Review Article

New advances in the treatment of chondrosarcoma under the PD-1/PD-L1 pathway

ABSTRACT

Bone sarcomas encompass a group of spontaneous mesenchymal malignancies, among which osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma are the most common subtypes. Chondrosarcoma, a relatively prevalent malignant bone tumor that originates from chondrocytes, is characterized by endogenous cartilage ossification within the tumor tissue. Despite the use of aggressive treatment approaches involving extensive surgical resection, chemotherapy, and radiotherapy for patients with osteosarcoma, chondrosarcoma, and chordoma, limited improvements in patient outcomes have been observed. Furthermore, resistance to chemotherapy and radiation therapy has been observed in chondrosarcoma and chordoma cases. Consequently, novel therapeutic approaches for bone sarcomas, including chondrosarcoma, need to be uncovered. Recently, the emergence of immunotherapy and immune checkpoint inhibitors has garnered attention given their clinical success in various diverse types of cancer, thereby prompting investigations into their potential for managing chondrosarcoma. Considering that circumvention of immune surveillance is considered a key factor in the malignant progression of tumors and that immune checkpoints play an important role in modulating antitumor immune effects, blockers or inhibitors targeting these immune checkpoints have become effective therapeutic tools for patients with tumors. One such checkpoint receptor implicated in this process is programmed cell death protein-1 (PD-1). The association between PD-1 and programmed cell death ligand-1 (PD-L1) and cancer progression in humans has been extensively studied, highlighting their remarkable potential as biomarkers for cancer treatment. This review comprehensively examines available studies on current chondrosarcoma treatments and advancements in anti-PD-1/PD-L1 blockade therapy for chondrosarcoma.

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INTRODUCTION

Chondrosarcoma is a relatively common malignant bone tumor originating from chondrocytes that is characterized by endogenous cartilage ossification within the tumor tissue. These malignant cartilaginous tumors exhibit a myriad of morphological characteristics and clinical behaviors.[1] It is the second most common type of bone sarcoma, constituting 20%–30% of all primary bone malignancies.[2] The lungs are the most common site for metastasis.[3] Primary chondrosarcoma develops in normal bones, unlike secondary tumors that develop within established enchondromas or osteochondromas.[4] Conventional chondrosarcomas, accounting for 85%–90% of all cases, are classified into central, periosteal, and peripheral subgroups.[5] Studies have reported that among patients with conventional chondrosarcomas, ~90% have grade 1–2 (i.e., low to intermediate) rarely metastasizing chondrosarcomas, whereas approximately 5%–10% have highly metastasizing grade 3 conventional chondrosarcomas.[6,7] Radiographic features aid in diagnosing chondrosarcoma subtypes, especially nonconventional variants including clear cell, mesenchymal, periosteal, and dedifferentiated chondrosarcomas.[5,8] Regarding patient survival rates, 5-year survival rates of 83%, 53%, and 7%–24% have been reported for low-grade, high-grade, and dedifferentiated chondrosarcomas, respectively.[8,9] Ostensibly, only mesenchymal and dedifferentiated chondrosarcomas appear to be sensitive to chemotherapy and radiation, whereas a majority of chondrosarcomas exhibit resistance to these treatment modalities.

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Limited treatment options are available for patients with highly metastatic or unresectable chondrosarcomas. Among the novel therapies proposed for these diseases, immunotherapy and molecularly targeted drugs show promise in treating malignancies.[8] Given that immune surveillance circumvention is considered a key factor in the malignant progression of tumors and that immune checkpoints play an important role in modulating antitumor immune effects, blockers or inhibitors targeting these immune checkpoints have become effective therapeutic tools for patients with tumors. One such checkpoint receptor implicated in this process is programmed cell death protein-1 (PD-1). PD-1 is largely expressed on the surface of several immune cells, whereas programmed cell death ligand-1 (PD-L1) is primarily expressed in tumor cells. The association between PD-1 and PD-L1 and cancer progression in humans has been extensively studied, underscoring their remarkable potential as biomarkers for cancer treatment.[10]

Therefore, the current review synthesizes available data on currently used chondrosarcoma treatment options and comprehensive and advanced information pertaining to PD-1/PD-L1 pathway-based therapies for treating chondrosarcoma. This paper covers the role of and mechanisms underlying the PD-1/PD-L1 pathway and inhibitors and their mechanisms of action, clinical applications, efficacy, and safety in chondrosarcoma treatment.

