VIEWPOINT

EVOLVING ISSUES IN ONCOLOGY

Vaccines as an Integral Component of Cancer Immunotherapy

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Editorial

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It is important to distinguish vaccines designed to prevent cancer from those designed to treat cancer. The mode of action of the human papilloma virus (HPV) vaccine for the prevention of cervical and other HPV-associated malignancies is similar to that of vaccines for the prevention of infectious disease (ie, the induction of antibodies directed against essential components of the microbe). Even though there have been stunning successes in the area of preventive vaccines, the history of therapeutic cancer vaccines, which principally involve the development of cell-mediated immunity (ie, T cells) directed against tumor antigens, has been far more challenging. However, the renaissance of cancer immunotherapy has rendered therapeutic cancer vaccines as a potential integral component of treatment.

The successes seen in cancer immunotherapy have shown cancers to be considered in 2 groups: so-called hot tumors, which contain abundant antitumor T cells, and many of which respond to immunotherapy, and cold tumors, which are generally devoid of endogenous T cells. Cold tumors constitute the majority of human solid tumors and do not respond to checkpoint inhibitor monoclonal antibody (CIMA) therapy. Melanoma is the prototype hot tumor. The abundance of somatic mutations in melanoma cells leads to the expression of neoantigens that the patient's immune system recognizes as foreign, leading to the influx of T cells directed against those neoantigens. This is why subsets of patients with melanoma respond to IL-2 therapy with its ability to activate T cells. Although a small percentage of patients with melanoma develop spontaneous remission, it remains a paradox that the majority of patients with melanoma do not respond to IL-2 given the abundance of endogenous T cells in their tumors.

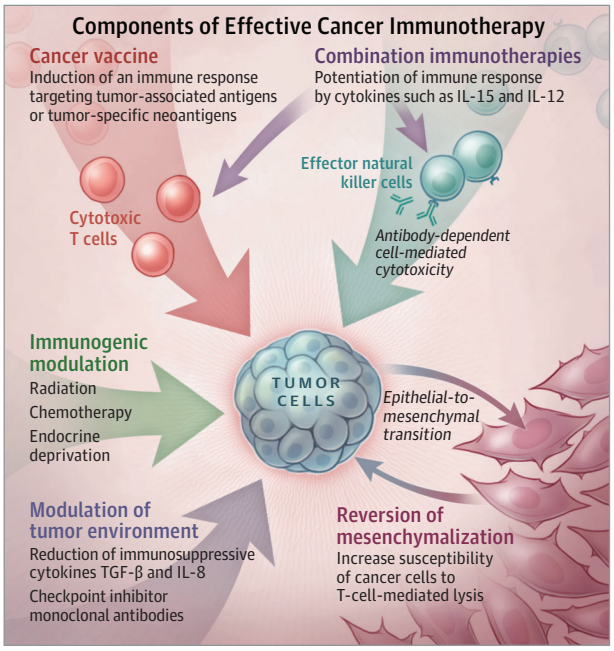
The renaissance in immuno-oncology came with the use of CIMAs. Preclinical studies revealed that the T cells present in most tumors were inactive and thus not able to lyse tumor cells; it was revealed that tumor cells were able to mount a defense mechanism by expressing checkpoint molecules such as PD-L1 on their surface to anergize T cells, an adaptive defense mechanism against the development of T-cell–mediated autoimmunity. The use of CIMAs has enabled an interference with this mechanism, allowing otherwise anergized T cells to lyse tumor cells expressing cognate antigens. However, the induction of autoimmune syndromes is one of the adverse effects of CIMAs and it is observed in approximately 10% to 15% of treated patients. The use of CIMAs as monotherapy or in combination therapy has led to clinical responses in approximately 10% to 60% of patients with melanoma,[1] but in only 10% to 20% of patients with solid tumors such as prostate, lung, breast, and colorectal.[2]

These developments provide insights into the expansion of cancer vaccine use. The vast majority of nonmelanoma solid tumors can be characterized as cold and do not respond to CIMA therapy. One potential therapeutic strategy would be to generate de novo T cells directed against tumor antigens to be used in combination with CIMAs. Several phase 1 and 2 clinical studies using cancer vaccines as monotherapy have shown promise. However, only 2 drugs tested in phase 3 trials met their primary end points: sipuleucel-T[3] (for the therapy of metastatic prostate cancer) and talimogene laherparepvec[4] (for metastatic melanoma). To further put this into historical perspective: (1) the phase 3 trials of cancer vaccines as monotherapy in cold tumors such as prostate and breast were initiated prior to the era of CIMAs, and (2) because more than 95% of agents entering oncology clinical testing do not get approved,[5] the less than half-dozen cancer vaccine monotherapy phase 3 trials that did not meet their primary end point should not render vaccines as a failed modality.

