Immunotherapy as a Future Treatment for Relapsed and Metastatic Primary Pulmonary Sarcomas

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Authors’ contributions

This work was carried out in collaboration between both authors. Authors VJ and AA contributed equally to the accumulation of background information and organization into the article. Authors VJ and AA contributed equally to the review and revision of the information included in this article.

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ABSTRACT

Primary pulmonary sarcomas (PPS) are aggressive tumors that are ideally treated with complete surgical resection, although seldom possible. Chemotherapy and radiotherapy have proven to be inadequate as second-line in the majority of cases, requiring investigation into novel approaches to treatment. Due to the high rate of recurrence and advanced disease progression, immunotherapy is a future treatment modality that must be investigated in order to provide better prognosis. Studies predominantly focus on other soft tissue malignancies such as osteosarcoma, and thus research pertaining to PPS is limited.

Keywords: Pulmonary sarcoma; immunotherapy; relapse; metastasis.

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1. INTRODUCTION

Primary pulmonary sarcomas (PPS) are exceedingly uncommon, [1,2] yet there is speculation as to an increase in incidence associated with radiation treatment for other malignancies [2]. Arising from the lung parenchyma, bronchi and pulmonary vasculature, [3] the three most common types include leiomyosarcoma, malignant fibrous histiocytoma and synovial sarcoma [4,5].

PPS often remains asymptomatic, but may present with the same symptoms as lung carcinoma, [4,5] such as atelectasis, cough with expectoration and hemoptysis [6]. Diagnosis occurs when a sarcoma of an extrathoracic location is ruled out, as metastatic sarcoma to the lungs is much more common [7]. Computed tomography imaging is crucial as a diagnostic modality in identifying these thoracic lesions [1,8], which may include areas of stippled calcification and focal areas of necrosis [3,9]. Immunohistochemistry for each sarcoma differs and overall structure is important in determination of grade and stage [3]. The ideal management of disease is through curative surgical resection, [7] yet is seldom possible due to unresectable disease or involvement of critical structures [8]. In such cases, radiation and chemotherapy are used as next-line therapy, most often producing suboptimal results [2,3,7]. It has been documented that second-line therapies provide a median survival of only 10-15 months [10]. In synovial sarcoma, the translocation of t(X;18)(p11.2;q11.2) results in the fusion products of either SYT-SSX1 or SYT-SSX2, in which the SYT-SSX1 variant is associated with a higher mitotic rate, worse prognosis and increased chance of relapse [2,3]. As this disease group is aggressive, and optimal therapies are either not possible or inadequate, novel approaches are necessary to improve prognosis.

Such an approach in recent focus is immunotherapy. The basis for this method stems from the observation made by Coley in 1891, when a recurrence of small cell sarcoma receded following erysipelas infection and further local injections of pathogen [11,12]. This was thought to occur as the malignant cells were caught in crossfire between the immune system and pathogen, subject to the antitumor effects elicited in the process [11]. This is supported by the fact that sarcomas occur three times more often in immunosuppressed patients when compared to the general population [13,14] as well as the stability of present disease with the use of non-specific immunomodulators [15,16].

High-dose treatment with interleukin (IL)-2 has been investigated in numerous studies [15]. The mechanism is based on stimulation of T and natural killer (NK) cells, and has been FDA-approved for treatment of metastatic melanoma and renal cell carcinoma [16]. More recent studies of metastatic solid tumors of various etiologies have demonstrated an unlikely relapse after a follow-up period of 30 months without disease, [16] although older reports of response rate vary from 0% to 33% [17,18]. IL-2 therapy is not often employed for sarcomas, and is associated with high toxicity [16] but shows potential as an adjunct in the arsenal of therapy for PPS.

Interferon gamma has been investigated in the past as a potential immunotherapy for malignancy by potentiating immune cells and increasing presentation of antigens to T lymphocytes [15]. This antitumor activity is demonstrated by a report in which more than half of patients with osteosarcoma receiving interferon therapy had partial responses [19]. Similarly, a study in 1989 by Edmonson et al. [20] demonstrated a 15% response rate using interferon for patients with metastatic bone sarcomas. In 2003, Roozendaal and colleagues [21] described a case of primary sarcoma in the calf with pulmonary metastasis refractory to treatment with chemotherapy. High-dose chemotherapy followed by peripheral stem cell transplantation was considered too toxic, thus the patient was initiated on interferon therapy. After six months the patient showed a significant partial response. However, these interferon studies predominantly focus on osteosarcoma, [16] and more investigation pertaining to the sarcoma subtypes of pulmonary origin are needed.

Another immunostimulatory therapy is liposomal-muramyl tripeptide phosphatidyl-ethanolamine (L-MTP), which is a synthetic analog of the bacterial cell wall [15]. In vitro studies have shown that L-MTP increases tumor cell killing by mononuclear cells, quantified by measurement of tumor necrosis factor (TNF)-alpha and IL-6 as immunomodulatory markers [16]. Furthermore, L-MTP in laboratory models had shown a reduction in the metastatic tumor burden, demonstrating a possible approach in aggressive and advanced malignancies as discussed [22]. Unfortunately,
this approach predominantly focused on osteosarcoma, yet has potential for other soft tissue malignancies such as PPS [23]. L-MTP may function similarly to IL-2 and interferon as a non-specific immunomodulator in cancer treatment.