COMMON TREATMENT METHODS FOR CHONDROSARCOMA

Treatment options for chondrosarcoma remain significantly scarce and exhibit limited therapeutic efficacy. Among the few available treatment options, surgery, extracorporeal irradiation (ECI), chemotherapy, and targeted therapies are the most prominent options.[11,12]

Surgical resection

Surgery is the main treatment option for chondrosarcoma, with comprehensive excision as its primary aim. The effectiveness of available treatments depends on the tumor's histologic grade and location. Low-grade central chondrosarcomas can be treated with intralesional curettage and burring supplemented by surgical adjuvants including hydrogen peroxide.[5,13] The most ideal approach for chondrosarcoma, either high-grade or intermediate-grade, is radical excision. Although certain surgical procedures, including curettage, have been proposed for low-grade chondrosarcoma management, they tend to have high recurrence rates. Hence, wide excision has been the recommended treatment option even in low-grade chondrosarcomas of the hand.[14]

Radiation therapy

Chondrogenic tumors are typically radioresistant due to their slow growth and low proportion of actively dividing cells, making radiation-induced cytotoxicity a substantial concern.[15,16] No level one evidence has supported radiation therapy for chondrosarcoma, although it can improve local failure rates after incomplete excision.[5] Moreover, radiation therapy can be administered with the intention of maximizing local control and potentially achieving a cure in cases where incomplete resection has been performed for high-grade conventional, dedifferentiated, or mesenchymal chondrosarcomas. Additionally, in settings where surgical resection is deemed inappropriate or would cause significant morbidity, radiation therapy can be used as a palliative treatment approach.[15]

Chemotherapy

Typically, chemotherapy remains a rather inefficient therapeutic approach for treating the most rampant conventional chondrosarcoma subtypes. Adjuvant chemotherapy has shown no proven benefits for advanced chondrosarcoma. Although several chemotherapy approaches have been recommended for cases with dedifferentiated and mesenchymal chondrosarcomas, phase III trial evidence to support these recommendations has been considerably lacking.[17,18] Nonetheless, some chondrosarcoma subtypes, including dedifferentiated chondrosarcomas with a high-grade spindle cell component, may benefit from chemotherapy.[19] However, evidence shows that chemotherapy is inefficient for conventional central and clear chondrosarcoma.[16] Further, adjuvant anthracycline-based therapy showed relatively modest efficacy for mesenchymal chondrosarcoma in a nonrandomized clinical cohort.[20] Despite the availability of published literature, prospective data on the effectiveness of chemotherapy for chondrosarcoma remain relatively scarce owing to the limited number of patients and the peculiarity of the disease.[21] Therefore, existing treatments for chondrosarcoma are rooted in the treatment approaches used for osteosarcoma.[22]

Chemoresistance and radioresistance in chondrosarcoma

Resistance to chemotherapy and radiotherapy is a common dilemma for patients with chondrosarcoma, given that chondrosarcoma tumors are known to be resistant to chemotherapy and radiotherapy, thereby making these standard treatment modalities ineffective for treating this disease.[23] P-glycoprotein, multidrug-resistance-1 gene (MDRI), high expression of Bcl-2 family proteins, slow proliferation, poor vascularity, and dense extracellular matrix are among the prominent factors associated with chemoresistance and radioresistance in chondrosarcoma patients, which lead to subpar delivery of anticancer agents.[8,21,24]

Nonconventional approaches and novel targets for chondrosarcoma treatment

Although numerous studies have demonstrated positive outcomes, clinicians have been apprehensive about using monotherapy for heterogeneous chondrosarcoma due to the tumor's capacity to adapt and develop resistance. Furthermore, owing to the lack of successful outcomes, the potential of monotherapy as an adjuvant therapy in combination with other treatments cannot be established. Additionally, the

peculiarity of this disease poses challenges in conducting randomized clinical trials to evaluate the effectiveness of anticancer agents. Nonetheless, ongoing clinical studies are being conducted to assess the efficacy and safety of novel anticancer agents for treating advanced chondrosarcomas.

