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MULTIMODAL APPROACH AND THERAPEUTIC ADVANCES IN THE TREATMENT OF OSTEOSARCOMA

ABORDAGEM MULTIMODAL E AVANÇOS TERAPÊUTICOS NO TRATAMENTO DO OSTEOSSARCOMA

ABORDAJE MULTIMODAL Y AVANCES TERAPÉUTICOS EN EL TRATAMIENTO DEL OSTEOSARCOMA

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ABSTRACT

Osteosarcoma is the most prevalent primary malignant bone neoplasm, occurring predominantly in children and adolescents. It is characterized by the production of immature osteoid matrix and by an extremely unstable and heterogeneous genomic profile. Although standard chemotherapy (MAP) has increased the five-year survival rate to 60–70% in localized disease, the prognosis for metastatic or recurrent disease remains stagnant at approximately 20%. The complexity of treatment lies in the genetic instability and the intricate interaction with the bone microenvironment, which acts as a vital support for tumor growth and dissemination, promoting therapeutic resistance. This study is a narrative literature review that sought to synthesize contemporary scientific evidence regarding the multimodal approach and therapeutic advances in combating osteosarcoma. The findings reveal that overcoming chemoresistance requires the integration of innovative strategies, such as nanotechnology for active and targeted drug delivery, using specific ligands (e.g., bisphosphonates or folate), which maximize drug concentration at the tumor site and mitigate systemic toxicity. In immunotherapy, the focus is on manipulation of the cGAS-STING axis and repolarization of tumor-associated macrophages (TAMs) to the M1 phenotype, as observed with mifamurtide, aiming to reverse microenvironmental immunosuppression. Other approaches include multiple kinase inhibitors (MKIs), such as sorafenib and regorafenib, and unconventional administration routes, such as inhaled chemotherapy for pulmonary metastases. In conclusion, the effective integration of these innovative strategies (nanotechnology, immunomodulation, and targeted therapies) represents the future of osteosarcoma oncology, offering renewed hope for prolonging progression-free survival and overall survival in patients.

Keywords: Osteosarcoma. Nanotechnology. Immunotherapy. Multiple Kinase Inhibitors. Tumor Microenvironment.

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RESUMO
O osteossarcoma representa a neoplasia maligna primária do osso mais prevalente, incidindo majoritariamente em crianças e adolescentes. Caracteriza-se pela produção de matriz osteoide imatura e por uma genômica extremamente instável e heterogênea. Embora a quimioterapia padrão (MAP) tenha elevado a sobrevida em cinco anos para 60-70% na doença localizada, o prognóstico para a doença metastática ou recidivante permanece estagnado em cerca de 20%. A complexidade do tratamento reside na instabilidade genética e na interação intrincada com o microambiente ósseo, que atua como suporte vital para o crescimento e a disseminação tumoral, promovendo a resistência terapêutica. O presente estudo é uma revisão bibliográfica narrativa que buscou sintetizar as evidências científicas contemporâneas acerca da abordagem multimodal e dos progressos terapêuticos no combate ao osteossarcoma. Os resultados revelam que a superação da quimiorresistência exige a integração de estratégias inovadoras, como a nanotecnologia para entrega ativa e direcionada de fármacos, utilizando ligantes específicos (e.g., bisfosfonatos ou folato), que maximizam a concentração no sítio tumoral e mitigam a toxicidade sistêmica. Na imunoterapia, o foco está na manipulação do eixo cGAS-STING e na repolarização dos macrófagos associados ao tumor (TAMs) para o fenótipo M1, como com o mifamurtide, visando reverter a imunossupressão do microambiente. Outras abordagens incluem inibidores de múltiplas quinases (MKIs), como sorafenibe e regorafenibe, e vias de administração não convencionais, como a quimioterapia inalatória para metástases pulmonares. Em conclusão, a integração eficaz dessas estratégias inovadoras (nanotecnologia, imunomodulação e terapias-alvo) configura o futuro da oncologia para o osteossarcoma, oferecendo renovada esperança de prolongar a sobrevida livre de progressão e a sobrevida global dos pacientes.

