Commentary

Manuscript Title

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

Vasa Jevremovic[1], Alex Agelidis[2]

1. American Northwest University, Travnik, Bosnia & Herzegovina
2. University of Illinois at Chicago, Chicago IL, United States

Abstract

Primary pulmonary sarcomas (PPS) are aggressive tumors that are ideally treated with complete surgical resection, yet this approach is seldom possible due to disease state. Chemotherapy and radiotherapy have proven to be inadequate as second-line in the majority of cases. Due to the high rate of recurrence and advanced disease progression, novel approaches such as those presented by immunotherapy must be investigated 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*

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* completed a trial determining that this vaccine could be safely administered to synovial sarcoma patients, resulting in significant stabilization of aggressive disease.[27] 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* have recently reported a 50% response rate with engineered T cell persistence.[31]

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 histiocytomas.[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 toremifen.[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.

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.

References

1. Aribas OK, Gormus N. (2001) Obstructing endobronchial malignant fibrous histiocytoma. *European Journal of Cardio-thoracic Surgery* 19:716-718
2. Etienne-Mastroianni B, Falchero L, Chalabreysse L, *et al*. (2002) Primary sarcomas of the lung. A clinicopathologic study of 12 cases. *Lung Cancer* 38:283-289
3. Weiss SW, Goldblum JR. Enzinger's and Weiss's Soft Tissue Tumors, 4th ed. St Louis: Mosby, 2001. pp 535-566, 727-746
4. Kasturi S, Rendla SB, Vemula S, Raju P S. (2014) Primary pulmonary synovial sarcoma: a rare case report. *Int J Res Med Sci* 2(4):1729-1731
5. Keel SB, Bacha E, Mark EJ, Nielsen GP, Rosenberg AE. (1999) Primary pulmonary sarcoma: a clinicopathologic study of 26 cases. *Mod Pathol* 12(12):1124-1131
6. Nascimento AG, Unni KK, Bernatz PE. (1982) Sarcomas of the lung. *Mayo Clinic Proc* 57:335-359
7. Goncalves MJ, Mendes MM, Joao F, Lopes JM, Honavar M. (2011) Primary pleomorphic sarcoma of lung – 11 year survival. *Rev Port Pneumol* 17(1):44-47
8. Falkenstern-Ge RF, Kimmich M, Grabner A, Horn A, Friedel G, Ott G, Kohlhaufl M. (2014) Primary pulmonary synovial sarcoma: a rare primary pulmonary tumor. *Lung* 192(1):211-214
9. Shirai T, Tsuchida S, Terauchi R, Mizoshiri N, Konishi E, Tomita Y, Shimada J, Fujiwara H, Kubo T. (2014) Primary pulmonary synovial sarcoma requiring differentiation from pulmonary metastasis of tibial adamantinoma: a case report. *BMC Res Notes* 7:736
10. Van Glabbeke M, Van Oosterom AT, Oosterhuis JW, *et al*. (1999) Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline- containing first-line regimens—a European organization for research and treatment of cancer soft tissue and bone sarcoma group study. *Journal of Clinical Oncology* 17(1):150-157
11. Coley WB. (1891) II. Contribution to the knowledge of sarcoma. *Annals of Surgery* 14:199-220
12. Wiemann B, Starnes CO. (1994) Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. *Pharmacology and Therapeutics* 64(3):529-564
13. Gatti RA, Good RA. (1971) Occurrence of malignancy in immunodeficiency disease. A literature review. *Cancer* 28(1):89-98
14. Penn I. (1995) Sarcomas in organ allograft recipients. *Transplantation* 60(12):1485-1491
15. D'Angelo SPD, Tap WD, Schwartz GK, Carvajal RD. (2014) Sarcoma Immunotherapy: Past Approaches and Future Directions. *Sarcoma* Article ID 391967, 13 pages. http://dx.doi.org/10.1155/2014/391967
16. Pollack SM, Logers ET, Rodler ET, Yee C, Jones RL. (2011) Immune-Based Therapies for Sarcoma. *Sarcoma* Article ID 438940, 7 pages. doi:10.1155/2011/438940
17. Rosenberg SA, Lotze MT, Yang JC, *et al*. (1989) Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Annals of Surgery* 210(4);474-485
18. Schwinger W, Klass V, Benesch M, *et al*. (2005) Feasibility of high-dose interleukin-2 in heavily pretreated pediatric cancer patients. *Annals of Oncology* 16(7):1199-1206
19. Ito H, Murakami K, Yanagawa T. (1980) Effect of human leukocyte interferon on the metastatic lung tumor of osteosarcoma: case reports. *Cancer* 46(7):1562-1565
20. Edmonson JH, Long HJ, Frytak S, Smithson WA, Itri LM. (1987) Phase II study of recombinant alfa-2a interferon in patients with advanced bone sarcomas. *Cancer Treatment Reports* 71(7-8):747-748

