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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 manuscripts 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.

Keywords

Regional immunotherapy; Surgical immunotherapy; Adoptive cell therapy

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 are 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⁾ By contrast, protumor factors are comprised of forkheadbox P3 (FoxP3) regulatory T lymphocytes, M2 tumor-associated macrophages, and myeloid-derived suppressor cells; these have been shown to promote

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immune tolerance and tumor growth. In a cohort of patients with colorectal cancer, Galon et al. 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.(2) The prognostic value of TILs, with regards to tumor aggressiveness and patient survival, has been demonstrated in several solid malignancies—non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), 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% CI, 74–87%; $p = 0.043$), while 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, 69–85%; $p = 0.004$).⁽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 (OS; 5-year OS, 46% vs. 66%; $p = 0.032$; HR = 0.58; 95% CI = 0.35–0.96).⁽¹⁰⁾ The significance of the growing solid tumor immunology knowledgebase 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 utilizes cytokines such as interleukin-2 (IL-2) or interferon-alpha (IFN- α), 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 via 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/PD-L1, thereby releasing the brake on effector T cells; or 3) deliver conjugated radio-isotopes, 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 (TCR) or a chimeric antigen receptor (CAR) 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 manuscript is 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 via 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](https://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; 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 immunotherapy arm of the trial was not administered by locoregional delivery, or if the results were preclinical, preliminary, or reports of ongoing studies (Figure 1).

SURGICAL IMMUNE INTERVENTIONS

In search of potential immunotherapeutic strategies, many agents have been investigated over the past several decades (Table 1; see Supplemental Table 1 for complete list of references). The increase in regional administration of cell-based and viral vector-based clinical trials seen over the last 5 years (Figure 2) highlights the progress made and future promise in the development of regionally delivered immunotherapeutic agents. Herein, we discuss key trials and published results presented by the route of delivery.

Intrapleural delivery

Bacille Calmette Guérin (BCG) was among the first regional immunotherapeutic agents evaluated for treatment of patients with NSCLC. Earlier attempts at local intrapleural delivery were attempted with bacterial-based immunotherapies such as *Corynebacterium parvum*, *Mycobacterium vaccae*, and *Streptococcus pyogenes* (OK-432).^(19–22) These agents were delivered through tube thoracostomies or pleural catheters percutaneously inserted, and, less commonly, during thoracotomies for tumor resection. The initial optimism regarding the efficacy of these agents was short-lived when separate, yet similar observations demonstrated increased rates of recurrence in the BCG groups and no survival benefit in the bacterial groups.^(23, 24) Since then, promising results have been observed with both cytokine and adoptive cell therapies. In MPM, where average median survival only ranges from 9 to 12 months with treatment, Astoul et al. studied the efficacy of regional IL-2 administration in 22 patients with MPM; they achieved 1 complete response and 11 partial responses.⁽²⁵⁾ Of those patients that responded, median survival was prolonged significantly when compared with nonresponders (28 months vs. 8 months, $p < 0.01$). Despite its demonstrated antitumor efficacy, the limitation of this therapy is poor tolerance. This presented as grade 3 systemic toxicities, such as congestive heart failure, sepsis, and acute kidney injury. This leads us to a promising alternative—adoptive cell therapy.

The 12 ongoing clinical trials of regional intrapleural immunotherapy include patients with primary (MPM) and metastatic (malignant pleural effusions from NSCLC and others) malignancies. In a Phase I clinical trial at Memorial Sloan Kettering Cancer Center, we are currently investigating the safety of intrapleurally administered autologous T cells genetically engineered to target mesothelin, which is a cancer-cell surface antigen (NCT02414269). Additionally, an ongoing oncolytic vaccinia virus trial is investigating the safety of intrapleural administration of a genetically modified vaccinia virus for the treatment of malignant pleural effusions in patients with mesothelioma or metastatic disease (NCT01766739). Both trials are based on our convincing preclinical data that demonstrates that locoregional administration improves efficacy, not only regionally, but systemically as well.^(18, 26, 27)

