Malignant Bone Tumors: Pathological Mechanisms, Current Therapies, and Future Directions

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Abstract. Malignant bone tumors represent a rare yet aggressive class of cancers with complex pathophysiological mechanisms and significant therapeutic challenges. This review summarizes the current understanding of their pathological processes and treatment strategies. It first examines the molecular and environmental carcinogenic mechanisms of bone tumors, highlighting the potential roles of nitrite-induced genetic mutations and tumor microenvironment alterations. The discussion then focuses on bone cancer pain, a major clinical issue, outlining its molecular mechanisms—including acidosis, osteolytic activity, and neural inflammation—and the progress in pharmacological and integrative management approaches. Modern treatments, including bisphosphonates, RANKL inhibitors, radiopharmaceuticals (e.g., $^{89}SrCl_2$ and ^{188}Re-HEDP), and traditional Chinese medicine formulations, are evaluated for their efficacy and limitations. Finally, the paper proposes future directions emphasizing early diagnosis via liquid biopsy, optimization of multimodal therapy, and personalized medicine. Through a synthesis of current research and emerging prospects, this review aims to provide a foundation for improving clinical outcomes and guiding future research on malignant bone tumors.

Keywords: Malignant Bone Tumors; Osteosarcoma; Carcinogenic Mechanisms; Bone Cancer Pain; Multidisciplinary Therapy.

1. Introduction

Malignant bone tumors, commonly referred to as bone cancers, are rare but highly aggressive malignancies that originate in bone or its associated tissues. They are generally classified into primary bone tumors, which arise directly from bone-forming cells (such as osteosarcoma and chondrosarcoma), and secondary or metastatic bone tumors, which result from the spread of malignant cells from other primary cancers, such as breast or prostate cancer. Epidemiological data from a clinical statistical analysis of 5,444 cases of primary tumors indicate a male-to-female ratio of 6:1. Of these cases, 55.70% involved individuals aged 11 to 31, and the lesions were located in the long bones of the lower limbs, accounting for 53.09%. [1]

Multiple factors contribute to the development of malignant bone tumors, including prolonged exposure to ionizing radiation, chemical carcinogens, hereditary susceptibility, chronic bone diseases, and immune dysfunction. On the cellular level, the disease arises from a complex interplay of genetic mutations, tumor microenvironment remodeling, and immune escape mechanisms, making it one of the most intricate pathologies in oncology. Bone cells are prone to abnormalities, and they can develop into cancerous cells over time. Malignant bone tumors, commonly referred to as bone cancer, originate from bones or their surrounding tissues. They are mainly divided into primary malignant bone tumors (such as osteosarcoma and chondrosarcoma) and metastatic malignant bone tumors (such as breast cancer and prostate cancer metastasis). Most teenagers and the elderly are prone to bone cancer. Its pathology is very complex, involving multidimensional mechanisms, such as genetic mutation, microenvironment remodeling, and immune escape, which have always been complex problems in the history of medicine. The more difficult part to solve is the profound impact of bone cancer pain, which has significantly damaged the patient's physiology and psychology. Given these challenges, understanding the pathological mechanisms and improving therapeutic strategies remain critical. This review synthesizes current knowledge on the molecular and environmental carcinogenic mechanisms, examines major clinical treatment approaches, and explores emerging directions in early diagnosis and multimodal therapy. By integrating mechanistic insights with therapeutic

advancements, the study aims to provide a comprehensive reference for improving clinical outcomes in the management of malignant bone tumors.

2. Pathological Mechanisms of Malignant Bone Tumors

The pathogenesis of malignant bone tumors involves complex genetic, chemical, and environmental interactions that lead to abnormal cellular proliferation and oncogenic transformation. Among the various environmental carcinogens, nitrite and its derivatives have been identified as potential contributors to tumorigenesis. In vivo, nitrites can react with amines and amides to form N-nitroso compounds, potent carcinogens capable of inducing DNA strand breaks, base mutations, and chromosomal instability. These compounds can disrupt tumor suppressor genes such as *p53* and *Rb*, impairing normal cell cycle regulation and promoting malignant transformation of bone cells.

