

The Progress and Development Prospects of Targeted Therapy for Bone Malignancies

Jingqi Zheng

Department of pharmaceutical preparation, China Medical University, Shenyang, 110122, China
Corresponding author: jzheng14@qub.ac.uk

Abstract:

Bone malignancy is a relatively uncommon type of tumor whose cause is not well understood, mainly affecting children and adolescents, and its cure rate and prognosis vary depending on the type of tumor. At present, targeted therapy is the latest research progress in bone malignancy, and some effective targets for the treatment of bone cancer have been confirmed through research, and a series of targeted drugs for specific targets have been developed and have been approved for marketing and achieved relatively good clinical efficacy. But the problems such as inhibiting the incidence of bone metastasis in other tumors and the side effects of some targeted drugs have not been effectively solved. This article reviews the recent research on the therapeutic targets of bone malignancies such as Glut-1, iNOS and RANKL, as well as the development of new targets such as PD-1/PD-L1. Glut-1 and iNOS are relatively complete, but there are few studies on the development of RANKL and PD-1/PD-L1, and their therapeutic mechanisms and efficacy lack sufficient theoretical evidence to support them. In addition, this article compares and reviews the efficacy of two common targeted drugs for bone malignancies, ibandronate sodium and zoledronic acid, and describes the development and research progress of the new targeted drug denosumab. The purpose of this article is to provide strong theoretical and data support for targeted therapy for bone malignancies in the future, but the impact of tumor microenvironment on targeted therapy and the side effects of targeted therapy have not been properly solved.

Keywords: Targeted therapy; bone malignancies; Glut-1; iNOS; RANKL; PD-1/PD-L1; targeted drugs

1. Introduction

The incidence of bone malignant tumors accounts for 0.2% of all malignant tumors, and most of them are osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma, malignant lymphoma, Ewing sarcoma, chordoma, and metastatic bone tumors. Among them, osteosarcoma is the primary malignant bone tumor with the highest incidence rate, about 0.4-0.5 per 100,000 people. It is worth noting that although the incidence of bone malignancy is not high, its clinical incidence is increasing year by year [1]. For bone malignancy, the cure rate can be as high as 50%-70% if detected early and treated in a standardized manner, but if it is an advanced bone malignancy, the cure rate will be greatly reduced, because the tumor may have spread to other sites. Generally speaking, bone malignant tumors have a higher mortality rate than other types of malignant tumors, usually in 80%~90%. However, early detection and standardized treatment can significantly improve the survival rate and reduce the mortality rate of patients, such as the most common osteosarcoma, 60%~80% of patients can achieve long-term survival through the

combination of multiple drugs with adjuvant chemotherapy and surgery. In addition, the prognosis of different types of bone malignancies is also different.

The main treatment methods for bone malignant tumors include: surgical resection, pain control, drug chemotherapy, radiation therapy, immunotherapy, supportive care, targeted therapy, and comprehensive treatment that combines the above multiple treatment methods. Among them, surgical treatment is one of the treatment methods that almost every patient will receive, which uses mass resection to remove the tumor and its surrounding normal tissues together to reduce the patient's symptoms and help prevent further aggravation or spread of the disease. In general, surgical treatment, chemotherapy and radiotherapy are performed simultaneously to improve the treatment effect. For some special parts that cannot be completely removed by surgery or the patient's special constitution, the combined application of chemotherapy and radiotherapy can kill the patient's tumor cells and improve their survival rate. In addition, radiotherapy and chemotherapy can be used alone or as adjuvant treatments before or after surgery to reduce tumor size, kill residual tumor cells,

or control tumor progression, but both also have certain side effects, so a more comprehensive treatment plan is required. In addition to this, supportive treatment through nutritional support, blood transfusion, anti-infection, etc. can strengthen the patient's resistance and reduce complications. Immunotherapy attacks tumor cells by activating the patient's own immune system to improve the patient's immune function and enhance the ability to resist the tumor. Both are also widely used in the treatment of bone malignancies.

