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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Hua-Feng Wei, MD, PhD, Research Associate, Cancer Center Lab, General Hospital of Chinese PLA, China and Second Military Medical University, International Joint Cancer Institute, Beijing 100853, China

AIM AND SCOPE

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCO covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, and oncology-related nursing. Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Immunotherapies in sarcoma: Updates and future perspectives

Marwan Ghosn, Elie El Rassy, Hampig Raphael Kourie

Marwan Ghosn, Elie El Rassy, Hampig Raphael Kourie, Department of Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Beirut 2038 3054, Lebanon

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Correspondence to: Elie El Rassy, MD, Department of Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Monot St, Beirut, PO Box 166830, Beirut 2038 3054, Lebanon. elie.rassy@hotmail.com
Telephone: +961-1-615300
Fax: +961-1-615300

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Abstract

Sarcomas are malignant tumors that are characterized by a wide diversity of subtypes with various cytogenetic profiles. Despite major treatment breakthroughs, standard treatment modalities combining chemotherapy, radiotherapy, and surgery failed to improve overall survival. Therefore, high expectations are foreseen with immunotherapy upon its maturation and better understanding of its mechanism of action. This paper presents a targeted review of the published data and ongoing clinical trials in immunotherapies of sarcomas, mainly adoptive cell therapies, cancer vaccines and immune checkpoint inhibitors.

Key words: Adoptive cell therapy; Cancer vaccines; Immunotherapy; Immune checkpoint inhibitors; Sarcoma

Core tip: This paper is a review that outlines the most recent updates on the immunotherapy treatment of sarcomas. After a brief review of the concept of immunotherapies and the different treatment modalities, we discuss the available data, the limitations and future perspectives of each treatment option.

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INTRODUCTION

Sarcomas are malignant tumors that derive from embryonic mesodermic tissues including fat, muscles, bones, nerves and blood vessels[1]. Epidemiologic studies report its predominance in the pediatric populations and its rare occurrence in adults[2]. Sarcomas are

characterized by a wide diversity of subtypes with various cytogenetic profiles conferring treatment resistances. These findings combined with an advanced stage at diagnosis substantially increase the years of life lost[3]. The standard treatment modalities combining chemotherapy, radiotherapy, and surgery have failed to improve overall survival (OS)[4]. Despite the major breakthroughs in the treatment armamentarium, the recent data reports a relative 5-year survival rate limited to 66% for bone and soft tissue sarcomas, 53.9% for osteosarcomas, 75.2% for chondrosarcomas, and 50.6% for Ewing's sarcomas[5].

Interestingly, Coley described in 1891 a complete regression of sarcomas secondary to severe episodes of erysipelas but failed to regenerate these results in other patients[6]. The Food and Drug Administration thereafter banned the use of toxin therapy without a new drug-approval process. Fortunately, Coley's paper has encouraged scientists to analyze the role of the immune system in carcinogenesis[7].

After more than a century since Coley's research efforts that marked the history of immunotherapy, we present a review on this elegant treatment modality in the management of sarcomas including adoptive cell therapies (ACT), monoclonal antibodies, vaccines, and immune checkpoint inhibitors (ICI).

APPROVED THERAPIES IN SARCOMAS FROM CHEMOTHERAPY TO TARGETED THERAPIES

Specialized centers in the management of sarcomas have demonstrated a better OS and low recurrence rate[8]. Yet, all patients are managed uniformly according to their prognosis dictated by the stage of the disease, which is determined by the grade, depth and size of the tumor[9]. For patients with localized disease, a complete resection with wide 2-3 cm margins followed by adjuvant radiation therapy is the mainstay treatment for a curative approach. However, survival is not only determined by local control since most patients die from systemic disease. The choice of the chemotherapy regimen depends on the tumor chemosensitivity which varies with the tumor subtype and grade, the patient's performance status, and the timing of metastatic disease[10]. Unfortunately, the benefits of adjuvant chemotherapy are limited to rhabdomyosarcomas, osteosacromas and Ewing's sarcomas. Moreover, Trabectidine is showing promising results encountered in the adjuvant and neoadjuvant settings of patients with myxoid liposarcomas[11]. The role of adjuvant and neoadjuvant chemotherapy in the management of soft tissue sarcomas is yet to be clearly established. The actual recommendations by NCCN and ESMO are to address this issue on a case by case basis according to the patient's performance status, comorbid factors, disease location, tumor size, and histologic subtype. In case of advanced and recurrent sarcomas, induction regimens include Cyclophosphamide and Ifosphamide, Vincristine, Doxorubicin, Dactinomycin, and Etoposide[12]. For patients with unresectable or metastatic disease, the management plan is limited to a palliative approach with Trabectedin or Ifosfamide and Doxorubicin based chemotherapy[13,14].