21. Roozendaal KJ, de Valk B, ten Velden TAA, van der Woude HJ, Kroon BBR. (2003) Alveolar soft-part sarcoma responding to interferon alpha-2b. *British Journal of Cancer* 89:243-245
22. Zhu L, McManus MM, Hughes DPM. (2013) Understanding the biology of bone sarcoma from early initiating events through late events in metastasis and disease progression. *Front Oncol* 3:230
23. Uehara T, Fujiwara T, Takeda K, Kunisada T, Ozaki T, Udono H. (2015) Immunotherapy for Bone and Soft Tissue Sarcomas. *BioMed Research International* Article ID 820813, 11 pages. http://dx.doi.org/10.1155/2015/820813
24. Kushner BH, Cheung IY, Modak S, Kramer K, Ragupathi G, Cheung NV. (2014) Phase I Trial of Bivalent Gangliosides Vaccine in Combination with β-Glucan for High-Risk Neuroblastoma in Second or Later Remission. *Clin Cancer Res* 20(5):1375-1382
25. Carvajal RD, Agulnik M, Ryan CW, Milhem MM, George S, *et al*. (2014) Trivalent ganglioside vaccine and immunologic adjuvant versus adjuvant alone in metastatic sarcoma patients rendered disease-free by surgery: A randomized phase 2 trial. *J Clin Oncol* 32:5s, (suppl; abstr 10520)
26. Slovin SF, Keding SJ, Ragupathi G. (2005) Special Feature: Glycobiology Of Xenotransplantation And Cancer Part I. *Immunology and Cell Biology* 83:418-428
27. Bloom JE, McNeel DG, Olson BM. (2012) Vaccination using peptides spanning the SYT-SSX tumor-specific translocation. *Expert Rev Vaccines* 11(12):1401-1404
28. Jungbluth AA, Chen YT, Stockert F, *et al*. (2001) Immunohistochemical analysis of NY-ESO-1 antigen expression in normal and malignant human tissues. *International Journal of Cancer* 92(6):856-860
29. Skubitz KM, Pambuccian S, Carlos JC, Skubitz APN. (2006) Identification of heterogeneity among soft tissue sarcomas by gene expression profiles from different tumors. *Journal of Translational Medicine* 6:article 23
30. Ayyoub M, Taub RN, Keohan M-L, *et al*. (2004) The frequent expression of cancer/testis antigens provides opportunities for immunotherapeutic targeting of sarcoma. *Cancer Immunity* (4):article 7
31. D'Angelo S, Merchant M, Melchiori L, Zhang H, Pandite L, Holdich T, Binder-Scholl G, *et al*. (2015) Optimizing engineered TCR T cell therapy for synovial sarcoma. *Journal of ImmunoTherapy of Cancer* 3:P159
32. Li XQ, Hisaoka M, Hashimoto H. Expression of estrogen receptors alpha and beta in soft tissue sarcomas: Immunohistochemical and molecular analysis. *Pathol Int*. 2003;53(10):671-679
33. Berczi I. Immunotherapy of Cancer-A Historical Note. *Journal of Cancer Therapy*. 2014;5:1186-1189
34. Baral E, Nagy E, Kangas L, Berczi I. Combination immunotherapy of the P815 murine mastocytoma with killer cells, IL-2 and anti-estrogens. *Anticancer Res*. 1997;17:3653-3658
35. Kim JR, Moon YJ, Kwon KS, Bae JS, Wagle S, Kim KM, Park HS, Lee H, Moon WS, Chung MJ, Jang KY. Tumor Infiltrating PD1-Positive Lymphocytes and the Expression of PD-L1 Predict Poor Prognosis of Soft Tissue Sarcomas. *PLoS One*. 2013;8(12);e82870
36. Sznol M, Chen L. Antagonist Antibodies to PD-1 and B7-H1 (PD-L1) in the Treatment of Advanced Human Cancer. *Clin Cancer Res*. 2013;19:1021-1034
37. https://clinicaltrials.gov/ct2/show/NCT02301039 Accessed on May 18, 2016.
38. Callahan MK, Wolchok JD. At the Bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy. *J Leukoc Bio*. 2013;94(1):41-53
39. Maki RG, Jungbluth AA, Gnjatic S, Schwartz GK, D'Adamo DR, Keohan ML, Wagner MJ, Scheu K, Chiu R, Ritter E, Kachel J, Lowy I, Old LJ, Ritter G. A Pilot Study of Anti-CTLA4 Antibody Ipilimumab in Patients with Synovial Sarcoma. *Sarcoma*. 2013;Article ID 168145, 8 pages
40. https://clinicaltrials.gov/ct2/show/NCT02500797 Accessed May 18, 2016.
41.