For malignant tumors that are not sensitive to chemotherapy, such as osteosarcoma, chemotherapy drugs lack specific affinity for tumors, and eventually only a small number of drugs reach the tumor site. It is necessary to increase the drug concentration in the systemic circulatory system, and the drug dose must be increased, thus increasing the toxicity and side effects of chemotherapy drugs [2]. In order to reduce systemic toxicity and improve the efficiency of chemotherapy in tumors, targeted therapy has become the key, as it can accurately target cancer targets and kill cancer cells with little or no damage to normal tissue cells, and immunotargeted therapy can block tumor cell signaling pathways and promote apoptosis of cancer cells [3]. In addition, metastasis is one of the main causes of tumor treatment failure and patient death, and the tumor microenvironment, as the living place of tumor cells, plays a crucial role in the process of tumor metastasis [4]. Abnormal tumor vasculature, extracellular matrix components, and abundant mesenchymal cells in the tumor microenvironment affect the distribution and penetration of drugs in tumor tissues, and their immunosuppressive status is also one of the important reasons for the failure of various anti-tumor diseases, including immunotherapy [5]. Therefore, the tumor microenvironment has a certain impact on the occurrence and progression of femoral malignancies and the targeted therapy of their immunity, and the study of potential targets related to the tumor microenvironment and its clinical treatment effects can provide new ideas for the treatment of pancreatic cancer.

At present, the most effective targeted drugs for bone malignancies, the efficacy of targeted therapy, the side effects of targeted therapy and drugs, and the difference between the therapeutic effect and the expected therapeutic effect achieved by targeted therapy combined with other pancreatic cancer treatments such as chemotherapy and immunotherapy are all in the stage of research exploration and clinical trials.

Based on the research progress of targeted therapy and targeted drugs for bone malignancies in the past five to ten years, this article summarizes and compares the therapeutic effects and side effects of targeted therapy for bone cancer with different targeted drugs targeting different tar-

gets, in order to find the most effective targets and targeted drugs for people with different physical conditions, and make a valuable contribution to the future research on the treatment of bone malignant tumors and the improvement of their cure rate.

2. Related Target Research and the Development of New Targets

For targeted therapy of bone malignant tumors, the main targets currently used for treatment mainly include: EGFR (epidermal growth factor receptor), ALK (anaplastic lymphoma kinase), VEGFR (vascular endothelial growth factor receptor) and BMPR (bone morphogenetic protein receptor), etc. This article provides a comparative review of the research progress of many researchers on the treatment of bone malignant tumors targeting Glut-1, iNOS, RANKL and PD1/PD-L1.

2.1 Research on Relevant Targets

2.1.1 Glut-1

Glut-1, glucose transporter-1, whose main function is to transport glucose into epithelial cells, is expressed in tissues such as colon, lung, stomach, esophagus, and breast; the antibody GLUT-1 can be used to distinguish reactive mesothelial hyperplasia from Malignant mesothelioma [6]. On the basis that glucose transporter-1 is an important factor related to malignant tumors, Mao Wenbin et al. used immunohistochemistry S-P method and CD34 labeling of vascular endothelial cells to detect Glut in osteosarcoma and adjacent normal bone tissue as well as bone fibrous dysplasia. The expression of -1 protein and two other malignant tumor factors (iNOS and HIF-1 α), as well as the microvessel density (MVD) in the above-mentioned tissues and fibers were detected. Through comparative statistical analysis of the test results, it was found that the positive expression rate of Glut-1 protein in osteosarcoma tissue was high, and it was significantly correlated with the expression of the other two factors and the stage of the tumor tissue. Therefore, it was concluded that Glut-1 It may play an important role in the occurrence and development of osteosarcoma [6]. Fan Jian et al. used immunohistochemistry and Western-Blot method to detect Glut-1 protein expression in osteosarcoma, osteochondroma and normal bone tissue specimens. Summary and analysis of the experimental results showed that Glut-1 was positive in osteosarcoma specimens, while almost all osteochondroma specimens were negative, and no positive expression of Glut-1 was found in normal bone tissue. It was concluded that Glut-1 is expressed at a high level in osteosarcoma tissue and can be used as a reference for judging the malignancy of osteosarcoma [7]. Therefore, Glut-1 can be used as an important target for osteosarcoma treat-

ment. In addition, because Glut-1 is closely related to the malignancy of bone tumors [8], it can become an important reference index for judging the malignancy of bone tumors and provide strong support for clinical treatment of bone tumors.