The rationale of using targeted therapies in sarcomas goes back to 1984 when sarcomagenesis was correlated to recurrent translocations[15]. Genetic profiling thus defined two groups of sarcomas. The first group is characterized by a simple karyotype associated with specific tumor genetic alterations that include chromosomal translocations, oncogenetic mutations, and recurrent gene amplifications. The second group is characterized by a complex karyotype associated with nonspecific and nonrecurring genetic alterations[16]. Subsequent to these advances, Pazopanib, a multitargeted tyrosine kinase inhibitor against VEGFR1-3, PDFGRA-B, and KIT was approved for pretreated metastatic nonlipomatous sarcomas based on the phase Ⅲ PALETTE study[17]. Clinical and preclinical mechanistic studies are being conducted to validate a possible therapeutic role of the various targeted therapies available. Among these novel targeted therapies, we report the trials of Cediranib and Sunitinib in alveolar soft part sarcoma, Tivantinib and Cabozantinib in clear cell sarcoma, Imatinib in dermatofibrosarcoma protuberans, Cabozantinib in endometrial stromal tumors, and Everolimus in perivascular epitheloid cell tumor[18].

ADVANCES IN IMMUNO-ONCOLOGY

In fact, the previous cancer treatment approaches addressed distinctive and complementary hallmarks of carcinogenesis that included sustained proliferative signaling, evasion of growth suppressors, resistance of cell death, enabling of replicative immortality, induction of angiogenesis and activation of invasions and metastasis[19]. The well-known conventional cytotoxic drugs and targeted therapies have reached a plateau in effect that required a re-assessment of the six hallmarks of carcinogenesis. Recent conceptual progress has added two new hallmarks, namely reprogramming of energy metabolism and signaling interactions of the tumor microenvironment[20].

The later resides in the concept of the cancer-immunity cycle and is actually a turning point in the history of cancer therapy[21]. This cycle is the result of a counterbalance between immune-stimulatory and inhibitory factors. It occurs physiologically and starts with the release of cancer cell antigens and ends with the apoptosis of cancer cells *via* the activated effectors of the immune system[22]. Subsequently, cancer immunoediting may proceed with any of the three following phases[23]. The elimination phase describes an activation of the innate and adaptive immune effectors in response to cytokine secretion. The equilibrium phase occurs in the setting of a balance between tumor immune destruction and proliferation. The immunologic phase takes place when the tumor cells are capable of evading the immune system[23].

Recent advances recommend addressing only one step of the immune cycle to avoid potential unwanted

activation of autoimmunity mechanism and normal cells damage. Therefore, immunotherapy aims at initiating or maintaining the cancer-immunity cycle by acting on its rate limiting step. Consequently, ICI often address the immunostar function of the tumor microenvironment[24]. The PD-1/PD-L1 axis is a potential therapeutic target in view of the confirmed expression of PD-L1 in various sarcomas[25]. Inhibition of this axis enables the immune system to quickly adapt to cancer resistances thus allowing durable responses with ICI[26].

IMMUNOTHERAPEUTIC MODALITIES EVALUATED IN SARCOMAS

Sarcomas mainly occur either secondary to the activation of oncogenes *via* translocations and inversions, or secondary to the natural expression of germ cell peptides[27,28]. The issuing peptides generate an immune cascade directed against the aberrant cells[29]. Consequently, multiple rationales to immunotherapy including ACT, therapeutic vaccines, and ICI have been assessed in the treatment of sarcomas (Table 1).

Adoptive cell therapy in sarcomas

Adoptive cell therapy is a new therapeutic strategy based on the modulation, manipulation and selection of autologous T-cells *in vitro* to overcome the tolerance of the immune system to the tumor cells. Those T-cells may be harvested from tumor infiltrating lymphocytes (TIL) and re-transfused into the same patient after ensuring their expansion. Lymphocyte T-cells may also be harvested from peripheral blood, and those that recognize tumor antigens are selectively expanded. Alternatively, lymphocyte T-cells may be genetically engineered either by modifying a T-cell receptor for cancer antigen (transgenic TCR) or by adding a chimeric antigen receptor (CAR) that recognizes a specific cancer antigen[30,31]. Apart from T-cells, NK ACT has also been proven efficacious with several advantages over the classical T-cell ACT in the absence of MHC/HLA restriction, namely their NKG2D-dependent cytotoxicity against autologous tumor cells[32,33].

