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Review

Immunotherapy for synovial sarcoma

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Abstract: Synovial sarcoma (SS) is a relatively common subtype of soft tissue sarcoma that typically affects young adults. Nearly all tumors harbor a translocation between *SS18* and *SSX1/SSX2* and the vast majority express the cancer testis antigen (CTA) NY-ESO-1. While patients with small, non-metastatic tumors are often cured surgically, outcomes remain poor for patients with locally advanced or metastatic disease, even when aggressive chemotherapy and radiotherapy are employed. Therefore, innovative systemic therapies that target the biology of the disease are needed to improve outcomes for these higher risk patients. One such category is tumor-directed immune therapies. In this review, we will discuss the current status of immunotherapy for SS, including the recent trial results, ongoing challenges, and future directions.

Keywords: sarcoma; synovial; immunotherapy; checkpoint inhibitors; NY-ESO-1; adoptive therapy; dendritic cell vaccines

1. Introduction

Synovial sarcoma (SS) is one of the most common soft tissue sarcomas (STS), accounting for 5–10% of all patients [1,2]. Young adults are most frequently affected, with the peak incidence in the third decade [1]. SS can occur anywhere in the body though extremity sites are the most common [3,4]. Approximately one quarter of patients present with distant metastases [1,5]. Lung is the most common metastatic site, followed by bone and liver [5]. Surgical resection is the standard treatment for patients with localized disease. Chemotherapy and radiation are employed for patients with high grade, large, locally advanced or metastatic tumors [2]. SS is initially relatively chemo-sensitive

compared to other STS. However, the course of the disease can be quite indolent and late recurrences are not uncommon [2].

The most common agents used in frontline therapy are anthracycline (doxorubicin) and ifosfamide [6–8]. Pazopanib, a tyrosine kinase inhibitor, and trabectedin, an agent with complex anti-tumor effects on DNA replication, are also frequently used with some success in recurrent/refractory disease [9,10]. Poor prognostic factors include presence of metastasis, large (> 5 cm) primary tumors, and non-extremity primary site [11–13]. In addition, reported outcomes for adults with SS are typically inferior to pediatric patients [14]. Generally, outcomes are very favorable for patients with small, localized tumors. For example, non-metastatic SS patients enrolled on the pediatric EpSSG study RMS2005 achieved a 5 yr OS of 90.7% [14]. Since outcomes remain poor for patients with metastatic or locally advanced disease, with reported 5 yr OS less than 30% [13], the development of new therapies is required to make progress in this disease.

Morphologically, SS are described as monophasic or biphasic [15]. Bisphasic SS is considered to be the classic histology, characterized by the presence of both epithelial and spindled cells. However, a similar proportion of SS are monophasic which is almost always the pure spindle cell type and can be difficult to distinguish from other similar appearing STS [15]. The cytogenetic feature that characterizes nearly all of SS is the chromosomal translocation t(X; 18)(p11; q11), the fusion of the *SS18* (also sometimes referred to in the literature as *SYT)* gene on chromosome 18 to *SSX1* or *SSX2* on the X chromosome [16]. SS typically harbor few recognizable genetic alterations. However, more than 80% of SS express the cancer-testis antigen (CTA) NY-ESO-1, an immunogenic "self" protein [17,18]. Because STS is rare, all non-rhabdomyosarcoma STS patients have historically been evaluated as one group in clinical trials. This sometimes makes it challenging to extract meaningful data on one subtype. With more focus on tumor-specific or biology-specific therapy, trials are increasingly designed with planned subgroup analyses. In this review, we discuss the current status of immunotherapy for SS. We will focus on three approaches: checkpoint inhibitors, adoptive therapies, and vaccine therapies.

2. Checkpoint inhibitors

In the last several years, there has been a surge of trials investigating the use of immune checkpoint inhibitors in a variety of advanced cancers. These agents target molecules that contribute to immune homeostasis by negatively regulating T cell activation, including cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1), with the intention of exposing malignant cells to more rigorous anti-tumor immunity. CTLA4 is a protein receptor that is upregulated early in T cell activation, especially CD4+ cells. The activity of the PD-1/PD-L1 pathway is notable during T cell expansion and exhaustion and can be important during their effector phase [19].