2.1.2 iNOS

iNOS, inducible nitric oxide synthase, is an isoenzyme subtype of nitric oxide synthase, which produces a large amount of nitric oxide and has neurotoxic effects. It is also a type of enzyme that uses oxidative stress (free radicals) from nitric oxide to assist macrophages in fighting pathogens in the immune system. It is also present in the cardiovascular system and only takes effect after the cells are stimulated and activated. Geng Yanhua et al. used immunohistochemistry EnVision method, χ^2 test and Spearman rank correlation analysis to detect the expression of iNOS in tumor tissues of osteosarcoma specimens without hard bone tissue and without decalcification with different clinical pathological characteristics. Statistical analysis showed that iNOS has a high positive expression rate in osteosarcoma, but its expression has nothing to do with the age of patients with osteosarcoma, but is related to the histological type of osteosarcoma. It was further concluded that iNOS is related to the occurrence and development of tumors and may synergistically promote the malignant progression of tumors [9]. Wu Lisheng et al. used immunohistochemistry to detect the microvessel density (MVD) of giant cell tumor of bone and the expression of iNOS in tumor tissue. It was found that the positive expression rate of iNOS in tumor tissues was high, and its MVD in positive giant cell tumor of bone tissues was significantly higher than that in negative giant cell tumor of bone tissues. It was concluded that MVD is an important indicator for evaluating the biological behavior of giant cell tumors of bone, and iNOS can promote tumor vascularization in giant cell tumors of bone [10]. Related study indicated that iNOS plays an important role in the occurrence, development, and metastasis of osteosarcoma [11]. It shows high expression levels in osteosarcoma and giant cell tumor of bone tissues and plays an important role in promoting. The two have a synergistic effect in tissue angiogenesis. The current research on iNOS in bone malignant tumors is relatively complete, providing strong evidence for using iNOS as one of the important targets in the targeted treatment of bone cancer.

2.1.3 RANKL

RANKL, or nuclear factor- κ B receptor activating factor ligand, also known as osteoclast differentiation factor, is expressed in osteoblasts and activates osteoclasts, but overexpression can lead to a series of bone diseases, and is also expressed in helper T cells (Th cell), which plays

a role in the immune system and plays a role in dendritic cell maturation. After reviewing the relevant studies on the role of bone protection protein/nuclear factor- κ B receptor activating factor/nuclear factor- κ B receptor activating factor ligand (OPG-RANKL-RANK) system in bone cancer pain in recent years, Deng Yulin et al. concluded that bone cancer pain, as one of the most common symptoms in patients with bone metastasis from malignant tumors, plays an important role in the occurrence and development of bone cancer, which is mainly related to the activation, development, and maturation of osteoclasts [12]. Wang et al. compared and analyzed the expression of RANKL in osteosarcoma specimens resected by surgery, Ewing sarcoma specimens and bone undifferentiated sarcoma specimens, and studied its expression in primary and metastatic lesions of bone primary malignant tumors and its potential value as a therapeutic target. They found that RANKL was not expressed in normal lung and normal bone tissue, but was expressed in the primary lesion of bone tumors, and the expression of RANKL in the lung metastasis specimens of bone tumors showed an overall low expression and a small number of high expression trends [13]. These studies could be concluded that the OPG/RANKL/RANK system plays an important role in the research of bone-related diseases as the ultimate pathway for bone destruction caused by various bone destruction factors, especially bone metastasis caused by malignant tumors [14]. However, there are relatively few studies on the expression level of RANKL in bone malignant tumor tissues, but there are still a certain number of clinical studies and successful experiments, which can be vigorously developed in the future, so as to provide more theoretical and data support for the treatment of bone cancer as a potential target for RANKL.

2.2 Development of New Targets

At present, for targeted therapy for bone malignancies, in addition to further expanding research on already developed targets, the development of new targets is also crucial.