An interesting therapy in development is vaccination for sarcomas. Vaccines targeting gangliosides GD2, GD3 and GM2 in patients with solitary metastases excised in combination with GM-CSF or IL-2 have the potential to stimulate the immune response to lysate sarcoma cells [16,24]. Furthermore, it has been observed that this therapy has no major toxicities, [24] an important advantage over chemo-radiation. A phase II trial using bivalent vaccination with GD2 and GD3 demonstrated a positive serologic response when compared to control groups, in patients that are surgically disease-free, receiving adjuvant therapy and are still being followed-up for survival and presence of recurrence (NCT01141491) [16,25,26]. Although studies have focused on neuroblastoma and other sarcomas, vaccination is of great interest for PPS as it highly expresses GD2 and GD3 [15]. More specifically targeted toward synovial sarcomas, a vaccine has been developed using HLA-A24-optimized SYT-SSX peptide [16,27]. Bloom et al. [27] completed a trial determining that this vaccine could be safely administered to synovial sarcoma patients, resulting in significant stabilization of aggressive disease. Stability was documented with a two-fold increase in cytotoxic T-lymphocytes in the group receiving the vaccination and lack of progression in serial computed tomography scans [27]. Vaccination seems to be a developing future direction of treatment for aggressive sarcomatous disease.

Cancer testis antigens are proteins that are not expressed in somatic cells and are typically found in association with sarcoma tumor cells and germline tissues [15]. More specifically, 80% of synovial sarcomas express NY-ESO, [15,28] 100% of synovial sarcomas express PRAME [29] and 14% of non-uterine leiomyosarcomas express MAGE-A3 [30]. These antigens are recognized by cytotoxic T-lymphocytes [15] and are thus possible targets in sarcoma treatment. Adoptive transfer of autologous T cells expressing one of the aforementioned peptides is a promising approach, and D’Angelo et al. [31] have recently reported a 50% response rate with engineered T cell persistence.

Estrogen receptors are expressed in soft tissue sarcomas with a rate of 37.5% to 43.3%, as indicated by one study, with especially elevated levels in malignant fibrous histiocytoma [32]. This presents an interesting approach for immunotherapy of PPS by molecular profiling of receptor expression via in situ hybridization [32] and treatment with agents such as tamoxifen and toremifene [33]. This vector of immune therapy both prevents tumor growth and sensitizes tumor cells to cytotoxic immune lysis [33]. Cure rates for mastocytoma in a study by Baral et al. [34] had been up to 75% when IL-2-activated NK cells and cytotoxic T cells were administered in conjunction with anti-estrogen agents. Such agents could be used in combination with other treatments when indicated by a positive receptor profile, as in malignant fibrous histiocytoma.

Programmed death receptor (PD-1) present on T cells is a target for cancer cells to dampen an immune response through expression of PD-1 ligands PD-L1 and PD-L2 [35]. Thus, this immune escape mechanism expressed in 19% to 92% of malignant cells is associated with a poor prognosis.[36] PD-L1 ligand was associated with deep seated sarcoma, distant metastases, high histological grade and tumor necrosis in one study, [35] all of which occur frequently with PPS histologies [2]. Targeting PD-1 with inhibitors is a potential mechanism to prevent immune suppression by these advanced sarcomas. A closed phase II trial is underway investigating the efficacy of pembrolizumab as a PD-1-antibody inhibitor in advanced soft tissue sarcomas (NCT02301039) [37]. Another target for immune checkpoint inhibitors is cytotoxic T-lymphocyte-associated protein (CTLA4), a T cell surface receptor that when engaged transmits an inhibitory signal to T cells [38]. Ipilimumab is an antibody to CTLA4 that had been investigated in the past as a potential agent for preventing immune evasion of synovial sarcomas, yet the results were not promising [39]. However, an ongoing phase II trial is investigating the new agent nivolumab with or without ipilimumab in the treatment of unresectable metastatic sarcoma (NCT02500797) [40]. Unfortunately, these studies focus on Ewing sarcoma and osteosarcoma without discussion pertaining to other sarcomatous etiologies.

2. CONCLUSION

Mainstay surgical resection is not always possible, and second-line therapies are often suboptimal. Thus, it may in the future be
plausible to utilize multiple immunotherapies in parallel or in conjunction with second-line radiation/chemotherapy to increase the odds of disease cure. At the present time, no guidelines or detailed information are available for optimization; however, specific approaches will need to be developed as studies demonstrate which prove effective. Investigation into this modality of intervention is necessary as a rise in pulmonary sarcomas may have a delayed association with the use of radiotherapy for other thoracic and chest wall malignancies.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