CTLA4 was the first checkpoint target subject to broad clinical investigation, achieving single agent success in several groups of advanced solid tumors [20–22]. The CTLA4 antibody Ipilumimab is currently FDA approved for advanced or unresectable melanoma as well as renal cell carcinoma. Trials evaluating PD-1 and PD-L1 inhibition have followed and have demonstrated success in similar patient populations [23–25]. Because CTLA4 and PD-1/PD-L1 modulate specific and distinct mechanisms of T cell immunity, combined checkpoint inhibition has been pursued with even more favorable results [26–28]. Unfortunately, this success has not extended to most sarcomas, including SS. SARC028 was a single arm phase 2 study conducted in North America that investigated

treatment with the PD-1 inhibitor, pembrolizumab, in subjects with recurrent or refractory bone and soft tissue sarcoma [29]. The study included 80 evaluable patients, with a total of 10 patients in the SS cohort. The objective response rate was 7/40 (18%) and 12-week progression free survival 55% for all patients with soft tissue sarcoma. There was one short-lived partial response within the SS cohort, and one patient with prolonged stable disease. Responses were mostly limited to patients with undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma. Interestingly, PD-L1 expression was observed in only 2 tumors out of 40 that had tissue available; both were UPS. A later clinical trial (Aliance A091401) prescribed the PD-1 inhibitor Nivolumab alone or in combination with ipilumumab to adults with locally advanced, metastatic, or unresectable soft tissue sarcoma [30]. Patients were randomized to monotherapy or the combined regimen with a total of 38 patients evaluated in each group. Objective responses were observed in 2 (5%) patients on the Nivolumab arm and in 6 (16%) on the nivolumab + ipilumumab arm. Responses were observed in patients with UPS, liposarcoma, angiosarcoma, leimyosarcoma, and myxofibroid sarcoma, but not in any of the 4 SS patients. Trials with similar objectives and treatment regimens are currently being conducted through pediatric cooperative groups (NCT02304458).

One challenge that is frequently considered in the design and interpretation of these studies is which biomarkers can be used to determine the likelihood of success with checkpoint inhibition. Among adult non-sarcoma patients, there is a trend toward more success in tumors with higher rates of nonsynonymous somatic mutations (NSSMs), increased TILs, and increased expression of PD-1 in TILs [31–34]. Sarcomas as a whole and SSs in particular have a low mutational burden [35]. In an analysis of the immune profile of common soft tissue sarcoma subtypes, UPS and LMS had the highest expression of PD-1 and PD-L1 as well as the highest level of T cell infiltration and clonality; synovial sarcoma was at the bottom of the list [36]. This correlates with the pattern observed in the trials described above, with UPS and LMS among the tumors most likely to respond to checkpoint inhibitor therapy. An ongoing National Cancer Institute (NCI)-sponsored phase 2 trial of pembrolizumab in combination with Interferon Gamma-1b has recently been amended to include metastatic and unresectable SS [NCT03063632]. Though Interferon Gamma (IFNγ) activity can generate conflictive effects on tumors, the combination is being tested based on observations that IFNγ production increased Major Histocompatibility Complex (MHC) expression by SS tumors as well as T cell infiltration [37]. Otherwise, the use of checkpoint inhibition in combination with other modalities of immunotherapy that may alter the immune landscape of these tumors remains largely untested.

The remaining immunotherapeutic approaches applied to SS focus largely on cancer testis antigens, including NY-ESO-1, which serve as attractive targets given their high level of expression as well as their consistent and heterogeneous expression in synovial sarcoma despite their variable presence in several other malignancies [38]. Though its exact function is unknown, NY-ESO-1, which is encoded by the *CTAG1B* gene on the X chromosome, stimulates both antibody and T cell responses [17,18]. Furthermore, its expression in adult tissues is limited to the testis, which is an immune privileged area and lacks MHC, affording presumed protection from off tumor toxicity [39,40]. Two common approaches that target NY-ESO-1 will be reviewed here, adoptive transfer of genetically engineered T cells and vaccine therapies.