In recent years, the development and application of PD-1/PD-L1 and its inhibitors have attracted much attention. PD-1/PD-L is programmed death 1 and its ligand. PD-1 is an important immunosuppressive molecule that can prevent autoimmune diseases by downregulating the immune system's response to human cells, as well as regulating the immune system by suppressing T cell inflammatory activity and promoting autotolerance, but it can also prevent the immune system from killing cancer cells. By binding with PD-1, PD-L1 can inhibit the activity of T cells, making T cells unable to recognize cancer cells. In recent years, PD-1/PD-L1 blocking has shown obvious

clinical effects in many malignant tumors, especially domestic PD-1 antibody drugs for the treatment of Hodgkin lymphoma have been approved for market. However, at present, there are few studies on immunotherapy in malignant bone tumors, and the clinical research progress of PD-1/PD-L1 remains to be clarified [15]. However, there are also a certain number of relevant studies, especially on the role of PD-1/PD-L1 pathway in osteosarcoma. ZHENG, Wang et al., by comparing and analyzing the expression of PD-1 in T lymphocytes of osteosarcoma patients and normal controls, found that the expression of PD-1 in T lymphocytes of osteosarcoma patients was significantly up-regulated compared with that of normal controls. In addition, the expression of PD-1 increased with the later stage, but no significant difference was found in the expression of PD-1 in different primary sites [16]. In addition, HUANG X et al. ,s study showed that PD-1/PD-L1 overexpression was closely related to poor prognosis of patients [17]. In summary, the expression level of PD-1/PD-L1 pathway is dysregulated in osteosarcoma and is involved in the occurrence and development of osteosarcoma, so its inhibitors may become one of the effective applications in the treatment of osteosarcoma. PD-1/PD-L1 information pathway has become a new target for targeted therapy of malignant bone tumors, and will have broad application prospects in this respect. In the future, focus could be paid on the development and research of this target and its related drugs and therapies to provide more theoretical support for the clinical treatment of PD-1/PD-L1.

3. Comparison of Efficacy of Common Targeted Drugs and Development of New Drugs

Targeted drugs used to treat bone malignancies vary according to the source of the tumor, the type of tumor, the genes and molecules, and the individualized differences of the patient. At present, targeted drugs for bone malignancies mainly include gefitinib, erlotinib and domestic icotinib for EFGR, which have been widely used in the treatment of bone cancer, in addition to targeted inhibitors for ALK, such as crizotinib, ceratinib and latatinib, which have also been developed for the treatment of bone cancer. This article will compare the efficacy and role of ibandronate sodium, zoledronic acid, and denosumab in the treatment of bone malignancies.

3.1 Comparison of Efficacy of Common Targeted Drugs crucial

3.1.1 Sodium Ibandronate

Ibandronate sodium, a bitenate bone resorption inhibitor, may inhibit the dissolution and formation of light apatite

mainly by binding with intraosseous apatite, thereby producing anti-bone resorption effects. For some patients with advanced osteosarcoma or chondrosarcoma, ibandronate sodium can be used as a targeted drug for treatment, so as to achieve the purpose of pain relief. In addition, bisphosphonates are one of the important means for the treatment of bone metastasis of malignant tumors [18], and ibandronate sodium is a new generation of bisphosphonates after clodronate sodium and pamidronate disodium and is considered to be one of the most effective bisphosphonate products. Yang et al. observed the appearance and symptoms of multiple groups of patients with pathological or cytologically confirmed malignant tumors after injection of ibandronate reagent, and concluded that ibandronate sodium has a good therapeutic effect on bone pain caused by bone metastasis of malignant tumors, and has mild adverse reactions, convenient use, and easy acceptance by patients, and has a good clinical application prospect [19]. In addition, Xing et al. pointed out that both oral and intravenous formulations of ibandronate sodium have been proven in clinical trials to be effective in reducing the incidence of bone-related events, reducing the degree of bone pain caused by bone metastasis, and improving the quality of life of patients with bone metastases [20]. In addition to the use of ibandronate alone, it can also be used in combination with other therapies, Pan Haixia et al. used the control of a number of patients with metastatic bone tumors in the treatment of ibendronate sodium combined with chemotherapy and chemotherapy alone after the symptoms of symptoms showed that the effective rate of combined chemotherapy to control local pain, the effective rate of repair treatment of lytic lesions and the effective rate of functional improvement were higher than that of chemotherapy alone, and then concluded that the treatment of pain caused by metastatic bone tumors with ibandronate sodium combined with chemotherapy was good, and the adverse effects of medication were mild. It can improve the quality of life of patients [21]. In addition, Liu Rui et al. compared the short-term efficacy, pain score, Karnofsky score (KPS), serum alkaline phosphatase (ALP) level and adverse reactions of multiple myeloma patients treated with ibandronate sodium or compound Sophora sophora injection combined with ibandronate sodium [22], and concluded that compound Sophora sophora injection combined with ibandronate sodium can treat multiple myeloma, effectively alleviate bone pain, improve efficacy and quality of life [22], and have a low incidence of adverse reactions.