Therefore, by considering the side effects and conducting clinical investigations for safety and efficacy assessment in large patient groups, the utility of novel nonconventional therapeutic options for treating patients with chondrosarcoma can be considerably improved.[21,25]

Some of the most prominent nonconventional approaches for treating chondrosarcoma include tumor microenvironment modulation, immunotherapy, epigenetic, molecularly targeted, antiangiogenic, combination, and herbal therapies.[15,22] Moreover, the identification of novel signaling pathways in various chondrosarcoma histologic subtypes has also prompted the development of different molecularly targeted therapies and investigations on their therapeutic efficacy. To date, several novel targets for chondrosarcoma therapies have been recognized and are currently under investigation.

Some of the proposed therapies for chondrosarcoma involve targeting (1) mutations of isocitrate dehydrogenases (IDH) 1 and IDH2,[22] (2) cyclin-dependent kinase,[26] (3) platelet-derived growth factor receptor,[27] (4) angiogenesis,[28] (5) the Hedgehog signaling pathway,[29] (6) bone morphogenetic protein-7,[30] (7) endothelin-1 (ET-1),[31] (8) sphingosine-1-phosphate,[32] (9) basic fibroblast growth factor,[33] (10) brain-derived neurotrophic factor,[34,35] (11) adipokines (i.e. adiponectin,[36] leptin,[37] and resistin[38]), (12) histone deacetylase,[39] (13) Bcl-2 family,[40] (14) apoptosis related to endoplasmic reticulum stress,[41] (15) matrix metalloproteinase expression,[42] (16) cyclin-dependent tumor cell activity,[26] (17) epidermal growth factor receptor (i.e., glucose metabolism inhibition),[43] (18) microRNAs,[44] (19) phosphoinositide 3-kinase (PI3K)-Akt-mTOR,[21] (20) SRC pathway,[21] and (21) tumor suppressor pathways.[7] Additionally, clinical investigations on immune checkpoint inhibition have demonstrated promising outcomes despite being in the earliest phases and obtaining mixed patient responses. Immunotherapy and significance of the PD-1/PD-L1 pathway

Immunotherapy research, particularly on immune checkpoint inhibition, has been ongoing in various cancers, including sarcomas. Several immunohistochemical investigations have demonstrated immune phenomena in chondrosarcoma.[45,46] Cohen Nowak *et al*. reported a case involving a patient with metastatic chondrosarcoma who exhibited a remarkably sustained response to immunotherapy after failing multiple lines of systemic therapy.[11] Moreover, in comparison to normal bones, chondrosarcoma tissues exhibit increased expression of PD-1.[47] One study found that PD-L1 immunoexpression status determines the response to immunotherapy in many cancers.[48] An analysis of the expression of PD-L1 protein in conventional mesenchymal, clear cell, and dedifferentiated chondrosarcomas revealed an upsurge in PD-L1 expression in 41% of dedifferentiated chondrosarcomas, which was considerably correlated with tumor-infiltrating lymphocytes and human leukocyte antigen class I expression.[49,50] Moreover, another study revealed that patients with chondrosarcoma showed positivity rates of 68% and 42% for PD-L1 and PD-L2 expression, respectively. Evidence has established a link between PD-L1 expression and younger age, larger tumor size, histological grade, and tumor recurrence.[45]