Nitrite exposure primarily occurs through contaminated water sources and dietary intake. Although the public drinking water supply contains nitrate control, it is only intended to prevent high-speed hemoglobinemia in infants, regardless of the risk of cancer or congenital disabilities. When a certain amount of nitrite is ingested, the risk of cancer and congenital disability may increase significantly. Nitrate will be reduced to nitrite, which can react with the nitrification of amines and amides to form N-nitro compounds, which are highly carcinogenic [2].

Epidemiological and experimental research in North America and Europe suggests that water rich in nitrite does not increase the risk of cancer. Chinese academic statistics indicate that nitrite in drinking water is closely related to cancer. This is because cancer cells are somewhat different from normal cells. Cancer cells can convert nitrite into NO, making them grow more tenacious (strengthening tumor blood vessel formation, increasing blood flow, and promoting rapid malignancy development). Therefore, although nitrite does not cause cancer, it will promote cell growth and vitality. Consuming nitrite in water can prevent cell cancer.

Moreover, multivariate regression analysis reveals that gastric cancer is associated with the median dose of nitrate in drinking water ($t = 3.98$, $p = 0.0001$, R-squared after correction = 50.61%); other types of cancer did not show any correlation. In addition, the meta-analysis of the first and second stages indicates that there is only a correlation between brain cancer, colon cancer, and glioma and the risk of colon cancer.

3. Bone Cancer Pain Pathology

Cancer pain is one of the common symptoms of malignant bone tumors, which is the main reason for the decline in patients' quality of life and loss of confidence in treatment. Bone cancer pain is a complex pain consisting of basic pain, spontaneous pain, and pain caused by exercise. Base pain is a long-term, dull pain that intensifies the disease during sleep. Traditional analgesics, such as weak opioid analgesics, analgesics, etc., can be controlled under normal circumstances. When treating basic pain, the other two pain patterns are uncontrollable and very painful. This kind of pain is explosive, has a rapid onset, a short duration, and is related to dose-related side effects. Osteoblasts (OC) also play an essential role in the pathological study of bone cancer. It is a polynuclear giant cell that can dissolve bones to form new ones and secrete various cytokines to participate in the hematopoietic process of the bone marrow. Some progress has been made by dividing the causes of bone cancer pain into several stages, researching and developing symptomatic drugs from different directions, and combining the treatment methods of traditional Chinese medicine and Western medicine [3].

The research direction of the pathological mechanism of bone cancer pain is divided into acidosis in bone cancer, bone destruction in bone cancer, nerve and inflammatory components in bone cancer, and the molecular mechanism of bone cancer pain. Following research, several effective treatment methods have been identified. First, acidosis is primarily caused by two acid-sensitive ion channels: the transient receptor potential vanilloid (TRPV1) and acid-sensing ion channel 3 (ASIC-3). As a result, the environment around osteoclasts is much higher than that around other tissue cells (pH

4.0~5.0). Diphosphate can reduce the impact of acidosis on osteoclasts [3]. In addition, Receptor Activator of Nuclear Factor-κB Ligand (RANKL) and Receptor Activator of Nuclear Factor-κB (RANK), and the discovery of Osteoclasogenesis inhibitory factor (OPG) play a key role in regulating osteostasis, the immune system, inflammation, cancer, and other aspects of pathophysiological conditions, and can also be used for treatment [4]. Secondly, the mechanical instability and fractures that osteoclasts produce will significantly impact nerve fibers, including mechanical deformation. Therefore, the way to treat bone damage is to maintain stability and prevent bone reconstruction. Diphosphate and KANKL can control acidosis and maintain bone stability, effectively reducing bone cancer pain. Third, surgical treatment and radiotherapy are also methods to treat bone cancer pain, but after radiotherapy, patients will have many side effects, such as nausea, vomiting, poor spirits, dizziness, and other symptoms; surgical treatment brings severe instability. Another one is non-steroidal anti-inflammatory drugs, producing analgesic effects by inhibiting the epoxy synthase pathway and reducing pain.

Additionally, traditional Chinese medicine has played a significant role in treating bone cancer pain. In recent years, significant progress has been made in treating malignant bone tumors by combining disease diagnosis with traditional Chinese medicine, including both internal and external applications, as well as acupuncture and other methods [2, 5].