3. Adoptive therapies

Adoptive transfer of tumor-specific T lymphocytes has emerged as one of the preeminent strategies in the development of novel cancer therapies, primarily through the use of genetically engineered T cell receptors (TCR) and chimeric antigen receptor (CAR)-based T cells. CAR T cell therapy has in particular had a major impact in the treatment of CD19+ hematologic malignancies [41,42]. TCR therapies are designed to bind MHC-bound antigen, and can be generated to detect relatively low levels of intracellular protein. CAR T cells are constructed using antibodies to cell surface proteins with co-stimulatory molecules that allow them to function in an MHC-independent manner. Adoptive therapies have been less prosperous thus far in the treatment of solid tumors, which pose unique challenges related to antigen selection, effective trafficking of effector cells to tumor sites, and proliferation in the tumor microenvironment [43]. However, there is some promising data from clinical trials employing T cells engineered to recognize NY-ESO-1. In a study published by Robbins et al., adult patients with NY-ESO-1+ metastatic melanoma and metastatic synovial sarcoma who had failed standard therapy were administered autologous T cells transduced with a TCR recognizing NY-ESO-1[44]. Patients underwent lymphodepletion with fludarabine/cyclophosphamide and received IL-2 to support the growth and persistence of adoptively transferred T cells. The objective response rate was 11/20 in the melanoma cohort and 11/18 in synovial sarcoma patients. The anti-tumor effects of chemotherapy and IL-2 was hypothesized to contribute to some shorter lived responses but thought to be less likely responsible for the several patients with prolonged response, including 2 synovial sarcoma patients with responses that lasted 1–3yr. T cell persistence varied and did not appear to correlate with response. In a more recently published study, 12 patients with NY-ESO-1+ synovial sarcoma were treated with autologous T cells engineered to express an enhanced affinity TCR receptor recognizing the NY-ESO-1 associated peptide (NY-ESO-1c259T cells) [45]. In this trial, patients did receive lymphodepleting chemotherapy but did not receive systemic IL-2. Overall response rate was 50%, with one complete response and 5 partial responses. The median time to response was 6.2 weeks, and median duration of response was 30.9 weeks. Long term (> 6 months) NY-ESO-1c259T cell persistence was observed in both responders and non-responders. 5 patients experienced grade 1–3 CRS but all recovered without significant complication. In one patient who eventually developed a CR, transient worsening of lung metastases was observed within 48 hours of infusion, supporting the hypothesis of immune-mediated tumor regression. Though lymphodepletion including fludarabine appears to be required to achieve the best response, these results indicate that the IL-2 administration may be omitted. NY-ESO-1 directed T cell therapy continues to be studied in clinical trials for SS and other NY-ESO-1-expressing tumors, as investigators attempt to refine the technology and employ strategies to enhance the efficacy. One strategy is the use of checkpoint inhibitors to help overcome the immunosuppressive properties of the tumor microenvironment. Several trials are underway to evaluate this approach of combination immunotherapy. Current adoptive therapy strategies for SS extend beyond NY-ESO-1. MAGEA4 is another CTA (encoded by the gene *MAGEA4*) expressed by the majority of SS in addition to several other malignancies [46]. It is usually co-expressed with NY-ESO-1 and, like NY-ESO-1, is associated with advanced disease [46]. A phase 1 dose escalation study of MAGEA4 directed T cell therapy in adults is being conducted by Adaptimmune. The third dose cohort is currently accruing and MAGEA4+ SS patients are eligible (NCT03132922). Additionally, there are many solid tumor-focused CAR T cell trials underway and

in development that are available to patients with SS whose tumors express the antigen target, including EGFR, B7-H3, and HER2/neu.

4. Tumor vaccines

Another strategy that has been promising is the development of vaccine therapies. Therapeutic cancer vaccines aim to modify a patient's immune responses so that malignant cells are targeted and eliminated. There are many categories of tumor vaccines, including those generated from tumor cells, immune cells such as dendritic cells (DCs), viruses, genetic material (DNA, RNA), and protein/peptides. Tumor vaccines trialed in sarcomas have included peptide vaccines against ganglioside antigens and breakpoint region of the SS18-SSX fusion as well as several dendritic cell vaccines with tumor cell lysate [47–50]. Rare responses were reported in some of the trials but overall these approaches have not demonstrated impressive, sustained immunologic response or tumor efficacy.

The role of DCs in particular in tumor vaccine therapy continues to evolve and remains a focus in SS. DCs are antigen presenting cells (APCs) that function by processing antigen into peptides which are loaded on the cell surface using MHC class I and presented to lymphocytes in the periphery [51]. DCs are able to produce robust CD8+ T cell responses, which has led to their appeal as a tool for anti-cancer immunotherapy [51–53]. Traditionally, DC vaccines are generated through ex vivo culture and tumor antigen loading, followed by adoptive transfer. DC-based vaccines have consistently demonstrated the capability to elicit tumor specific immune responses and have proven relatively safe over the test of time [54]. However, challenges remain in terms of the cost, per patient labor investment, and desire for more consistent long-term anti-tumor efficacy [54]. Traditional DC vaccines continue to be developed as DCs are also being incorporated into more complex immunotherapy approaches, including in vivo DC-targeted vaccines. The latter approach has recently been investigated as a method to target NY-ESO-1 in SS.