Furthermore, the PD-1/PD-L1 pathway plays a significant role in immune evasion given that their interaction downregulates the T-cell-mediated response.[51] Additionally, studies have found that inhibiting the PD-1 and PD-L1 interactions promoted a remarkable antitumor effect.[52] Moreover, solid tumor oncology has undergone transformation through the utilization of immune checkpoint blockade with anti-PD-1 and anti-PD-L1. In general, positive clinical outcomes are associated with the correlation between tumor mutational burden and PD-L1 expression.[53] Furthermore, sarcoma typically exhibits genomically stable characteristics and a low tumor mutational burden. A comprehensive analysis of tumor mutational burden across more than 100,000 cancer genomes encompassing 167 different cancer types revealed that chondrosarcomas, in particular, ranks among the lowest 10% in terms of tumor mutational burden.[54] Additionally, PD-L1 expression is low in sarcomas.[55]

A few clinical studies have investigated the efficacy of immune checkpoint inhibitors efficacy in sarcomas. The SARC028 trial assessed pembrolizumab efficacy in advanced bone and soft tissue sarcomas, with one partial response detected in five chondrosarcoma patients.[55] Another trial found that a combination of doxorubicin and pembrolizumab promoted favorable tolerability, with tumor shrinkage observed in three out of eight chondrosarcoma patients.[56] Although numerous clinical trials are currently in progress, further investigations on checkpoint blockade in chondrosarcomas are warranted. A phase 2 trial evaluating nivolumab as monotherapy or combined with ipilimumab showed overall response rates of 5% and 16%, respectively, in bone sarcoma.[57] This finding facilitates the development of treatments for patients with chondrosarcoma by investigating novel combinations of immune checkpoint blockade.

Mechanism for the involvement of the PD-1/PD-L1 pathway in tumor immune escape

The immune system normally surveils malignant cells, recognizing and removing them to prevent tumor growth. The PD-1/PD-L1 axis, an extensively studied negative regulatory immune checkpoint pathway, plays a crucial role in this process.[58] Tumor cells augment PD-L1 expression, which interacts with PD-1 receptors on immune cells, primarily T cells. This triggers inhibitory signals within immune cells, which dampen the antitumor response, activate a signaling

cascade within T cells, and activate SHP-2, which inhibits critical T-cell activation and effector pathways. Consequently, T-cell activity is reduced, impairing their capability to recognize and eliminate tumor cells and weakening the overall antitumor immune response.

Figure 1 describes the immune checkpoint signaling pathway. Upon T-cell activation, PD-L1 interacts with PD-1, inducing conformational changes and ITIM and ITSM phosphorylation within the PD-1 intracellular domain. This recruits SHP-2, which suppresses the PI3K/Akt and RAS/mitogen-activated protein kinase/extracellular-signal-regulated kinase (ERK) signaling pathways, inhibiting T-cell activation, proliferation, survival, and effector functions. SHP-2 recruitment near the T-cell receptor (TCR) attenuates essential signaling events near the TCR, including the suppression of ZAP70 phosphorylation mediated by Lck.[59] Moreover, it impacts other downstream signaling pathways, including those involving PI3K/Akt, RAS, ERK, VAV, and phospholipase Cγ.[60,61]

Additionally, PD-1 ligation results in the targeting of two main pathways, PTEN-PI3K-Akt and RAS-MEK-ERK.[60,62] Furthermore, several downstream biochemical signaling events are prone to the influence of PD-1. Therefore, targeting the PD-1/PD-L1 pathway with immune checkpoint inhibitors greatly increases the potential for cancer immunotherapy, given that blockade of PD-1/PD-L1 interactions through these inhibitors ultimately restores T-cell activity and enhances antitumor immune response and tumor regression.

Immunotherapeutic strategies for targeting the PD-1/PD-L1 pathway

Recent advances in cancer immunotherapy, particularly immune checkpoint inhibitors, have significantly enhanced the specificity and potency of immune responses against cancer. The PD-1 and anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) immune checkpoints play an inhibitory role in immune functions, and immune checkpoint inhibition has the potential to more efficiently reactivate T cells and enhance the eradication of cancer cells.[63] Numerous studies have underscored the therapeutic potential of these inhibitors.[64] Approaches include PD-1/PD-L1 inhibitors, combination therapies, biomarker-guided treatments, novel antibodies, vaccine and adoptive cell therapy combinations, and strategies exploring resistance mechanisms.