Table 1. The results of the analysis of the correlation rules of traditional Chinese medicine compound treatment of CIBP (%)

consequent	former term	support degree	confidence coefficient
Drynaria fortunei	*Psoraiea corylifolia*	38.71	60.00
Prepared *Rehmannia* Root	*Drynaria fortunei*	46.77	62.07
Cornus officinalis	*Drynaria fortunei* Prepared *Rehmannia* Root	29.03	62.50
Scorpio	*Drynaria fortunei* Prepared *Rehmannia* Root	29.03	69.07
Drynaria fortunei	Scorpio	37.10	69.57
Psoraiea corylifolia	Scorpio	37.10	60.87
Prepared *Rehmannia* Root	Scorpio	29.03	60.87
Prepared *Rehmannia* Root	*Taxillus chinensis*	29.03	72.22
Scorpio	*Taxillus chinensis*	29.03	61.11
Scorpio	*Drynaria fortunei* Prepared *Rehmannia* Root	25.18	61.11
Scorpio	*Drynaria fortunei* Prepared *Rehmannia* Root	25.18	61.11
Prepared *Rehmannia* Root	*Cornus officinalis*	25.18	87.50
Drynaria fortunei	*Cornus officinalis*	25.18	75.00
Bombyx batryticatus	*Cornus officinalis*	25.18	62.50
Dioscorea apposita	*Cornus officinalis*	25.18	68.75
Poria cocos	*Cornus officinalis*		

The higher the support and confidence levels are, the better the efficacy of this medicine is. The *Drynaria fortunei* and *Rehmannia Roo*t is the greatest pharmaceutical formulation. The above data diagram of traditional Chinese medicine compound treatment of CIBP symptomatic treatment is "beneficial to the liver and tonic the kidney, activate blood and dissolve stasis, attack and tonic, and take into account the specimen", which has a highly considerable effect on the treatment of bone cancer pain.

4. Other Treatment Methods

ˆ89Sr has been injected with preliminary clinical experience in treating metastatic bone cancer. Eight cases of bone cancer patients have been injected with ˆ89SrCI2, 1.11MBq/kg (30μCi/kg), and another prostate cancer patient without bone metastatic pain has been injected with this dose to

observe ˆ89Sr delayed bone metastasis foci. The time of appearance. Studies show that 87.5% of patients with bone metastasis experience reduced or disappearing pain, which remains relieved for 3 to 6 months. After observation, there are no apparent side effects in the patient, which is an effective treatment for metastatic bone tumor pain. 89SrCl2 combined with Tc-M DP combined treatment is another more effective treatment method, with an efficiency of 88.2%, significantly higher than that of a single treatment. Among them, the treatment of breast invasive cancer has the best effect, followed by adenocarcinoma, and finally, squamous carcinoma. The side effects of combined treatment are not superfluous compared to those of a single treatment. In addition, the use of 188Re-HEDP to treat metastatic bone cancer still has apparent curative effects. In 58 patients treated, 14 cases of pain disappeared, and 36 were significantly relieved. One case of complete disappearance of metastasis, one case of reduction of more than 50%, and four cases of reduction of more than 25% [12].

5. Limitations and Prospects

Utilize liquid biopsy technology to screen, diagnose, and detect malignant bone tumor diseases in their early stages, and carefully analyze them to enhance the efficiency and quality of treatment. In-depth research on drug treatment methods such as bisphosphonates, RANKL inhibitors, and traditional Chinese medicine. For example, treating metastatic bone cancer with nucleon gives high hopes to the in-depth research of 188Re-HEDP. Continue to conduct in-depth research on drug treatment, surgical treatment, and radiotherapy methods and apply them to alleviate patients' pain, improve their quality of life, and make greater contributions to medical research.

6. Conclusion

This paper summarizes the primary pathological mechanisms and treatment options for malignant bone tumors. It summarizes the current research findings and treatment methods for major diseases such as bone cancer pain. Next, suggestions for future treatment methods will be presented. Start improving research techniques from the very beginning, such as utilizing liquid biopsy technology to more effectively detect cancerous cells. Finally, it is worth noting that the primary objective of this research on malignant bone tumors is to enhance the quality of life for patients and contribute to the advancement of cancer research.

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