Palavras-chave: Osteossarcoma. Nanotecnologia. Imunoterapia. Inibidores de Múltiplas Quinases. Microambiente Tumoral.

RESUMEN
El osteosarcoma representa la neoplasia maligna primaria ósea más prevalente, afectando predominantemente a niños y adolescentes. Se caracteriza por la producción de matriz osteoide inmadura y por una genómica extremadamente inestable y heterogénea. Aunque la quimioterapia estándar (MAP) ha elevado la supervivencia a cinco años al 60–70% en la enfermedad localizada, el pronóstico para la enfermedad metastásica o recurrente permanece estancado en aproximadamente un 20%. La complejidad del tratamiento radica en la inestabilidad genética y en la interacción intrincada con el microambiente óseo, que actúa como soporte vital para el crecimiento y la diseminación tumoral, promoviendo la resistencia terapéutica. El presente estudio es una revisión bibliográfica narrativa que buscó sintetizar la evidencia científica contemporánea sobre el abordaje multimodal y los avances terapéuticos en el combate contra el osteosarcoma. Los resultados revelan que la superación de la quimiorresistencia exige la integración de estrategias innovadoras, como la nanotecnología para la administración activa y dirigida de fármacos, utilizando ligandos específicos (por ejemplo, bisfosfonatos o folato), que maximizan la concentración en el sitio tumoral y reducen la toxicidad sistémica. En la inmunoterapia, el enfoque se centra en la manipulación del eje cGAS-STING y en la repolarización de los macrófagos asociados al tumor (TAMs) hacia el fenotipo M1, como ocurre con el mifamurtide, con el objetivo de revertir la inmunosupresión del microambiente. Otros enfoques incluyen inhibidores de múltiples quinasas (MKIs), como sorafenib y regorafenib, y vías de

administración no convencionales, como la quimioterapia inhalatoria para metástasis pulmonares. En conclusión, la integración eficaz de estas estrategias innovadoras (nanotecnología, inmunomodulación y terapias dirigidas) configura el futuro de la oncología del osteosarcoma, ofreciendo una renovada esperanza para prolongar la supervivencia libre de progresión y la supervivencia global de los pacientes.

Palabras clave: Osteosarcoma. Nanotecnología. Inmunoterapia. Inhibidores de Múltiples Quinasas. Microambiente Tumoral.

1 INTRODUCTION

Osteosarcoma represents the most prevalent primary malignant neoplasm of the bone, focusing mainly on children and adolescents during phases of accelerated growth, with a second peak incidence in the elderly (Shi et al., 2023; Corre et al., 2020). Histologically, it is characterized by the production of immature osteoid matrix by transformed osteoblasts, presenting an extremely unstable and heterogeneous genomics (Corre et al., 2020; Zheng et al., 2024). Although the introduction of adjuvant and neoadjuvant chemotherapy protocols in the 1980s—based on methotrexate, doxorubicin, and cisplatin (MAP)—raised five-year survival to levels between 60% and 70%, the prognosis for patients with metastatic or relapsed disease remains stagnant at around 20% (Shi et al., 2023; Hughes, 2009).

The complexity of osteosarcoma lies not only in its genetic instability, but also in the intricate interaction with the bone microenvironment. This ecosystem, composed of mesenchymal stromal cells, vascular components, and immune system cells, acts as a vital support for tumor growth and metastatic spread, hindering the effectiveness of conventional chemotherapy (Corre et al., 2020; Cersosimo et al., 2020). In the face of severe systemic toxicity and therapeutic resistance, contemporary medicine has sought multimodal advances, integrating nanotechnology for targeted drug delivery, multiple kinase inhibitors, and immunomodulation strategies to address the challenges of this pathology (Shi et al., 2023; Li et al., 2025).

