REVIEW ARTICLE

Immuno-oncology and Its Opportunities for Interventional Radiologists: Immune Checkpoint Inhibition and Potential Synergies with Interventional Oncology Procedures

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ABSTRACT

Immunotherapy, specifically the use of immune checkpoint inhibitors, offers a new approach to fighting cancer. Although the results of treatment with immune checkpoint inhibition alone have been remarkable for certain cancers, these results are not universal. Preclinical and early clinical studies indicate the potential for synergistic effects when immune checkpoint inhibition is combined with immunogenic local therapies such as ablation and embolization. This review offers an overview of immunology as it relates to immune checkpoint inhibition and the possibilities for synergy when combined with interventional radiology treatments.

ABBREVIATIONS

APC = antigen-presenting cell, CTLA-4 = cytotoxic T-lymphocyte antigen-4, DC = dendritic cell, HCC = hepatocellular carcinoma, HIF-1α = hypoxia-inducible factor-1α, MDSC = myeloid-derived suppressor cell, PD-1 = programmed death-1, PDL = programmed death ligand, RF = radiofrequency, RT = radiation therapy

Immunotherapy has revolutionized cancer care in the past several years. An entirely new class of drugs, the immune checkpoint inhibitors, are being investigated for use in every type of cancer. The US Food and Drug Administration has already approved their use in the treatment of lymphoma, melanoma, non–small-cell lung cancer, renal-cell cancer, urothelial cancer, and head and neck squamous-cell cancer, with more approvals expected to come. In fact, to most oncologists, the term "IO" refers to immunooncology more often than anything related to interventional radiology. The immunologic mechanisms upon which these agents rely offer tremendous opportunities for interventional oncology. The present review provides a concise overview of the immunology relevant to immune checkpoint inhibitors and the opportunities that exist for interventional radiologists to lead the research and development of combination immunooncologic therapies.

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THE IMMUNE SYSTEM AND IMMUNE CHECKPOINT INHIBITION

The immune system comprises two components, the innate and the adaptive immune systems. The innate system provides a rapid inflammatory response to molecular patterns that indicate pathogen invasion or tissue damage. This inflammatory response initiates a series of downstream

mechanisms to eliminate the pathogen, initiate tissue repair, and trigger the adaptive immune response.

The adaptive immune response is more specific and relies on the function of B and T cells. Antigen-presenting cells (APCs), such as dendritic cells (DCs), link the innate immune response to the adaptive immune response. DCs continually sample antigens in their immediate environment, and, in the setting of an activated innate immune response, DCs migrate to local lymph nodes to present antigens to T cells. The environment in which the DC acquired the antigen, the mechanism through which the DC internalized the antigen, as well as a number of costimulatory and coinhibitory signals determine whether presentation of the antigen to a T cell will result in a stimulatory or inhibitory effect on the T cell (1,2).

Cell-mediated responses refer to immune responses that are performed by particular immune cells and occur independent of circulating antibodies. These are primarily carried out by T cells, which include helper, killer, and regulatory T cells. Cytotoxic $CD8^+$ T cells cause cell death, including that of virus-laden cells and tumor cells. The activity of cytotoxic T cells, however, is modulated by other immune cells, including regulatory T cells and myeloid-derived suppressor cells (MDSCs). Regulatory T cells are a key component of self-tolerance—the mechanisms that prevent one's immune system from attacking healthy cells—and exert immunosuppressive effects by down-regulating the induction and proliferation of cytotoxic T cells. MDSCs also have immunosuppressive activity, in part by expanding the population of regulatory T cells. Regulatory T cells and MDSCs play a role in suppressing the immune response against tumors, and the presence of regulatory T cells and MDSCs in a tumor microenvironment has been shown to correlate with poor outcomes (3–5). In hepatocellular carcinoma (HCC), for example, regulatory T cells are increased in the blood and within tumors, and the accumulation of regulatory T cells has been associated with HCC progression (6,7). MDSC concentration in HCC inversely correlates with recurrence-free survival and prognosis following tumor ablation (8), and depletion of regulatory T cells and MDSCs in HCC can cause immune reactivation against tumor antigens (5,9).