Different monoclonal antibodies capable of blocking PD-1 (on T cells) and PD-L1 (on tumor cells) interactions have been widely used as PD-1/PD-L1 checkpoint inhibitors. Some clinically available antibodies against PD-1 are nivolumab (2014), pembrolizumab (2014), cemiplimab (2018), dostarlimab (2021), and retifanlimab (2023).[62,65,66] Meanwhile, PD-L1-specific antibodies include atezolizumab (2016), avelumab (2017), and durvalumab (2017).[65] Additionally, PD-1/PD-L1 inhibitors can be used in combination with other therapies to enhance the antitumor immune response. These strategies may involve other immune checkpoint inhibitors (e.g. CTLA-4 inhibitors), targeted therapies, chemotherapy, or radiation therapy. Synergistic effects can be achieved by simultaneously targeting multiple pathways.

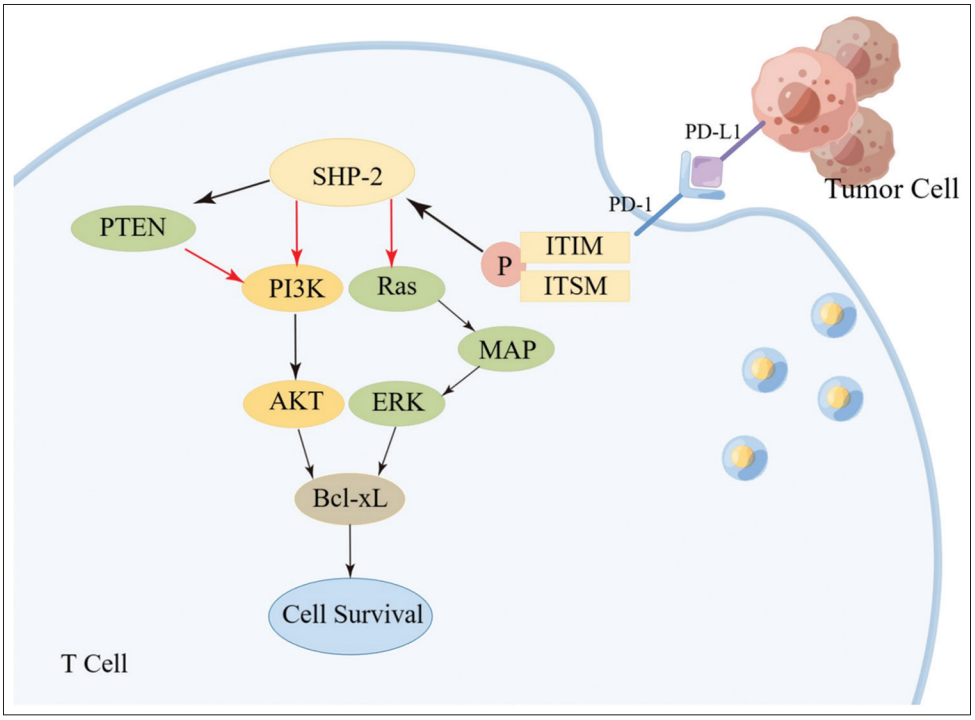

Figure 1: The PD-1/PD-L1 immune checkpoint signaling pathway. Black arrows indicate activation, whereas red lines represent inhibition

The immunosuppressive tumor microenvironment can be overcome using strategies including chimeric antigen receptor (CAR) T-cell therapy or tumor-infiltrating lymphocyte therapy. Additionally, exploring resistance mechanisms and using combination strategies might improve the efficiency of PD-1/PD-L1 inhibitors.[67,68] Evidently, immunotherapy strategies that target the PD-1/PD-L1 pathway have shown remarkable potential in terms of stable responses and improved patient outcomes across various cancer types.