LV305 is an integration deficient, DC-targeted lentiviral vaccine that encodes NY-ESO-1 and enters DCs via interaction with DC-SIGN (CD209), a cell surface protein on immature DCs [55,56]. It was developed from ZVex, a dendritic cell-targeting lentiviral vector platform that selectively targets immature DCs through DC-SIGN via an envelope derived from the alpha virus, Sindbus [57]. Once LV305 gains access and is processed by DCs, NY-ESO-1 peptides are presented on the cell surface by MHC molecules where they interact with T cells [56]. LV305 was tested as a single agent in a Phase 1 clinical trial that included patients with NY-ESO-1 sarcoma, melanoma, ovarian cancer, and non-small cell lung cancer [55]. Study participants received escalating doses via 3–4 intradermal injections every 3 weeks. No severe adverse events (SAEs) were reported. Only one patient achieved a partial response, but 54% of sarcoma patients demonstrated stable disease and more than 80% of patients were alive one year after study entry. The one partial response was a 44-year-old woman with heavily pre-treated synovial sarcoma that was progressive at the time of study entry [58]. That patient met criteria for response at 8 weeks (24.7% reduction) and attained her best response at 24 months (84.8% reduction), which persisted at 3 years. Interestingly, that patient did have evidence of an immune response to NY-ESO-1 pre-treatment, as measured by CD8+ cells stained with NY-ESO-1, which was enhanced post treatment, as well as increased TCR sequences in TILs and increased TCR clonality post treatment. She also had high titers of NY-ESO-1 antibodies, but without significant difference pre vs. post LV305 therapy. Overall, her course is consistent with the theory that LV305 vaccine treatment amplified T cell immunity to NY-ESO-1, which resulted in a

significant and sustained tumor response. A succeeding phase 1 trial evaluated the CMB305 regimen, which adds a G305, a second protein/peptide vaccine to "boost" LV305 treatment [56]. The G305 consists of a full-length NY-ESO-1 and glycopyranosyl lipid A (GLA), an agonist for toll-like receptor 4 (TLR4), which is found on many immune cells. Patients on this regimen received LV305 dosing ("priming") on days 1, 21, 49, and 77 and G305 on day 35, then every 4 weeks for 3 doses, then every 8 weeks for up to 1 year. 49 patients with aggressive, recurrent/refractory disease were enrolled, including 25 sarcoma patients (14 synovial sarcoma). Median progression free survival was 4.7 months, not significantly different from LV305 alone, but overall survival at 18 months was quite favorable at 76%. Anti-NY-ESO-1 T cells and antibodies as well as antigen spreading (development of immune responses to other antigens) were measured in a comparison of 64 pooled recurrent patients of various tumor types (all NY-ESO-1+) who received the LV305 vaccine vs. the CMB305 regimen [59]. CMB305 was superior in all three categories. A randomized phase 3 trial to evaluate CMB305 as first line systemic therapy in metastatic or locally advanced SS has been haulted due to slow accrual in the setting of a trial which would take years to identify an improvement in OS, the primary outcome measure. Like in adoptive therapy, checkpoint inhibition is a proposed strategy to enhance the immunogenicity and anti-tumor effects of vaccine therapy. Though SS and other sarcomas may not be particularly sensitive or susceptible to checkpoint inhibitors alone, the expression pattern of these proteins may be altered after successful vaccination, creating more vulnerability to combination therapy [58]. Intriguingly, the SS patient who achieved a significant and prolonged response to LV305 developed increased PD1 expression in NY-ESO-1 specific T cells post treatment [58]. A randomized, phase 2clinical trial of the PD-L1 inhibitor atezolizumab with or without CMB305 in adults with recurrent, metastatic or locally advanced NY-ESO-1+ sarcoma has recently completed accrual (NCT02609984). Unfortunately, logistical problems have made this agent difficult to test in the Phase 3 setting; further work analyzing combination treatments will be important for the design of new vaccine based strategies that increase response rates. While this particular vaccine does not appear to be moving forward in the near future, the general approach is promising and future studies will need to focus on using the right combination in the right patient population.

5. Conclusions

We anticipate that immunotherapy and NY-ESO-1 as a target antigen will continue to be the major focus of developmental therapeutics for SS upcoming clinical trials. Newer approaches will be more complex, combining checkpoint inhibition with adoptive therapies and tumor vaccines. Analysis of on-going trials in other solid tumors combining immunotherapies broadly across medical oncology will be informative.

Conflict of interest

Dr. Pollack receives research funding from Merck, EMD Serono, Incyte, Presage, Janssen, Oncosec and Juno. He receives honoraria from Seattle Genetics, Bayer, Tempus, Daiichi Sankyo and Blueprint Medicine.

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