However, the role of these immunomodulatory cells in cancers is not universal. Whereas high levels of regulatory T cells have also been associated with a poor prognosis in various other cancers such as breast, pancreatic, ovarian, and renal-cell cancers, high levels of regulatory T cells correlate with better prognoses in follicular lymphoma and colorectal cancer (3).

The immune response against tumors relies on cytotoxic $CD8^+$ T cells, the activity of which is determined by a balance of costimulatory and coinhibitory signals. Interactions via the major histocompatibility complex receptors establish the specificity of an immune response to a particular antigen, but costimulatory/coinhibitory interactions that occur between secondary receptors and ligands on the T cell determine whether this immune response will be stimulated or inhibited (3). Costimulatory signals are critical for T cells to recognize and act against foreign antigens, but coinhibitory signals, which rely on interactions between immune checkpoint proteins, are necessary for T cells to recognize self antigens for self-tolerance (10).

The B7–CD28 interaction is currently one of the most clinically relevant costimulatory interactions. B7, which is expressed on APCs, binds with CD28 on the T cell at the time of antigen presentation and promotes activation of the T cell. Yet an immune checkpoint protein, cytotoxic T-lymphocyte antigen-4 (CTLA-4), is also expressed on T cells and competes for interaction with B7 on the APC. Tight binding between B7 and CTLA-4 will result in inhibition of the T cell (**Fig 1**) (11,12). Another clinically important immune checkpoint protein expressed on T cells that causes coinhibition, programmed death-1 (PD-1), interacts with its ligands, programmed death ligands (PD-Ls) 1 and 2, which are found not only on APCs, but also on other immune cells and tissues throughout the body, including tumor tissue (**Fig 2**) (13). Multiple immune checkpoint proteins may be expressed simultaneously, and the net effect on the function of T cells is determined by the sum of costimulatory and coinhibitory interactions (10,14).

T-cell exhaustion refers to the progressive loss of cytotoxic $CD8^+$ T-cell function and eventual T-cell death. Immune checkpoint proteins play a role in T-cell exhaustion as a physiologic inhibitory process to maintain self-tolerance as well as to modulate potentially harmful sustained immune responses. Chronic exposure to an antigen, including exposure to tumor-associated antigens, can result in T-cell exhaustion (10,14). Although exhausted T cells do have the ability to recognize new antigens, they are in a hyporesponsive state. Exhausted T cells express high rates of the coinhibitory receptors CTLA-4 and PD-1, and blocking these receptors can restimulate the exhausted T cells. For example, PD-1 inhibition can increase the number of T cell clones that recognize tumor antigens, and CTLA-4 inhibition increases the number of T cells in tumor tissue (14–16). However, even though PD-1 inhibition alone has been shown to restimulate exhausted T cells, T-cell exhaustion can also result from numerous synergistic coinhibitory signals (14,15). For example, overcoming T-cell exhaustion in the setting of chronic hepatitis C has been shown to require blockade of CTLA-4 and PD-1 rather than blockade of either immune checkpoint protein alone (17).

Immune checkpoint inhibitors that have received Food and Drug Administration approval are monoclonal antibodies against PD-1, PD-L1. or CTLA-4. PD-1 inhibitors include nivolumab and pembrolizumab, which have shown benefits in melanoma, head and neck cancer, non-small cell lung cancer, Hodgkin lymphoma, renal and bladder cancer. PD-L1 inhibitors include atezolizumab, avelumab, and durvalumab, which have been used in non–small-cell lung cancer, bladder cancer, and Merkel-cell cancer. Ipilimumab is a monoclonal antibody against CTLA-4 and has been approved for the treatment of melanoma. Tremelimumab is