Mechanism of action and types of PD-1/PD-L1 inhibitors

Figure 2 presents a schematic representation depicting the T cell release of interferon gamma (IFN-γ) to increase the efficiency of tumor killing. After recognizing tumor antigens presented on MHC class I, $CD8^+$ T cells become activated. This activation triggers the release of IFN-γ, which binds to the IFN-γ receptor and subsequently induces PD-L1 expression in tumor cells. Consequently, PD-1 on the surface of T cells is upregulated, leading to the conjugation of PD-L1 and PD-1 and the initiation of the inhibitory effects of the PD-1/PD-L1 axis.

Blocking the interaction between PD-1 and PD-L1 abolishes the inhibition of $CD8^+$ T cells, thereby enhancing antitumor activity.[69] Notably, PD-1/PD-L1 inhibitors block this interaction, thereby restoring T cell function and enhancing cancer cell recognition and elimination. Recent studies have investigated the efficacy of PD-1/PD-L1 inhibitors, including monoclonal antibodies and peptide/nonpeptidic inhibitors. Structural modifications to peptidomimetic inhibitors can generate small molecules with the desired properties. Small-molecule inhibitors/drugs have advantages over monoclonal antibodies, prompting the exploration of peptide-based and nonpeptidic small-molecule inhibitors of PD-1/PD-L1.[70] The following discussions describe the types of PD-1/PD-L1 inhibitors.

Antibody-based inhibitors. Studies have shown that antibody-based PD-1/PD-L1 inhibitors reduce tumors in various advanced cancers, emphasizing the importance of inhibiting the PD-1/PD-L1 pathway. A few antibody-based PD-1/PD-L1 inhibitors for chondrosarcoma treatment have been reported in the literature. Notably, the SARC028 clinical trial investigated the effects of pembrolizumab in five patients with chondrosarcoma, with the results demonstrating a highly equitable response in only one patient.[55] Another study also assessed the effects of nivolumab and found that a patient with dedifferentiated chondrosarcoma exhibited a limited response after six cycles. Moreover, after four cycles of nivolumab, a highly stable disease pattern was observed in a patient with mesenchymal chondrosarcoma.[71] Current trials are investigating combined immune checkpoint blockades with anti-CTLA-4 or mTOR inhibitors for nonresectable sarcomas and other advanced tumors.[46,72]

Aptamer-drug conjugate-based inhibitors. Evidence has shown that aptamer-drug conjugates (APDCs) are promising tools for immunomodulation and antitumor activity. Several DNA aptamers, including MP7 and AptPSL1, have been designed to block the PD-1/PD-L1 interaction.[73,74] Although APDCs have been proven useful as PD-1/PD-L1 inhibitors for various cancers, information on chondrosarcomas has been limited.

Peptide-based inhibitors. The first peptide-based inhibitor, AUNP-12, was reported in 2014.[75] Since then, other peptide-based inhibitors, including a small peptide and a cyclic peptide derivative, that stimulate spleen cell proliferation and reduce lung metastasis in mice have been identified.[76] Peptide-based immunomodulators of PD-1 are remarkably helpful in developing vaccines and therapeutics, particularly against infectious diseases.[77] Peptide-based

