Immunotherapy for Resected Pulmonary Metastases

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KEYWORDS

• TIL • IL-2 • Interferon • Anti-PD-1 • Anti-PD-L1 • Cancer vaccine

KEY POINTS

- It is hypothesized that adjuvant immunotherapy may reduce the risk of recurrence of malignancies following resection of lung metastases.
- Adjuvant immunotherapy tested in melanoma and renal cell carcinoma includes tumor-infiltrating lymphocytes; cancer vaccines; cytokines, such as interleukin 2 and interferon; and checkpoint blockade molecules.
- Adjuvant immunotherapy tested in sarcomas have included interferon, liposomal muramyl-tripeptide-phosphatidylethanolamine, chimeric antigen receptor T cells, and cancer vaccines.
- Adjuvant immunotherapies tested in colorectal cancer have included tumor cell and dendritic cell–based vaccines.

BACKGROUND ON IMMUNE SYSTEM AND IMMUNOTHERAPY/IMMUNITY IN THE LUNG

The high rate of recurrence after metastasectomy of most malignancies demonstrates that controlling micrometastatic disease remains a challenge. Although there has been considerable interest in applying chemotherapy and targeted therapies to prevent recurrence, immunotherapy has appeal, as by its very nature the immune system has both innate and adaptive elements that could provide long-term control of tumors, prevention of new tumors, and, potentially, elimination of the more aggressive clones, all possible with limited cycles of therapy. Furthermore, it is clear from most animal models of immunotherapy that immune effectors are most effective against the smallest volumes of disease, such that adjuvant therapy may have the greatest potential to demonstrate efficacy of immunotherapy.

Immunotherapy takes advantage of or interacts with the processes that lead to activation of immune responses naturally.[1] Tumor-specific immune responses depend on the uptake of tumor proteins, peptides, and genetic material (antigens) released during cell death by professional antigen-presenting cells (dendritic cells), which process and present the tumor antigens to T cells along with costimulatory molecules, which leads to T-cell activation and indirectly B-cell activation.

It is well established that T cells and antibodies that recognize tumors (T cells through T-cell receptor [TCR] recognition of their cognate peptide presented within major histocompatibility complex [MHC] class I or II molecules on the tumor surface and antibodies by binding to 3-dimensional structures recognized by their complementarity determining regions) are present in the tumor-bearing host and can have antitumor activity. T-cell activation can also be countered by upregulated expression of inhibitory molecules (eg, CTLA4).[2] Activated T cells traffic to and infiltrate the tumor. Those that are not suppressed by regulatory T cells and

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myeloid-derived suppressor cells and their cytokines have the opportunity to bind to tumor cells expressing their cognate antigen and set off a cascade of events culminating in tumor cell death; however, some T cells that express the activation marker programmed death-1 (PD-1)[3] are suppressed by tumor-expressed PD ligand-1 (PD-L1). T-cell destruction of tumor releases antigens that can begin the cycle again if they are taken up by dendritic cells. Therefore, immunotherapies may be applied at all key steps in the immunity cycle, the initial phase of antigen delivery to dendritic cells (vaccines), T-cell activation (cytokines), trafficking of T cells to tumor (chemokines), and then T-cell attack on tumor cells recognized by the TCR (tumor-infiltrating lymphocytes [TILs] and chimeric antigen-receptor T cells [CAR-Ts]), and preservation of T-cell functionality (anti-PD-1 and anti-PD-L1 antibodies). Because metastasectomy provides fresh tumor tissue, it is particularly suited to strategies that use tumor-derived components as part of the immunotherapy strategy. For example, TILs may be retrieved from disaggregated tissue and cultured in vitro before re-administration as adoptive immunotherapy. Although TILs may be functionally suppressed in the tumor milieu, when cultured ex vivo in interleukin 2 (IL-2), their functionality as demonstrated by expression of TCR zeta and epsilon chains, p56, FAS, and FAS-ligand is increased. Other tumor constituents, including the malignant cells themselves and peptide, protein, and mRNA derivatives, may be used as components in cancer vaccines.

Although the lungs have a different immune milieu by virtue of the exposure to a panoply of air-borne allergens compared with the bowel or liver that are exposed to orally administered antigens or the skin that is exposed to contact immunogens and the different microbiome, there are limited data on whether considerations for immunotherapy for resected pulmonary metastases should be different than that of immunotherapy for resected liver metastases, for example. Therefore, this review attempts to focus on issues relevant for pulmonary metastasectomy but also discusses immunotherapy for other sights of metastases where relevant. What may differ is the immune response, in particular the T-cell infiltration into tumor, for different malignancies. For example, Rosenberg's group at the National Cancer Institute observed that fewer CD3+ T cells were found to infiltrate gastrointestinal (GI) cancer compared with melanoma metastases (to liver and lungs) and very few TILs from GI cancer metastases were tumor reactive.[4] Therefore, the author discusses immunotherapy considerations for different tumors separately.

MELANOMA

It is well established that the immune system responds to melanoma and it is in melanoma that many of the established tumor antigens were first identified and new discoveries on targeting tumor antigens are being made.[5] Higher total and CD8+ T-cell frequency in melanoma metastases is associated with improved overall survival (OS),[6] and numerous immunologic approaches have demonstrated antitumor activity for unresectable metastatic disease.[7] Immunotherapy with interferon-α (IFN-α) and its pegylated form[8] have long been a standard adjuvant therapy based on the recurrence-free survival (RFS) and OS benefit in resected stage III melanoma. IFNs have direct antitumor activity and are involved in activation of T and B cells, macrophages, and natural killer (NK) cells. More recently, the anti-CTLA4 antibody ipilimumab improved recurrence-free survival compared with placebo in resected stage III melanoma.[9] Tested in a randomized study following resection of stage IIIB/IIIC/IV or mucosal melanoma, recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) showed an improvement in disease-free survival (DFS) and a trend toward improved OS in the subgroup of patients with stage IV disease compared with placebo.[10] These data support the hypothesis that immunotherapy could have a role in resected metastatic melanoma, including pulmonary metastasectomies.

Although none were focused on pulmonary metastases, several studies have evaluated patients who have undergone lymphadenectomy or metastasectomy to determine whether various immunotherapies might reduce recurrence. Single-arm studies of vaccines following metastasectomies, in aggregate, have demonstrated long-term survival, although the number with lung metastasectomies is small.[11] Unfortunately, a phase III randomized protocol comparing polyvalent-cultured melanoma cell vaccine (Canvaxin) combined with BCG versus BCG alone for patients with resected stage III/IV melanoma was closed early for futility due to failure to improve DFS and OS and a decrease in survival for vaccinated patients.[12] A single-arm study of patients with stage III/IV melanoma (the majority with macroscopic lymph node metastases but some with resected stage IV disease) who had no evidence of disease after surgery tested dendritic cells (DC) electroporated with mRNA encoding a fusion protein between MAGE-A1, -A3, -C2; tyrosinase; MelanA/MART-1; or gp100 and an HLA class II–targeting sequence along with IFN-α-2b.[13] The median OS had not been reached; the 2-year and 4-year survival rates