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Editorial

EDITORIAL

Local Immunotherapy: A Way to Convert Tumors From "Cold" to "Hot"

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Most treatments for advanced malignancies, including immunotherapies, are administered systemically. The important question is whether we can achieve the same or better results with less toxicity by delivering treatment directly to the tumor or draining lymph nodes. In theory, local delivery should prevent high levels of the drug in systemic circulation, thus reducing toxicity. Furthermore, delivering higher concentrations of immunotherapeutic agents at the injection site should induce a more robust, systemic antitumor immune response against the most immunogenic neoantigens within the tumor (1). The goal of this approach is to eradicate the tumor at the injection site(s) and also to create a "danger signal" that induces a systemic $CD8^+$ tumor-infiltrating lymphocyte (TIL) response that targets cancer throughout the body, the process known as an "abscopal effect" (2).

In this issue of the Journal, Murthy et al. (3) review the literature on local (intratumoral and intranodal) immunotherapies alone or in combination with systemic therapies in preclinical and early-phase studies. The authors discuss the rationale and several possible targets for local immunotherapy agents such as anti-OX40 monoclonal antibody, various cytokines (IL-2, IL-12, TGF-ß antagonists, etc.), and oncolytic viruses. They conclude that, given advances in endoscopic and image-guided techniques, the combination of intratumoral and systemic immunotherapies is a promising and feasible therapeutic approach.

Intratumoral delivery of an immunotherapeutic agent is not new. In the 19th century, Coley used this approach to trigger an inflammatory response and tumor lysis (4). Since the 1970s, clinicians have treated nonmuscle-invasive bladder cancer with bacillus Calmette-Guerin (5) and have for several decades successfully treated superficial skin cancers with topical imiquimod (6). The US Food and Drug Administration recently approved local immunotherapy with the oncogenic virus talimogene laherparepvec (T-VEC) for advanced melanoma after a pivotal phase III study demonstrated a better durable response rate compared with GM-CSF (16.3% vs 2.1%, $P < .001$), along with a trend toward improved overall survival ($P = .051$) (7). Intratumoral injections have proven safe and feasible in patients with solid tumors such as hepatocellular carcinoma (8), non–small cell lung cancer (9), head and neck tumors (10), glioblastoma multiforme (11), and colorectal cancer (12), among others.

One of the goals of local immunotherapy is to overcome the inhibitory effects of the tumor microenvironment (TME) in order to enhance immunogenicity, generate TILs, and drive a systemic tumor-specific T cell response strong enough to kill cancer cells with minimal toxicities. The TME plays an important role in immune inhibition, immunosurveillance, and immunoediting (13). Besides cancer and mesenchymal cells, the TME contains a variety of immune cells, including myeloid-derived suppressor cells, regulatory T cells, tumor-associated macrophages, helper and effector cytotoxic T cells, dendritic cells, and several pro- and anti-inflammatory cytokines secreted by both cancer and immune cells (14). Preclinical and clinical studies have evaluated immunotherapeutic agents' ability to cause local inflammation, improve tumor recognition, and generate an immune response against a broad spectrum of antigens. Agents studied have included immunomodulatory antibodies (CD40, CD137, OX40, GITR), cytokines (IL-2, IL-12, GM-CSF), TLR agonists, STING agonists, cancer vaccines, and oncolytic viruses (2).

Our group reported results of a phase I study of an intraprostatic vaccine in locally recurrent or progressive prostate cancer (15). Patients ($n = 21$) were vaccinated subcutaneously with recombinant vaccinia (rV)-PSA-TRICOM on day 1, followed by intraprostatic boosts with recombinant fowlpox (rF)-PSA-TRICOM on days 29, 57, and 85. Three cohorts also received intraprostatic rF-GM-CSF injections. The treatment was safe and feasible, with no dose-limiting toxicities. Overall, 19 of 21 patients had either improved ($n = 9$) or stable ($n = 10$) PSA

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values. The statistically significant increase in $CD4^+$ ($P = 0.0002$) and $CD8^+$ ($P = .0002$) tumor infiltrates in post- vs pretreatment tumor biopsies indicated the ability of this approach to induce statistically significant intratumoral inflammation.

A drawback of current immunotherapies is that they are effective in only a minority of patients. In the future, the main challenge will be to generate T cell responses in patients with immunologically "cold" tumors. Preclinical and early clinical studies have suggested that intratumoral therapies (in situ vaccination or localized radiation), alone or in combination with systemic immunotherapy, are able to convert a "cold" tumor to a "hot" tumor, thereby increasing the potential for a response to immune checkpoint blockade (16). Several ongoing clinical trials are evaluating the combination of T-VEC with systemic ipilimumab (NCT01740297) or pembrolizumab (NCT02263508) in advanced melanoma. Early reports suggest that the combination of T-VEC and ipilimumab is more effective than either agent alone (17).

Localized immunotherapy has several advantages over systemic therapy: 1) agents can be "off-the-shelf," easily produced, and cost-effective; 2) it can potentially generate an immune response against a broader antigen repertoire; and 3) it allows the use of agents that could have increased toxicity if given systemically. This approach also has several limitations. Targeted lesions need to be above a certain size threshold and relatively accessible, which can be a problem if repeated treatment is necessary. Anatomical distance usually determines an injection site for local immunotherapy; however, injecting a primary tumor may result in better response due to mutations shared with metastases (18). Optimal injection volume and best delivery methods are still unknown, while bleeding or infection present associated risks.

Many preclinical and early clinical studies have shown that local immunotherapy is feasible and can induce an immune response and tumor cell death while avoiding systemic toxicities. However, larger randomized studies are needed to confirm the antitumor efficacy of in situ vaccination and its combination with systemic immunotherapies such as immune checkpoint inhibitors.

Note

The authors declare no conflicts of interest.

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