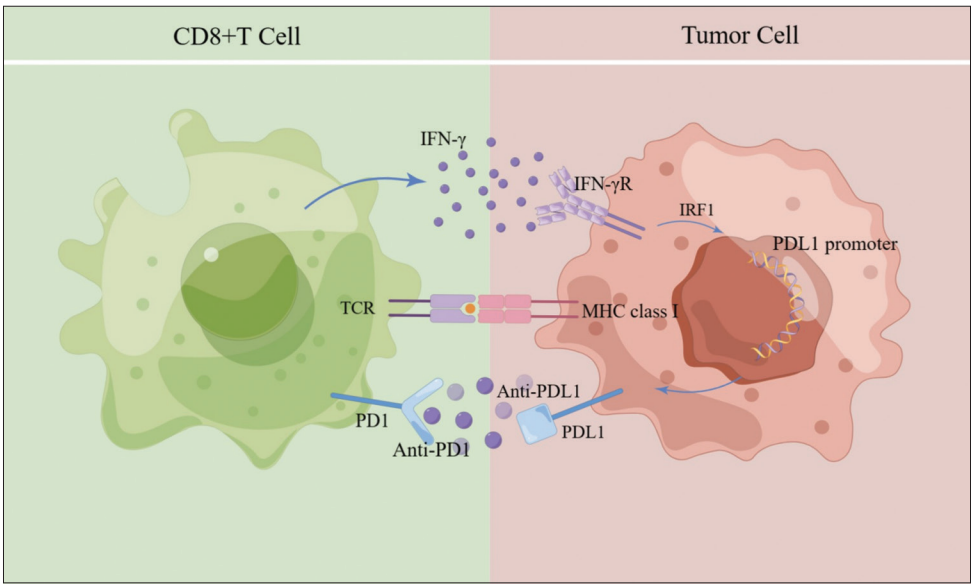

Figure 2: Mechanism of PD-1/PD-L1 blockade

immunomodulators have shown potential in vaccine and therapeutic development; however, more research is needed, particularly for chondrosarcoma.

Small-molecule inhibitors (nonpeptidic). Nonpeptidic small-molecule inhibitors, including sulfamethoxine and sulfamethimazole antibiotics, have demonstrated low cytotoxicity and effective modulation of the PD-1/PD-L1 pathway. BMS-8 and BMS-202 are examples of small-molecule inhibitors that inhibit PD-1 activation.[76,78] Although small-molecule inhibitors have advantages over mABs and have been successfully applied to various cancers, their use in chondrosarcoma requires further investigation.

Combined application of PD-1/PD-L1 pathway inhibitors and other therapeutic modalities

The emergence of immune checkpoint inhibitors as a strategy for regulating the immune system has opened new treatment options for patients with advanced cancer. Among these, PD-1/PD-L1 axis inhibitors have become widely used for treating different types of cancer. However, not all patients with advanced cancer have shown improvement from PD-1/PD-L1 inhibitors, with only a small percentage of patients exhibiting a response. Further research has revealed that the presence of PD-1 and its ligands alone cannot sufficiently guarantee a positive response to treatment. This is because multiple parallel immune checkpoint pathways can contribute to tolerance against anti-PD-1/PD-L1 therapy.[79]

Consequently, combining other immune checkpoint pathway inhibitors has been explored as a potential strategy to enhance treatment sensitivity. Studies have demonstrated that administering a combination of antibodies targeting two immune checkpoint molecules can improve the antitumor response in preclinical animal models. Various immune checkpoint inhibitors have been investigated for combination therapy, including CTLA-4 inhibitors, TIM-3 inhibitors, LAG-3 inhibitors, indoleamine 2,3-dioxygenase inhibitors, TIGIT inhibitors, B7-H3 monoclonal antibodies, and VISTA inhibitors. Combining different immune checkpoint inhibitors has emerged as a potential approach for enhancing treatment sensitivity and improving outcomes in patients with advanced cancer.[79] Figure 3 presents the different combinatorial approaches used for this purpose.

Ongoing clinical trials are currently exploring the efficacy of these combinations in various cancer types. Notably, the use of immune checkpoint inhibitors (i.e., CTLA-4, PD-1, and PD-L1, among others) through combined novel strategies has considerable potential for advancing cancer treatment. These novel combination immunotherapy approaches have demonstrated remarkable progress in improving the prognosis of patients with various types of tumors, including melanomas, non-small cell lung cancers, urothelial carcinomas, renal cell carcinomas, head and neck squamous cell cancers, and Hodgkin's lymphomas.[80] However, the primary focus of our