To our knowledge, the use of TIL has never been reported in the treatment of sarcomas whilst the use of NK ACT has been limited to case reports[33]. On the other hand, tumor antigens such as GD2 (93% of sarcomas) and NY-ESO-1 (80% to 100% of different subtype of sarcomas) were found to represent interesting targets for adoptive cells therapies. Moreover, other cancer testis antigens such as LAGE, MAGE-A3 and PRAME were frequently expressed in sarcomas and would be potential immunotherapeutic targets. In this setting, a phase I study evaluated the ability of adoptively transferred autologous T-cells transduced with a T-cell receptor (TCR) directed against NY-ESO-1 to mediate tumor regression in patients with metastatic synovial cell sarcoma expressing NY-ESO-1. The results showed an objective clinical response in 4 out of 6 patients[31].

Two ongoing trials are evaluating genetically engineered NY-ESO-1 T-cells for children and adults in metastatic synovial sarcoma (NCT01343043). Another phase I trial is testing the role of CAR T-cell therapy targeting the GD2 protein in children and young adults with sarcomas and rhabdomyosarcomas (NCT00743496).

Therapeutic vaccines in sarcomas

The therapeutic effects of cancer vaccines rely on the activation of dendritic cells upon the presence of an immunogenic predetermined antigen. However, most of the initial studies of vaccines in sarcomas did not determine specific antigens and used inefficaciously the entirety of the tumor cells[34,35]. Later studies used SYT-SSX, a fusion derived peptide present in 90% of synovial sarcoma, and also failed to demonstrate an objective response[36-38]. Takahashi *et al*[39] personalized the peptide vaccination patients with refractory sarcoma and administered multiple tumor antigens chosen according to preexisting peptide-specific IgG titers. The median OS was 9.6 mo with disease stabilization occurring in 30% of patients but no objective responses were seen. Another vaccination modality used *in situ* vaccination through combining preoperative gamma radiation (50 Gy) with intratumoral dendritic cells injection. The studied population was limited to high risk, localized, and resected extremity soft tissue sarcoma and resulted in 71% progression free survival at one year[40].

Major efforts in this field are being conducted namely in children with Ewing sarcomas. Recent data demonstrated a 75% OS at one year with FANG immunotherapy in adolescent patients with Ewing's sarcoma. The treatment was well tolerated with a favorable OS[41]. A seemingly interesting phase Ⅰ trial designed for the treatment of pediatric patients with relapsed high-risk Ewing sarcoma, osteogenic sarcoma, rhabdomyosarcoma, synovial sarcoma, and neuroblastoma is using a combination of Decitabine demethylating agent and a cancer vaccine composed of dendritic cells pulsed with overlapping peptides of NY-ESO-1, MAGE-A1, and MAGE-A3 (NCT01241162). Another dendritic cell vaccine is also being assessed in combination with Gemcitabine in a phase Ⅰ trial for adults and children with soft tissue and bone sarcomas (NCT01803152).

Immune checkpoint inhibitors in sarcomas

The concept of ICI relies on deactivating the suppressed activity of the immune system. ICI remove the brakes (PD-1 and CTLA4) thus enhancing the immune function of already sensitized T-cells. Effectively, PD-1 and CTLA4 inhibitors are showing interesting results with acceptable response rates in different cancers, including those considered for a long time as non-immunogenic[42]. Unlike CTLA4 inhibitors, the response to PD1 and PDL-1 inhibitors has been correlated with the expression of PD-1 and PDL-1 on tumor cells and to the mutational load of the tumors[42]. Moreover, PD-1 and PDL-1 expression seems to vary between sarcoma subtypes, a finding that may direct immunotherapy management in patients with sarcomas[43].