Intracranial delivery

In patients with recurrent malignant gliomas, those with tumors with lymphocytic infiltration present on histology have had better prognoses, thus providing the rationale for immunotherapy.⁽²⁸⁾ Achieving antitumor efficacy has been difficult with systemic immunotherapies due to the impenetrability of the blood-brain barrier. The feasibility of local immunotherapy has been demonstrated in several clinical trials, most of which have focused on direct intracranial delivery of lymphokine-activated killer (LAK) cells with IL-2 via Ommaya reservoirs placed surgically at time of resection.^(29–32) Hayes et al. administered intracavitary LAK cells plus IL-2 via an indwelling catheter placed during surgical resection in 28 patients with recurrent primary malignant gliomas. They achieved long-term survival >2 years in 6 of 28 patients with minimal IL-2 related toxicities, such as transient fevers, headaches, and neurologic irritation.⁽²⁹⁾ With observed toxicities limited, as compared with their systemic counterparts, the approach of intracranial immunotherapy offers an additional option for treatment of patients with these refractory diseases.

Intraperitoneal delivery

The peritoneal cavity is an ideal route to increase the probability of directly exposing diffuse tumor burden to higher concentrations of an administered agent. Using our previously listed search terms, two-thirds of the published clinical trials we found have used this approach to treat advanced ovarian cancer, which is a disease predominantly confined to the peritoneal cavity.(33) The remaining one-third targeted peritoneal implants or malignant ascites from gastrointestinal malignancies, including gastric and colorectal cancers, as well as mesothelioma. There have been 14 clinical trials, ranging from Phases I to III, that have evaluated intraperitoneal radiolabeled monoclonal antibodies with various conjugates, including Yttrium-90 (^{90}Y), Iodine-131 (^{131}I), Rhenium-186 (^{186}Re), Lutetium-177 (^{177}Lu), and Astatine-211 (^{211}At).(34–44) The attached murine monoclonal antibodies (i.e., HFG1, NR-LU-10, OC125, CC49, B72.3) target various cancer-associated antigens. The intraperitoneal route of antibody administration allows for high local concentrations with relatively slow systemic absorption and toxicity.(45) In these studies, access to the peritoneum was via laparoscopy or percutaneous insertion of Tenckhoff catheters, and, less commonly, peritoneal dialysis catheters or abdominal ports. Several early studies have demonstrated antitumor efficacy and survival advantage in patients with minimal tumor burden; however, they were limited by hematologic toxicity that resulted from systemic absorption.(34, 39, 42) More recent trials have addressed this challenge by use of chelating agents, either directly conjugated or administered as pretreatment.(35, 36) Despite minimizing systemic toxicity and allowing for higher dose administration, this therapy continues to be limited by heterogeneous antigen expression as well as antibody penetration of solid tumors. As such, surgical resection prior to locoregional antibody administration may prove efficacious, not only in ovarian, but also in gastric cancer. A novel murine monoclonal antibody that targets the antigen epithelial cell adhesion molecule (EPCAM) in gastric cancer, catamuxumab, was recently approved in Europe for treatment of malignant ascites based on a significantly prolonged puncture-free survival (median, 46 vs. 11 days; $p < 0.0001$).(46) This trial and a subsequent trial have demonstrated reduction in the volume of malignant ascites and induction of innate immune responses.(47) Clinical trials are currently ongoing to combine surgical resection of advanced gastric cancer with subsequent intraperitoneal administration of catamuxumab.(48) Other agents that have been delivered intraperitoneally, including cytokines and effector immune cells, have yielded limited results with mild decreases in ascites volume or tumor markers in select patients.(49, 50)

