (2) Antibiotic chemotherapy drugs

These are mainly antitumour substances of microbial origin, such as adriamycin, bleomycin or epi-amycin, and are now widely used in chemotherapy. The main side effects are gastrointestinal discomfort, nausea and vomiting, hair loss and damage to liver and kidney function [43-44].

##### Anti-metabolic chemotherapy drugs

Structurally, anti-metabolic chemotherapy drugs are different from the normal metabolites of the body, mainly by competing with the metabolites for the relevant enzymes and receptors, which can effectively prevent the normal metabolism of the body. The main side effects are diarrhoea; painful oral mucositis [45-46].

#### 3.3.2. Commonly Used International Chemotherapy Regimens

##### (1) The Rosen T-series regimen in the USA

The Rosen T-series regimen has undergone continuous research and development over the years, and in 1973 Rosen determined the post-operative chemotherapy regimen for the preparation of large tumours for resection, based on the degree of necrosis of the tumour tissue after surgery. For grade III-IV response cases, the T5 regimen was continued postoperatively, while for patients with grade I-II response, the T4 regimen, i.e., the addition of CTX, was used postoperatively instead, which was the earliest application of neoadjuvant chemotherapy. Subsequently, because the combination of BCD was effective in osteosarcoma, Rosen added BCD to the T regimen, resulting in the T7 regimen. In 1978, Rosen devised the T10 regimen, adding cisplatin to patients with a preoperative response of grade I-II, particularly for patients with pulmonary metastases, and the addition of DDP postoperatively improved patient survival. In Rosen's results, the T10 regimen was superior to the T7 regimen, but a re-clinical study of the T10 regimen by CCSG and CCSG-82 concluded that the T10 regimen did not improve survival in patients with poor preoperative chemotherapy outcomes. In Rosen's observation of the efficacy of the T7 and T10 chemotherapy regimens, almost all patients with 100% histological necrosis survived, so he concluded that preoperative chemotherapy was effective in

preventing tumour metastasis and designed the T12 regimen to reduce unnecessary chemotherapy side effects, and the T12 regimen showed a five-year survival rate of about 80% at follow-up. 1991 Rosen built on the T12 regimen and in 1991, Rosen added IFO, which was effective in osteosarcoma, to the regimen, forming the T19 regimen, which was used to improve the effectiveness of preoperative chemotherapy and is widely used today [47].

#### (2) The Italian Bacci regimen

The Bacci Institute, a leading bone tumour centre in Italy, began its research into chemotherapy for osteosarcoma in 1972 and began applying neoadjuvant chemotherapy in 1983, and has continued to update its protocols, mainly exploring the implications of neoadjuvant chemotherapy and the safety of limb preservation. In 1991, Bacci used a combination of MTX, DDP and ADM in 125 cases of osteosarcoma, of which 74% were graded as Kaw and V. The 2-year survival rate was 87%. The Institute is currently treating osteosarcoma with neoadjuvant chemotherapy using a dual pathway, with a sustained tumour-free survival rate of 87% at one to three years follow-up, a local recurrence rate of only 8% and a limb preservation rate of 92% [48].

### 3.4. Targeted Therapy

Targeted therapy refers to the use of targeted drugs to treat some malignant tumours. Targeted drugs are new types of drugs in treatment, which can precisely identify tumour cells and eliminate them through various mechanisms, thus killing tumour cells while reducing the damage to normal cells. Targeted therapy is therefore an ideal treatment for malignant tumours as it is more effective and has fewer side effects. Compared with other methods, targeted therapy brings less side effects such as nausea, vomiting, hair loss, abnormal liver function, etc. [4], and is better tolerated by patients. Targeted therapy is mainly used to treat malignant tumour disease, but the treatment of malignant tumour disease varies according to the type and period. If the tumour is in the early stage or locally advanced stage, a holistic and comprehensive therapy mainly based on post-operative treatment, supplemented by chemotherapy, radiotherapy and targeted therapy will be used. For patients with mid-stage or advanced malignant tumours, who cannot be treated by surgery, targeted therapy is an important treatment method. Therefore, the most important thing is to assess whether the patient has a target that can be used through immunohistochemistry or genetic testing, and to choose the most suitable treatment plan by taking into account the patient's condition, drug response and economic conditions [49-50].

### 3.5. Immunotherapy

Immunotherapy is based on the theory of immunology. When the immunological function of the body is insufficient or excessive, the immunological function of the body can be artificially increased or controlled through biological, chemical and physical methods, and by adjusting the normal disorder of the immunological function of the body, the immunological function can be fully functional so as to effectively cure the lesion. Immunological therapy can stimulate the immune function of human body and kill tumor cells, while tumor therapy can enhance the immunogenicity of tumor antibodies, thus activating and improving the immune response ability of human body to tumor, enhancing the sensitivity of tumor cells to anti-tumor immune response, inducing tumor-specific effector cells and molecules in vivo

and in vitro, thus achieving the activation of the anti-tumor function of human body immune cells that are actively regulated by oneself, preventing cancerous changes, and promoting the immune response of human body. It also helps to prevent cancer, remove residual cancer foci after surgery, avoid metastasis and recurrence, increase the clinical cure rate and prolong the survival rate of patients, thus improving the quality of life during the survival period. Immunological therapies are divided into specific and non-specific immunotherapies according to the specificity of the drug [51-55].

#### 3.5.1. Specific Immunotherapy

Vaccination: for example, the induction of a specific anti-tumour immune response by a tumour vaccine. This therapy is characterized by a slow onset of treatment, but a long duration of action. Infusion of the specific immune response product: The specific immune response product is administered directly to the body. Specific antibody-directed therapy or elimination of subpopulations of immune cells: this treatment improves the efficacy and reduces the side effects of the therapeutic drug toxin[56-57].