3.1.2 Zoledronic Acid

Zoledronic acid, referring to zoledronic acid injection, is a targeted drug, is a bisphosphonate drug, has the effect

of inhibiting osteoclasts, can be used to treat multiple myeloma, postmenopausal osteoporosis and other diseases caused by bone pain, can also be used to treat recurrent fractures and osteosarcoma. If the patient has bone metastases, it can also be treated as prescribed, and it usually has a certain effect. Peng Liubao et al. concluded that zoledronic acid is used in the treatment of bone metastasis caused by a variety of malignant tumors, has good efficacy, mild adverse reactions, and will not change with the change of tumor type; [23]. Liang Huifang et al. confirmed the clinical efficacy of zoledronic acid in patients with bone metastasis of malignant tumors after injection, and the results showed that zoledronic acid had a high effective rate for bone pain relief, a high effective rate for complete relief of bone metastases, and a significant efficiency of life ability, and the side effect was temporary fever. Therefore, it is concluded that zoledronic acid for injection has a definite analgesic effect on the pain of osteolytic metastasis of malignant tumors, and the incidence of adverse events is low, the dosage is small, and the medication time is short, which is worthy of clinical promotion [24]. In addition, Zhang et al. pointed out that for prostate cancer patients without bone metastasis, early treatment with zoledronic acid injection can significantly reduce the level of bone metabolites, improve bone metabolic balance and bone mineral density, reduce the occurrence of bone-related events, and improve the quality of life of patients, but it has no obvious advantages in reducing the rate and time of bone metastasis [25]. Cheng Jing et al. compared the clinical manifestations of many patients with localized bone metastases treated with zoledronic acid combined with local radiotherapy and radiotherapy alone, and the results showed that the pain relief rate and recalcification rate of osteolytic lesions in the combined treatment group were higher than those in the radiotherapy group alone, and the proportion of patients with new bone metastases after treatment in the combined therapy group was very low, so it was concluded that zoledronic acid combined with radiotherapy in the treatment of localized bone metastases of malignant tumors had a definite effect, strong control of bone pain, could efficiently repair osteolytic lesions, and could reduce the incidence of new bone metastases [26]. In addition, zoledronic acid combined with radiotherapy can improve the quality of life of patients, and does not increase adverse reactions [27], and also shows significant effects in repairing osteolytic lesions and reducing new bone metastases.

This article compares the therapeutic efficacy of ibandronate sodium and zoledronic acid and finds that they have good efficacy in osteosarcoma and bone metastasis of malignant tumors when used alone, and can effectively relieve bone pain with mild adverse reactions. When partic-

ipating in combination therapy, both can not only improve the efficacy, relieve the pain of patients, and improve the quality of life of patients. However, zoledronic acid does not have obvious advantages in reducing the rate of bone metastasis, and there are few studies on ibandronate in this regard, which is not supported by sufficient theoretical evidence. In addition, although both are highly effective drugs for the treatment of bone metastasis of osteosarcoma and malignant tumors, compared with zoledronic acid injection, ibandronate sodium injection has more significant clinical efficacy and fewer adverse reactions in the treatment of bone tumors [28], has more obvious cost-utility advantages, and is more worthy of clinical application.