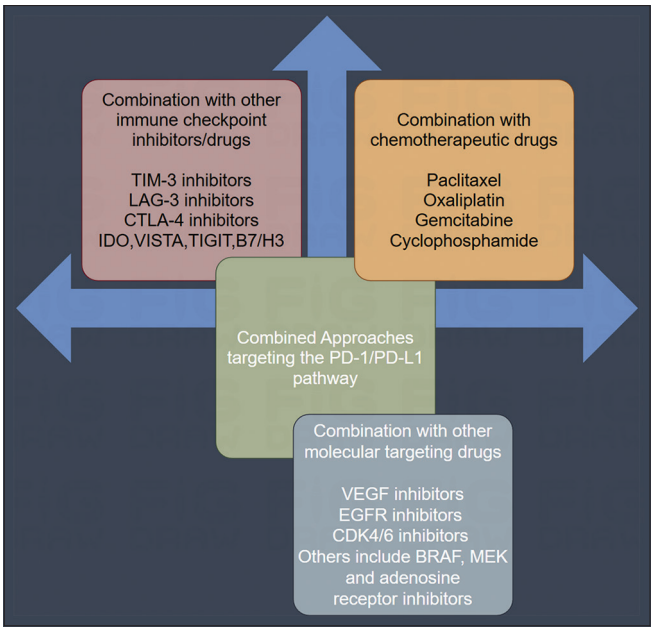

Figure 3: An overview of the various combined approaches and PD-1/PD-L1 inhibitors used in oncology

investigation is the application of these approaches in the treatment of chondrosarcoma, a rare type of bone cancer that arises from cartilage cells. Nonetheless, despite the promising results shown by immunotherapy in some cancer types, the utility of combined immunotherapy approaches in chondrosarcoma requires further investigation given the limited availability of information in this domain.

CONCLUSION AND FUTURE PROSPECTS

Chondrosarcoma is a common malignant bone tumor originating from chondrocytes that is characterized by endogenous cartilage ossification within the tumor tissue. Accounting for approximately 20%–30% of all primary bone malignancies, chondrosarcoma is the second most prevalent type of bone sarcoma after osteosarcoma. Furthermore, chondrosarcoma poses significant treatment challenges given that the available therapeutic options are limited to surgery and chemoradiation. However, the suitability of these treatments varies depending on individual factors, including chondrosarcoma type, histological and pathological grade, patient age, and physical fitness. Moreover, patients diagnosed with highly metastatic or unresectable chondrosarcomas have limited treatment options due to the development of resistance against standard anticancer agents.

Recent *in vitro* and preclinical studies have identified potential new treatment avenues, although further therapeutic targets need to be identified. However, among the various novel therapies proposed, immunotherapy and molecularly targeted drugs have shown remarkable potential for the treatment of human malignancies. Thus, to enhance clinical outcomes in patients with advanced chondrosarcoma, several novel

approaches, including immunotherapy and targeted molecular drugs, are necessary. Considering that, the circumvention of immune surveillance is a key factor in the progression of malignant tumors and that immune checkpoints play an important role in modulating antitumor immune effects, blockers or inhibitors targeting these immune checkpoints have become effective therapeutic tools for patients with tumors. One such checkpoint receptor implicated in this process is PD-1. Furthermore, the association between PD-1 and PD-L1 and cancer progression in humans has been extensively studied, which highlights their remarkable potential as biomarkers for cancer treatment.

More recently, evidence has shown that the use of immune checkpoint inhibition-based therapies promotes remarkable clinical outcomes in different cancer types, including metastatic melanomas, renal cell carcinomas, lung cancers, and breast cancers. Immune checkpoint blockade is a currently evolving therapeutic approach for different malignancies, with the milestones achieved herein spearheading the investigation of the potential utility of these approaches in different bone sarcomas, including chondrosarcoma. At present, ongoing sarcoma research has spanned from fundamental reports to clinical trials exploring immune checkpoint inhibition, the results of which are anticipated to be published in the near future. Notably, immunotherapy has shown promising potential for treating chondrosarcoma, although clinical investigations are necessary to validate these findings. The primary objectives of these clinical trials should be to assess the effectiveness of immunotherapy treatment as monotherapy or combination therapy for chondrosarcomas followed by the investigation of immune-related adverse events. Most evidently, the continuation of clinical trials is of utmost importance for bone sarcomas in general and chondrosarcomas in particular. Moreover, predictive biomarker discovery is yet another cornerstone that will ultimately allow the design of personalized medicine for patients with chondrosarcoma using immune checkpoint inhibition-based therapies.

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Conflicts of interest

There are no conflicts of interest.

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