#### 3.5.2. Non-specific Immunotherapy

Non-specific immunotherapy refers to the stimulation of immune function through cytokines and non-specific activators, such as the use of immunosuppressive drugs and non-specific immune boosters. These diagnostic approaches have the advantage of lacking specificity, showing a wide range or effects on the body's immune action and being prone to adverse reactions [58-61].

### 3.6. Gene Therapy

There are two types of gene therapy, gene modification and gene replacement, and gene enhancement and gene inactivation therapies. Gene therapy is an emerging diagnostic technique that involves the introduction of exogenous normal genes into target cells to correct inherent errors in genes for the purpose of treating disease. Since then, research on gene therapy has become widespread worldwide and by 1995, there were more than 100 gene therapy clinical programmes worldwide. The NIH-sponsored evaluation found that only a few of the treatment protocols were truly effective, leading to the need to strengthen research on key fundamental issues in gene therapy and to strengthen the review and regulation of gene therapy clinical trial protocols. A means of diagnosing cancer using a genetic approach is anti-vascular gene therapy, which combines genes associated with cancer blood vessels with gene transfer technology to achieve inhibition of cancer blood vessel growth and thus control of cancer cell growth. There are gene therapies that target oncogenes, anti-cancer gene therapy, and genetic virus therapy. Although gene therapy is gradually becoming a treatment for difficult diseases, it is also ethically controversial because of its genetic alterations [62-64].

## 4. Discussion

Osteosarcoma is the most common primary malignancy in children and adolescents. At the time of diagnosis, 30% of patients with limited osteosarcoma and 80% of patients with metastatic osteosarcoma present with a recurrence of the cancer. One of the leading causes of death in patients with osteosarcoma is the development of pulmonary metastases. Although it can occur at any age, it is mainly in the second and third decades of life that the incidence is highest. Many

variables are associated with poor prognosis in osteosarcoma, including the presence of metastatic disease, non-osteoblastic histological subtypes, tumour location, genetic variants, poor response to neoadjuvant chemotherapy and inadequate surgical margins, among others. Chemotherapy has a significant role in the control of high-grade osteosarcoma, and when combined with appropriate local control through surgical resection or amputation, can improve survival rates, but it can be extremely damaging to the patient both physically and mentally. No clear molecular targets have been identified for the treatment of osteosarcoma and there has been no significant progress in molecular therapy [65-67].

#### 4.1. Osteosarcoma Drug Resistance

Osteosarcoma is heterogeneous and can vary greatly from patient to patient, or after metastasis, with genotypic changes from the original primary bone tumour. Osteosarcoma is resistant to certain drugs, but if resistance develops, the effect of chemotherapy is significantly reduced and the intended therapeutic goal is not achieved. When patients apply antibiotics for a long period of time, the sensitive strains that make up the majority of the body are constantly killed, and drug-resistant strains multiply and gradually replace the sensitive strains, making the bacteria increasingly resistant to that drug, which is the main reason for the development of drug-resistant bacteria. [7]. Natural resistance (intrinsic resistance) also exists, were pathogens in nature, such as a particular strain of bacteria, can also be naturally resistant. Microorganisms are not inherently susceptible to antimicrobial substances due to differences in their internal structure and chemical makeup, for example, streptococci are naturally resistant to aminoglycan antibiotics. Natural resistance is genetically determined by the cell chromosome. Drug resistance is a major problem limiting the efficacy of treatment in osteosarcoma [68-69].

#### 4.2. Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy can be used to treat patients early in the course of osteosarcoma to remove potential microscopic metastases, to assess the effectiveness of intraoperative chemotherapy through mass necrosis rates, and to guide postoperative chemotherapy to reduce recurrence rates and improve limb preservation rates, to calcify the margins of the mass, which indicates improvement, and to reduce the edematous zone of the tumour. This gives the physician more time to plan for limb preservation and select an appropriate prosthesis, increases the one-to-one patient care plan and ensures effective chemotherapy delivery. However, the efficacy of neoadjuvant chemotherapy concepts varies greatly due to the selective nature of the chemotherapeutic approach and the inadequate number of drugs used [70].

#### 4.3. Molecular Mechanisms

In China, research in this area started in the 1980s and has increased in the last three years, mainly in the areas of network pharmacology, proliferation and molecular docking. Internationally, research on molecular mechanisms originated in the mid-twentieth century and has emerged in the last three years, with a focus on molecular mechanisms and network pharmacology. There are many cancer-related signalling pathways, such as WNT, AKT-MAPK, etc. However, research has not yet identified a key node that can completely control carcinogenesis, and a lot of practice and research is

needed to increase clinical data on molecular mechanisms. The molecular mechanisms underlying the development of osteosarcoma still need to be further investigated [71-73].

#### 4.4. Outlook

The five-year survival rate for osteosarcoma is still relatively low, mainly due to chemotherapy resistance and the occurrence of pulmonary metastases, and although the overall level of technology for the treatment of osteosarcoma has improved since the 1970s, medical treatment is still limited. In particular, surgical diagnosis and conventional chemotherapy have failed to achieve satisfactory results in the case of recurrent and metastatic osteosarcoma. In recent years, the development of immunotherapeutic techniques, new methods and new drugs has provided new opportunities and challenges for the management of osteosarcoma, which had been stagnant for many years. The results of clinical trials with single therapies often make it difficult to achieve a complete and effective treatment for osteosarcoma. The immune microenvironment of osteosarcoma patients is complex and variable, and the combination of surgery, chemotherapy and biologic therapies is the key to breakthroughs in osteosarcoma.

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