Table 1 Summary of the phase Ⅰ/Ⅱ trials of immunotherapies in sarcoma

Treatment modality	Ref.	Agent	Phase/Patients	Indication	RR	Survival
Adoptive cell therapy	Robbins *et al*[31], 2011	Adoptively transferred autologous T cells transduced with a T-cell receptor directed against NY-ESO-1	Ⅰ/6	Metastatic synovial cell sarcoma expressing NY-ESO-1	RR: 4/6	N/A
Vaccines	Mahvi *et al*[34], 2002	GM-CSF treated tumor cells	Ⅰ/16	Melanoma and sarcomas	RR: 1/16	N/A
	Dillman *et al*[35], 2004	Autologous tumor cell line-derived vaccines	Ⅰ, Ⅱ/23	Recurrent or metastatic sarcoma	No objective response assessed	10 patients lived more than 1 year
	Kawaguchi *et al*[36], 2005	Vaccination By SYT-SSX junction peptide	Ⅰ/6	Disseminated synovial sarcoma	RR: 0/6	N/A
	Kawaguchi *et al*[38], 2012	SYT-SSX breakpoint peptide vaccines	Ⅰ, Ⅱ/21	Metastatic synovial sarcoma	RR: 1/21 SD: 6/21	N/A
	Takahashi *et al*[39], 2013	Personalized peptide vaccination	Ⅱ/20	Refractory bone and soft tissue sarcoma	SD in all patients	Median OS: 9.6 mo
	Finkelstein *et al*[40], 2012	Combination of external beam radiotherapy with intratumoral injection of dendritic cells	Ⅰ, Ⅱ/17	Neoadjuvant treatment in high-risk soft tissue sarcoma	RR: 9/17	One-year PFS: 70.6%
	Ghisoli *et al*[41], 2015	FANG autologous immunotherapy	Ⅰ/12	Advanced and metastatic Ewing's sarcoma	RR: 1/12	One-year OS: 75%
Checkpoint inhibitors	Makki *et al*[44], 2013	Ipilimumab	Ⅱ/6	Advanced synovial sarcoma	RR: 0/6 (closed prematurely)	Median OS: 8.75 mo

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; N/A: Not available; OS: Overall survival; PFS: Progression free survival; RR: Response rate.

Unfortunately, the efficacy of ICI in sarcomas has been evaluated in only one study so far. It is a phase Ⅱ study that administered Ipilimumab (3 mg/kg intravenously every 3 wk for 3 cycles), a CTLA-4 inhibitor, to six patients with synovial sarcoma. The median OS was 8.75 mo ranging between 0.8 and 19.7 mo. The study was closed prematurely when none of the patients had an objective tumor response. All patients expressed NY-ESO-1 but its titers did not change after treatment administration[44]. PD-1 and PDL-1 inhibitors present a different mechanism of action compared to anti-CTLA4 agents and consequently may present better response rates[43]. Many ongoing phase Ⅰ trials are assessing the role of anti-PD1 agents in sarcomas as single agent or in combination with Ipilimumab and Dasatinib (NCT0 1643278).

PERSPECTIVE

The proof of the immunotherapy concept in sarcomas has been undoubtedly validated with the benefits encountered upon the use of liposomal muramyl-tripeptide-phosphatidyl-ethanolamine, an immunoactivator agent derived from BCG. However, its role remains controversial in view of the discordant results between the preliminary data and final results in both the adjuvant and metastatic setting. Even though the actual trend is moving towards immunotherapy as an essential tool in the treatment of cancer, the recent ASCO 2016 meeting was unfortunately disappointing in this regard. Five studies have been presented, of which one trial of chemotherapy (Busulphan and Melphalan), three trials of tyrosine kinase inhibitors, monotherapy (Anlotinib and Regorafenib) or in combination with chemotherapy (Gemcitabine plus Pazopanib), and one study reporting the evident detrimental impact of disease progression and altered quality of life on the long-term care and survival of patients with sarcomas. The ongoing trials including the promising results of immunotherapies are awaited. The available results reported a failure of Pembrolizumab in multiple soft tissue sarcomas (NCT02301039) and Nivolumab in metastatic uterine leiomyosarcoma (NCT0 2428192) despite the promising findings encountered with Nivolumab in retrospective experiences[45]. In fact, the biological preclinical rationale is not fully elucidated in view of the absence of any correlation between PD-L1 expression and OS[46]. Thus, the actual state of knowledge does not predict the patient profile that might benefit from immunotherapy.

CONCLUSION

The cornerstone treatment for sarcomas consists of complete surgical resection, chemotherapy, and radiotherapy. Unfortunately, these treatment options fall short from achieving an optimal clinical outcome. Immunotherapy is therefore expected to further improve the survival of patients with sarcomas. Until recently, the field of immunotherapy has not yet matured enough to present robust effects. The better understanding of onco-immunotherapy principles is essential to adjust the design of clinical trials and the selection of inclusion criteria. The published data shows that ACT is yet to be more elucidated and evaluated, vaccine therapy requires tailoring and personalization, and ICI, preferably PD-1 and PDL-1 inhibitors, necessitate better patient selection. Such results

would allow more understanding of the antitumor immunity mechanisms and improvement of the treatment arsenal against sarcomas.

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