3.2 Development of New Targeted Drugs

At present, in addition to researching and improving the efficacy of the above-mentioned common targeted drugs, the development of new targeted drugs is also important. Denosumab generally refers to denosumab injection, which is a targeted preparation. The main component of denosumab injection is human immunoglobulin G2 monoclonal antibody, which is the first and only RANKL inhibitor in China. After the drug enters the body, because it has high affinity and specificity for human RANKL [29], it can selectively bind to RANKL and block this substance from activating osteoclasts and inhibiting osteoclast formation. At the same time, it can also destroy osteoclast function and survival rate, thereby reducing bone resorption. Currently, it is used clinically to treat bone-related malignant diseases, such as primary bone tumors, multiple myeloma, giant cell tumor of bone, osteosarcoma, and bone metastasis of malignant tumors. Shen Yan et al. observed the pathological manifestations of patients with giant cell tumor of bone after Denosumab treatment and lesion curettage and found that after treatment, the patient's histological manifestations were that giant cells almost completely disappeared, and the tumors appeared as spindle-shaped single cells with medium to high density. Mainly composed of nuclear cells, accompanied by high mitotic activity, focal necrosis and immature new bone formation, forming an osteosarcoma-like morphology, and no recurrence was seen for several months after surgery. Therefore, it is concluded that pseudosarcomatoid changes accompanied by high mitotic activity are a rare tissue phenotype in the histological spectrum of giant cell tumor of bone after Denosumab treatment, which is easily misdiagnosed as true sarcoma or malignant transformation of giant cell tumor of bone. Diagnosis is crucial [30]. Sun Yingjia and others also pointed out that the fully humanized RANKL antibody denosumab can inhibit osteoclast formation by preventing the combination of RANKL and RANK, thereby achieving a new breakthrough in the treat-

ment of tumor bone metastasis [31]. In addition, Li Shaoli et al. pointed out that for patients with giant cell tumors of bone that cannot be surgically resected, the previous NCCN Clinical Practice Guidelines for Malignant Bone Tumors recommended denosumab and continuous embolization as the first choice. The two can be used alone or combined. It is used for treatment, but many recent studies have suggested that denosumab may increase the risk of local recurrence in patients with giant cell tumors of bone and may also cause the malignant transformation of giant cell tumors of bone [32]. Compared with other targeted drugs, Chen Wanjing et al. compared the efficacy of denosumab and zoledronic acid in the treatment of malignant tumors with bone metastasis and found that denosumab can significantly alleviate bone-related time to occurrence of events (SREs) and reduces the concentration of bone metastasis markers, but there is no significant difference between the two in terms of overall survival (OS) time, disease progression time, and adverse reactions after treatment. Therefore, it is concluded that denosumab is superior to zoledronic acid in terms of clinical effectiveness and safety, and provides a new solution for the clinical prevention and treatment of patients with malignant solid tumors and bone metastases [33]. Compared with traditional bone cancer targeted drugs, Denosumab has the characteristics of precise blocking and powerful inhibition. It can effectively control the development of the disease, improve patient survival rate and quality of life, and has higher clinical effectiveness and safety. In the future, research can focus on improving the clinical efficacy of denosumab and reducing the risks of medication, so as to provide stronger support for effective targeted treatment of bone malignant tumors.

4. Conclusions

This article summarizes the research methods and progress of Glut-1, iNOS, RANKL and other therapeutic targets for bone malignancies, and prospect the current research progress and future research direction of PD-1/PD-L1 as a new target. In addition, the efficacy of common targeted drugs for bone malignancies such as ibandronate sodium and zoledronic acid were summarized and compared. At the same time, the current research and development progress of this new targeted drug, desumab, was summarized, and the future research directions and achievements were prospected. The targeted therapy of bone malignant tumor aims to solve the defects and limitations of conventional therapy of bone malignant tumor. Currently, the targeted therapy of bone malignant tumor is relatively perfect, and there are many targets that can obtain good therapeutic efficacy and some targeted drugs approved for market, all of which have been applied in clinical treatment and