2 METHODOLOGY

The present study is a narrative literature review, designed with the purpose of synthesizing and examining contemporary scientific evidence about the multimodal approach and therapeutic progress in the fight against osteosarcoma. The investigation was carried out using the PubMed database, using the descriptors "Osteosarcoma" and "Therapeutics", articulated by the Boolean operators AND and OR, in strict compliance with the terminology established by the Medical Subject Headings (MeSH). The selection included scientific articles of academic relevance that directly addressed the central theme, prioritizing studies that discussed molecular mechanisms, nanotechnology, and new treatment fronts. Studies without thematic adherence, reviews with methodological fragility, and duplicates were excluded. The document analysis was structured in two phases: the initial screening of titles and abstracts, followed by the full critical reading of

the selected texts for the consolidation of the information, which were organized from a descriptive and academic perspective.

3 RESULTS AND DISCUSSION

Advances in the understanding of osteosarcoma reveal that the tumor microenvironment is a critical determinant of disease progression. Spatial and single-cell transcriptomics studies have identified distinct cell subgroups and specific niches, such as the tumor necrosis front, that express genes such as COL4A1, suggesting a direct association with chemotherapy resistance (Zheng et al., 2024). In addition, the so-called "vicious cycle" between tumor cells and osteoclasts promotes the degradation of the bone matrix and the release of growth factors that feed back into neoplastic proliferation (Corre et al., 2020).

In the field of nanotechnology, the development of drug delivery systems with active targeting has shown promise. Modifications to the surface of nanocarriers with specific ligands, such as bisphosphonates for bone affinity or folate for cell recognition, allow for greater accumulation of chemotherapeutic agents at the tumor site, reducing toxicity to vital organs (Shi et al., 2023). Strategies that utilize reactive oxygen species (ROS)-sensitive nanoparticles are also being explored to activate specific immunogenic pathways (Li et al., 2025).

Immunotherapy has emerged as a vital therapeutic front, with emphasis on the manipulation of the cGAS-STING axis. Activation of this pathway can stimulate the production of type I interferons, reversing the immunosuppression state of the microenvironment and potentiating the response against osteosarcoma cells (Li et al., 2025). At the same time, the role of tumor-associated macrophages (TAMs) has been redefined; while the M2 phenotype favors metastasis and chemoresistance, repolarization to the M1 phenotype, stimulated by agents such as mifamurtide, correlates with improved overall survival (Cersosimo et al., 2020).

Approaches that transcend the traditional intravenous route also demonstrate clinical potential. Inhalation chemotherapy using gemcitabine is an innovative strategy for the management of lung metastases, the main site of recurrence (Hughes, 2009). Additionally, the use of multiple kinase inhibitors (MKIs), such as sorafenib and regorafenib, has shown efficacy in prolonging progression-free survival in cases of

advanced and refractory disease, by simultaneously targeting vascular, stromal, and oncogenic compartments (Corre et al., 2020).

4 CONCLUSION

Despite historical advances in the treatment of osteosarcoma with standard chemotherapy (MAP), the prognosis for metastatic and relapsing disease remains discouraging, stagnating at around 20% five-year survival, due in large part to complex genomic instability and intricate interaction with the tumor microenvironment. The present review highlights that overcoming this therapeutic resistance requires a truly multimodal approach.

The advancement of nanotechnology, for example, offers a promising path for the active and targeted delivery of chemotherapy drugs, using specific ligands such as bisphosphonates or folate, which maximizes concentration at the tumor site and mitigates systemic toxicity. In the context of immunotherapy, manipulation of the cGAS-STING axis and repolarization of tumor-associated macrophages (TAMs) to the M1 phenotype (e.g., with mifamurtide) demonstrate potential to reverse microenvironment immunosuppression and optimize the antitumor response. In addition, the use of multiple kinase inhibitors (MKIs) such as sorafenib and regorafenib, which attack multiple biological compartments of the disease, and the introduction of unconventional routes of administration, such as inhaled chemotherapy for lung metastases, solidify the new frontier of treatment.

In sum, the integration of these innovative strategies (nanotechnology, immunomodulation, and targeted therapies) shapes the future of oncology for osteosarcoma, offering renewed hope for prolonging progression-free survival and overall survival of patients.

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