Evidence is emerging demonstrating synergy in the use of cancer vaccines plus CIMAs. Advances in basic immunology and translational immunotherapy are rapidly unravelling the complexity of the immune system and, consequently, agents and strategies are being developed that can be and are being used to increase the efficacy of therapeutic cancer vaccines. As such, the use of vaccines could be considered a necessary, albeit insufficient, component of an effective anticancer therapeutic regimen among patients with low T-cell count tumors.

Preclinical studies are revealing that the hallmark of an effective immuno-oncology strategy for cold tumors is the use of multiple immuno-oncological agents to target different components of the immune system (**Figure**). These include the (1) induction of an immune response to tumor-associated antigens, or tumor-specific neoantigens caused by immunogenic mutations, via vaccine administration; (2) potentiation of that immune response by type 1 cytokines such as IL-15 or IL-12 immunocytokine; (3) reduction of immunosuppressive entities in the tumor microenvironment with the use of CIMAs and agents to target immunosuppressive cytokines such as TGF-β and IL-8; and (4) use of agents to modify tumor cell phenotype to render otherwise resistant tumor cells more susceptible to T-cell–mediated lysis; preclinical and early clinical studies have shown that nonlethal doses of radiation also have this ability along with certain chemotherapeutic and small molecule–targeted agents.

Figure. Vaccines as an Integral Component of a Multifaceted Approach to Cancer Immunotherapy



Tumor-specific neoantigens are generally more immunogenic than tumor-associated antigens; however, algorithms for selecting which mutations are most immunogenic are imperfect and generating a patient-specific vaccine is time-consuming. In contrast, an off-the-shelf approach can generate effector cells that if properly facilitated can kill tumor cells and lead to a broadening of the immune response that could include tumor-specific neoantigens.

There is a spectrum of cancer vaccine platforms: recombinant vectors, peptides and proteins in adjuvants, and autologous dendritic cells either pulsed with peptide or transfected with tumor-derived nucleic acid. Preclinical studies have shown that each platform has the ability to present different epitopes of given tumor-associated antigens or tumor-specific neoantigens to the immune system and to activate different components of the host immune system. These studies also show the sequential use of 2 diverse vaccine platforms (vs only 1) is more effective in inducing antitumor immunity.

Subsets of human carcinoma tumor cells have been shown to exhibit stem-like characteristics and are resistant to standard-of-care therapies. This process to a stem-like phenotype has been shown to be due to an epithelial to mesenchymal transition or mesenchymalization, which is principally driven by transcription factors such as twist, snail, and brachyury. Vaccines directed against molecules driving this and other important tumor-promoting biological processes are now in clinical trials, including vaccines targeting brachyury,[6] *HER2*,[7] and oncogenes such as *MUC1-C*.[8]

Agents targeting TGF-β and IL-8 to reverse tumor mesenchymalization are also being used with vaccines to render tumor cells more susceptible to T-cell–mediated lysis.[9] Several CIMAs have now been designed with the ability to also mediate antibody-dependent cell-mediated cytotoxicity, thus engaging the patient's innate immune system to further enhance vaccine-induced adaptive immunity (Figure).[10] Precisely how and when cancer vaccines will be used in regimens of immuno-oncology involving multiple agents requires investigation. Due to the relatively low level of toxicity observed with the use of most immuno-oncological agents, adaptive design clinical trials are being initiated in which immuno-oncological agents are sequentially added when a safety signal is obtained.

The plethora of immune-mediating agents now available for clinical studies is designed to potentiate a vaccine-induced antitumor immune response, resulting in T cells directed against tumor-associated antigens in the tumor microenvironment. Cancer vaccine therapy is now situated to be an essential component for a successful antitumor response for so-called cold tumors that are not responsive to the use of single or combination CIMA therapy.

ARTICLE INFORMATION

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