achieved good therapeutic effect. The development and research of new targets and new drugs is also steadily underway. In addition, targeted therapy combined with other therapies to treat bone malignancies can achieve better efficacy, especially in terms of inhibiting bone pain. However, currently available targeted therapeutic targets and targeted drugs still have some drawbacks in reducing the incidence of new bone metastases and avoiding the influence of tumor microenvironment. In addition, this paper did not summarize and compare the side effects of targeted therapy for bone malignancies on other cells or organs, such as gastrointestinal reactions, hepatotoxicity, cardiovascular toxicity, and effects on respiratory and blood systems, as well as the research and development of therapeutic methods and adjuvants to avoid or treat side effects. The author believes that the targeted therapy of bone malignancies can also learn from the experience of other cancer targeted therapies and the successful cases of existing targeted therapies with significant effects, providing more reliable theoretical support for the development and improvement of new targets and new targeted drugs in the future. In the future, focus can be paid on the impact of tumor microenvironment on targeted drugs for targeted therapy of bone malignant tumors and the side effects caused by drugs, so as to break through the difficulties as soon as possible. In addition, researchers can develop more potential targets and benefit groups, and personalized targeted treatment programs for bone malignancies can be developed for patients with different physical conditions in combination with other treatment methods and drugs, providing new ideas for improving or improving quality of life, relieving disease pain, and completely curing bone malignancies, so as to benefit more patients.

References

- [1]Zhang Yongjian, Li Hongzhuan, Shi Hengwei, et al. Treatment of malignant bone tumor from deficiency phlegm and stasis. *Research of Traditional Chinese Medicine*, 2022, 35(7): 4.
- [2]Tian Dawei, Cai Lin. Targeting therapy of osteosarcoma. *Chinese Journal of Bone and Joint Surgery*, 2014, 000 (007): 548-550.
- [3]Zeng Xinxin, Wang Shengtao, Gui Peng, et al. Research Progress of Immunotargeted Therapy for Osteosarcoma. *Chinese Journal of Immunology*, 2019, 035(2): 236-239.
- [4]Yang Fang, Yu Yan. *Chinese Journal of Lung Cancer*, 2015, 18(1): 48-54.
- [5]Yang Mengmeng, Han Xiaopeng, Qin Chao, et al. Targeting and remodeling strategies for the tumor microenvironment. *Acta Pharmacologica Sinica*, 2022, 57(1): 98-108.
- [6]MAO Wenbin, Shao Zengwu, Pei Hong, et al. Expression of HIF-1 α , iNOS and GLUT-1 in osteosarcoma and their relationship with angiogenesis. *Chinese Journal of Cancer*,

2007(1): 46-49.

[7]Fan Jian, Yu Guangrong, Yuan Feng, et al. Glut-1 expression and clinical significance in benign and malignant bone tumors. *Journal of Tongji University (Medical Edition)*, 2013(3): 28-31, 35.

[8]Pei Hong, Shao Zengwu, Xiong Xiaoqian, et al. Expression of glucose transporter-1 in different bone tumors. *Chinese Journal of Bone Tumor and Osteopathy*, 2007(1): 7-10.

[9]Geng Y H, Wang C X, Chen P H. The expression of iNOS and HIF1 α in osteosarcoma and their clinicopathological correlation. *Journal of Clinical Medicine*, 2008(3): 291-292.

[10]Wu Lisheng, Chen Xiaoliang, Li Yujun. Expression of VEGF and NOS in giant cell tumor of bone and their relationship with tumor angiogenesis. *Chinese Journal of Bone Cancer and Osteopathy*, 2003(3): 161-165.

[11]MAO W B, Shao Z W. The expression of iNOS and HIF-1 α in osteosarcoma and its relationship with angiogenesis. *Chinese Journal of Bone Cancer and Osteopathy*, 2006(4): 210-213.

[12]Deng Yulin, Wang Juyong, Cai Tingting. Research progress of OPG-RANKL-RANK system and bone cancer pain. *Modern Oncology Medicine*, 2017(24): 4079-4082.

[13]Wang Jun, Bao Qiyuan, Peng Cheng et al. Analysis of RANKL expression in bone malignancies and observation of efficacy of disuzumab. *Chinese Journal of Bone and Joint*, 2019, 12(05): 337-344.

[14]Wang Huabei. Research status of OPG/RANKL/RANK axis in bone related diseases. *Chinese Journal of Clinical Research*, 2012(1): 80-81.

[15]Huang Haifeng, Zhu Hua, Yang Xian-Teng, et al. Progress in research on tumor immune PD-1/PD-L1 signaling pathway in malignant bone tumors. *Chinese Journal of Oncology*, 2019, 41(6): 410-414.

