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Surgical immune interventions for solid malignancies

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Abstract

BACKGROUND: The purpose of this study was to systematically review clinically translatable immunotherapeutic agents that are delivered regionally for solid malignancies.

DATA SOURCES: PubMed and ClinicalTrials.gov were searched for published and registered clinical trials, respectively. The search yielded 334 relevant publications, of which 116 articles were included for review after exclusion criteria were applied.

CONCLUSIONS: There has been an increase in the regional administration of cell-based and viral vector–based clinical trials over the last 5 years. Surgical interventions have been developed for intrapleural, intracranial, intraperitoneal, and intratumoral routes of access to enhance the local delivery of these therapies. Multimodality therapies that combine regional immunotherapy with other local and systemic therapies are demonstrating continued growth as the field of immunotherapy continues to expand.

Tumor immune microenvironment is prognostic in solid tumors

The tumor immune microenvironment is shaped by a complex interaction between immune cells, cytokines, and the tumor itself. This results in a "tug of war" between protumor and antitumor forces that sculpt the path of either tumor progression or regression. Antitumor immune factors comprised predominantly of tumor-infiltrating lymphocytes (TILs), such as CD4+ helper T lymphocytes, CD8+ cytotoxic T lymphocytes, and CD20+ B lymphocytes, that correlate with improved survival.[1] In contrast, protumor factors comprised forkhead box P3 (FoxP3) regulatory T lymphocytes, M2 tumor–associated macrophages, and myeloid-derived suppressor cells; these have been shown to promote immune tolerance and tumor growth. In a cohort of patients

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with colorectal cancer, Galon et al[2] further demonstrated that tumor progression is not only influenced by the type of immune cells present but also by immune cell density and location relative to the tumor core and invasive margin. The prognostic value of TILs, with regard to tumor aggressiveness and patient survival, has been demonstrated in several solid malignancies—non–small-cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), and colorectal, breast, ovarian, renal, and pancreatic cancers.[1,3–8]

Our group has investigated prognostic immune markers in patients with NSCLC and demonstrated that type, density, and location of prognostic immune markers differ, even within subtypes of cancer. We have shown that in lung adenocarcinoma high densities of stromal FoxP3+ regulatory T cells were associated with shorter recurrence-free probability (RFP; 5-year RFP, 80% vs 85%; 95% confidence interval [CI], 74% to 87%; $P = .043$), whereas those patients with concomitantly high quantities of stromal CD3+ T cells were found to be at a significantly lower risk of recurrence (5-year RFP, 77% vs 85%; 95% CI, 69% to 85%; $P = .004$).[9] In squamous cell carcinoma, a ratio of high CD10+ neutrophil infiltration to low CD20+ B-cell infiltration was associated with significantly shorter overall survival (5-year overall survival, 46% vs 66%; $P = .032$; hazard ratio, .58; 95% CI, .35 to .96).[10] The significance of the growing solid tumor immunology knowledge base is that the prognostic value of these findings can be additive or can even enhance the classic tumor–node–metastasis (TNM) staging system in predicting tumor recurrence and patient survival. Currently, there is an open multinational clinical trial that is investigating the prognostic significance of TILs in colorectal cancer, in conjunction with TNM staging, with the ultimate goal of including immune markers in the international solid tumor classification system (NCT02274753). These findings support our rationale to further investigate the tumor immune microenvironment and to develop immunotherapies that can modulate this dynamic interaction to tilt the balance in favor of tumor elimination.

Immunotherapeutic strategies for solid tumors

With the evolution of immunotherapy for solid tumors progressing in the arena of regional administration, we explore how surgical interventions are able to manifest a local route of delivery for enhancing efficacy of this treatment. Immunotherapeutic approaches to solid tumors result in a final common pathway of endogenous effector cell activation, which mediates antitumor immune response. Cytokine therapy, which uses cytokines, such as interleukin-2 (IL-2) or interferon-alpha, has demonstrated remarkable results in select solid tumors, most notably melanoma. Insights into the mechanism behind this efficacy have suggested that these cytokines stimulate endogenous effector cellular immune reactions that result in tumor control.[11] Monoclonal antibody therapy operates through several different mechanisms where resultant attachment to the target ligand may (1) induce an immune response locally by activating adaptive immune system cells; (2) inactivate an inhibitory pathway, such as PD-1 and/or PD-L1, thereby releasing the brake on effector T cells; or (3) deliver conjugated radioisotopes, cytotoxic drugs, or chemotherapeutic agents directly.[12] Viral-based immunotherapy functions as either a vector for delivery of vaccines or by selective replication within cancer cells.[13] Adoptive cell therapies initially began with harvesting TILs from surgical specimens and reinfusing those tumor-reactive T cells back into the patient.[14] The advent of genetic modification has allowed for more direct approaches to activate killer immune cells against cancer. T-cell specificity can be redirected by introduction of either a cloned T-cell receptor or a chimeric antigen receptor with expansion ex vivo and subsequent reinfusion to the patient.[15] Therefore, generation of tumor-targeted effector cells eliminates “middle man” limitations of having to first activate the innate immune system cells, as with cytokine, antibody, and viral-based therapies.

Challenges faced by the application of these strategies for solid tumors include heterogeneous antigen expression, anti-inflammatory immune microenvironments, and inadequate infiltration from the peripheral blood to the tumor site.[15–17] One practical approach to bypassing the barrier to solid tumor immune infiltration is regional or local delivery.[18] The aim of this article was to highlight the clinically translatable immunotherapeutic agents and modes of delivery that have been evaluated, in both published and currently ongoing clinical trials, to provide perspective on the enhancement of regional immunotherapies through surgical approaches.

Methods

Search strategy

We performed a literature search on PubMed using the restriction “Clinical Trial” for the following search terms: intrapleural, intracranial, intrathecal, intraperitoneal, intrahepatic, intraportal, and intratumoral cancer immunotherapy; regional cancer immunotherapy; and local delivery cancer immunotherapy. We searched on ClinicalTrials.gov using the following search terms: pleural immune, intrapleural immunotherapy, intrapleural cell, intracranial immune, intracranial immunotherapy, intracranial cell, intraperitoneal immune, peritoneal immunotherapy, intraperitoneal cell therapy, cancer intratumor immunotherapy, and intratumor immune.

Inclusion/exclusion criteria

All publications that reported on clinical trials for intrapleural, intracranial, intrathecal, intraperitoneal, intrahepatic, intraportal, and intratumoral delivery of immunotherapy were included. Publications were excluded if they did not involve investigation of an immunotherapeutic agent, if the