Intratumoral delivery

Direct injection of malignant lesions was investigated in cutaneous malignancies such as melanoma and cutaneous lymphoma. Successes with systemic IL-2 immunotherapy for melanoma have prompted investigation of methods for targeting cytokines to malignant lesions while reducing systemic toxicity.(11, 51) Cytokine delivery via direct injection of single or mixed cytokines, cytokine cDNA, antibody-conjugated cytokines, or viral vector-mediated delivery have been tested in Phase I and II clinical trials.(11, 51–57) Of these, adenoviral-vector delivery of interferon-gamma has shown significant response rates, with local tumor regression in 8 out of 15 patients with cutaneous lymphomas.(56) Additionally, this trial demonstrated systemic responses in 4 out of 15 patients, which highlights systemic distribution despite a regional intratumoral injection. Intratumoral oncolytic viral therapies

have been evaluated in pancreatic and hepatocellular cancers with some increases in lymphocyte infiltration.(58, 59) Bacterial-based vaccines have also been evaluated for intratumoral injection into breast, head and neck, and gastric cancers.(60–64) The streptococcal-derived agent, OK-432, was injected successfully into the tumor preoperatively and reduced the rate of lymph node metastasis.(63) However, bacterial-based vaccines injected intratumorally have not yielded significant differences in overall outcome of solid tumors.(60–64) Intratumoral injection of cell-based therapies has been evaluated in esophageal cancer, hepatoma, and melanoma with limited results.(65–67) An evaluation of chimeric antigen receptor therapy directly injected into head and neck squamous cell tumors is currently ongoing.(68)

Selective catheterization of tumor-feeding vessels for delivery of immunotherapeutic agents is another method being evaluated in clinical trials. Isolated limb perfusion with melphalan was indicated for advanced extremity in-transit melanoma and combination therapies with immunotherapy have been investigated.(69, 70) Hepatic arterial infusions of cell-based and radiolabeled antibodies have been reported.(71–74) For example, autologous T-cell therapy via hepatic arterial infusion has demonstrated a decreased level of circulating tumor antigens.(75)

MULTIMODALITY IMMUNOTHERAPY

Investigations into single modalities have resulted in enhanced knowledge and armamentarium available for treatment of solid tumors. By combining regional immunotherapy with surgery, chemotherapy, radiation therapy, and even systemic immunotherapy, researchers and clinicians are constantly reshaping and refining the landscape of cancer treatment. Clinical evidence supporting joint administration of radiation therapy, which has been shown to elicit tumorspecific immune responses, with dual checkpoint blockade has demonstrated improved antitumor efficacy over single modality treatments in a cohort of patients with melanoma; it is also the subject of an ongoing Phase I clinical trial (NCT02659540).(76, 77) Additionally, there is an ongoing clinical trial evaluating preoperative cryotherapy for antigen epitope spreading versus anti-CTLA4 monoclonal antibody therapy followed by surgical resection (NCT01502592). These studies provide the rationale for continued investigation into optimal treatment regimens employing regional immunotherapy in combination with other local and systemic therapies for a multimodality approach to tumor eradication. Optimal timing and dosage for each therapy are the new frontiers.

As the multi-dimensional field of immunotherapy continues to expand with development of novel agents, routes of delivery, and combination therapies, new challenges will inevitably arise in the arena of clinical response monitoring. The difficulty lies in the ability to evaluate therapeutic efficacy objectively within existing clinical measurements by computerized tomography (CT) or positron emission tomography (PET) scans. New criteria, such as immunerelated response criteria (irRC), are being investigated for their clinical utility, alone or when incorporated into the existing TNM staging or World Health Organization (WHO) classification, in characterizing response patterns of solid tumors to immunotherapy systematically.(78)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart of Study Methodology

*Search terms consisted of “mode of delivery” combined with “immunotherapy,” “regional cancer immunotherapy, and local delivery cancer immunotherapy. Results were restricted by article type: clinical trial.

Locoregional Immune Interventions: Clinical Trials by Year

Figure 2.
Clinical trials registered with clinicaltrials.gov, shown by year and immunotherapeutic agent.