[16]Zheng W J, Xiao H, Liu H, et al. Expression of programmed death 1 is correlated with progression of osteosarcoma. *APMIS*, 2015, 123(2): 102-107.

[17]Huang X, Zhang W Y, Zhang Z C, et al. Prognostic value of programmed cell death 1 ligand-1 (PD-L1) or PD-1 expression in patients with osteosarcoma: a meta-analysis. *J Cancer*, 2018, 9(14): 2525-2531.

[18]Zheng Hu, Weng Lingling. Research progress of bisphosphonates. *Chinese Journal of Pharmaceutical Sciences*, 1997, 32 (9): 522.

[19]Yang Jin, Nan Kejun, Sun Hong. Comparison of efficacy of ibandronate sodium and Pamidronate disodium in the treatment of bone metastatic cancer pain. *Shaanxi Oncology Medicine*, 2003(1): 53.

[20]Xing Dieoyuan, Feng Fengyi. Clinical evaluation of

ibandronate sodium in the treatment of malignant tumor with bone metastasis. *Cancer Advances*, 2008(1): 11-15.

[21]Pan Haixia, Zhu Xueqiang, Deng Ying, et al. Ibandronate sodium combined with chemotherapy for metastatic bone tumors. *Journal of Pharmaco Epidemiology*, 2008(3): 141-143.

[22]Liu Rui, Fan Ningjian, Wang Yingman, et al. Efficacy of Compound Kushen Injection Combined with Sodium Ibandronate in the Treatment of Multiple Myeloma Bone Pain. *Evaluation & Analysis of Drug-Use in Hospitals of China*, 2022, 22(4): 424-427.

[23]Peng Liu-Bao, Cui Wei. Research progress on clinical application of zoledronic acid. *Chinese Journal of New Medicine and Clinical Medicine*, 2007(3): 237-240.

[24]Liang Huifang, Xing Shijiang, Pan Hongying, et al. Clinical efficacy of Zoledronic acid in the treatment of bone metastatic cancer. *Modern Oncology Medicine*, 2008(3): 434-435.

[25]Zhang Xiao, Lu Yi, Mo Qi-Wang, et al. Clinical study of Zoledronic acid injection delaying the progression of bone metastasis in prostate cancer through bone metabolism. *Chinese Journal of Sex Science*, 2022(4): 36-39.

[26]Cheng Jing, Xue Jun, Wu Hongge, et al. Clinical efficacy of zoledronic acid combined with radiotherapy in the treatment of bone metastases. *China Oncology*, 2008(7): 552-554.

[27] Liu Xin-Hong. Therapeutic effect of Zoledronic acid combined with radiotherapy on bone metastases of malignant tumors. *Modern Oncology Medicine*, 2011(7): 1412-1414.

[28]Wang Jian, Huang Fen, Liu Bo, et al. Clinical effect analysis of Zoledronic acid needle and ibandronate sodium needle in the treatment of bone tumor. *Oncology Pharmacy*, 2015(6): 454-457.

[29]Narayanan P. Denosumab: a comprehensive review. *South Asian J Cancer*, 2013, 2(4): 272-277.

[30]Shen Yan, Yang Tong, Chen Guidong, et al. Analysis of rare tissue morphological characteristics of pseudosarcomatoid lesions associated with high mitotic activity in giant cell tumors of bone treated with Denosumab. *Chinese Journal of Cancer Prevention and Treatment*, 2023, 15(4): 406-410.

[31]Sun Yingjia, Lu Shun. New breakthrough in the treatment of metastatic bone tumors. *World Clinical Drugs*, 2009(2): 110-117.

[32]Li SL, Dong Y, Yuan Y. Updated interpretation of the 2nd edition of NCCN Clinical Practice Guidelines for Malignant Bone tumors in 2023. *Journal of Practical Oncology*, 2023, 38(1): 1-4.

[33]Chen Wan-Jing, Wang Bei, GAO Xiu-Fei, et al. Meta-analysis of safety and efficacy of Dinomumab and zoledronic acid in the treatment of malignant tumors with bone metastasis. *Zhejiang Medical Journal*, 2017, 39(18): 1536-1547.