Table 1
Surgical Immune Interventions: Published Clinical Trial Results

Clinical trials with published results, depicted by route of administration

Class	#	Immunotherapeutic Agent	Malignancies	Phase
Intrapleural				
Vaccine	6	Bacillus Calmette-Guerin (BCG)	Non-small cell lung cancer	I–III
Cytokine therapy	5	Interleukin-2	Malignant pleural mesothelioma, malignant pleural effusion	I–II
Bacterial-based therapy	4	Streptococcus pyogenes (OK-432), Corynebacterium parvum, Nocardia rubra	Lung Cancer, malignant pleural effusion	II
Cell-based therapy	1	Autologous activated macrophages	Malignant pleural mesothelioma	II
Radiolabeled antibody therapy	1	I31-Iodine-labeled tumor necrosis therapy antibody	Lung cancer	I
Intracranial/Intrathecal				
Radiolabeled antibody therapy	7	I31-Iodine-labeled 3F8 monoclonal antibody (I31I-3F8), I31-Iodine-labeled anti-tenascin monoclonal antibody	CNS and leptomeningeal metastases, malignant glioma	I
Combination therapy	5	Lymphokine-activated killer cells with interleukin-2	Malignant glioma	I–II
Cytokine therapy	3	Tumor necrosis factor-alpha, recombinant interleukin-2	CNS tumors, Malignant glioma	I
Viral vector-mediated biologic therapy	1	Dendritic cells	Recurrent malignant glioma	I–II
Cell-based therapy	1	Mononuclear cells	Malignant glioma	I
Intraperitoneal				
Radiolabeled antibody therapy	14	90-Yttrium-labeled, I31-iodine-labeled, I77-Lutetium, and I86-rhenium-labeled monoclonal antibodies	Ovarian cancer, gastrointestinal tumors	I–III
Cell-based therapy	6	T lymphocytes, gamma delta T lymphocytes, peripheral blood mononuclear cells	Ovarian cancer, gastric cancer	I–II
Monoclonal antibody therapy	6	Bispecific monoclonal antibody (bs-MAb), catumaxumab, MOv18 monoclonal antibody	Ovarian cancer, gastric cancer, malignant ascites, peritoneal carcinomatosis	I–III
Cytokine therapy	5	Interferon-alpha, interferon-gamma, interleukin-2, granulocyte macrophage colony stimulating factor	Malignant ascites, peritoneal mesothelioma, gastric cancer, colorectal cancer	I–II
Combination therapy	3	Tumor-infiltrating lymphocytes with interleukin-2 and interferon-gamma; lymphokine-activated killer cells with interleukin-2; tumor-infiltrating lymphocytes with interleukin-2	Ovarian cancer	I
Intrahepatic/Intraportal				
Cytokine therapy	4	Interferon-gamma, interleukin-2	Hepatocellular carcinoma	I
Cell-based therapy	4	Autologous macrophages, activated leukocytes, dendritic cells	Metastatic liver tumors	I
Viral vector-mediated biologic therapy	2	Oncolytic vaccinia virus, BCG extract	Hepatocellular carcinoma	I
Radiolabeled antibody therapy	2	I31-Iodine-labeled anti-Hepama-1 and anti-HCC monoclonal antibodies	Hepatocellular carcinoma, metastatic colon cancer	I

Class	#	Immunotherapeutic Agent	Malignancies	Phase
Combination therapy	1	Lymphokine-activated killer cells with interleukin-2	Metastatic liver tumors	I
Intratumoral				
Cytokine therapy	10	Interleukin-2, interleukin-12, interferon-gamma, granulocyte macrophage colony stimulating factor, tumor necrosis factor, alpha-gal glycolipids	Melanoma, renal cell carcinoma, gastric cancer	I–II
Viral vector-mediated biologic therapy	10	Vaccinia virus, adenovirus	Melanoma, neuroblastoma, hepatocellular carcinoma	I
Bacterial-based therapy	5	Streptococcus pyogenes (OK-432), corynebacterium parvum	Gastric cancer, colorectal cancer, thyroid cancer, breast cancer, head and neck squamous cell carcinoma	II
Cell-based therapy	4	Tumor-infiltrating lymphocytes, dendritic cells, T-cell receptor modified T lymphocytes, chimeric-antigen receptor T lymphocytes, mononuclear cells	Melanoma, head and neck squamous cell carcinoma, renal cell carcinoma, hepatoma	I–II
Combination therapy	3	Leukocytes with interleukin-2, activated macrophages with streptococcus pyogenes (OK-432), adenovirus with tumor-infiltrating lymphocytes	Melanoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, glioblastoma	I
Vaccine	3	BCG, DNA-Hsp65	Metastatic cancer, melanoma, head and neck squamous cell carcinoma	I–II