White Paper

Cancer Immunotherapy: The Latest Breakthroughs

A Goodman & Gilman’s White Paper
Introduction

In the past 5 years, the ability to harness the power of the immune system in the treatment of cancer has brought about a paradigm shift whereby some of the most feared diseases, such as melanoma and lung cancer and even late-stage metastatic disease, can be eradicated. For some cancers, response rates are surprisingly high: 87% in Hodgkin lymphoma even in heavily pretreated patients\(^1\), and 50% in patients with metastatic melanoma treated with combinations of PD-1 and CTLA-4 immune checkpoint antibodies. Immune checkpoint inhibitors are currently approved for the treatment of bladder cancer, Hodgkin lymphoma, kidney cancer, lung cancer, and melanoma; more approvals are anticipated in the near future based on several hundred ongoing clinical trials.

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CANCER IMMUNOTHERAPY

T-cell responses are modulated by a balance between costimulatory signals, exemplified by CD28 ligation, and coinhibitory signals, such as those provided by CTLA-4 or PD1 ligation. Immune checkpoints refer to inhibitory (often negative-feedback) pathways that limit the amplitude and duration of an immune response. Under normal physiological conditions, immune checkpoints protect tissues from damage during an immune response and contribute to the maintenance of self-tolerance. In conditions of chronic viral infections and cancers, chronic antigen persistence results in the development of dysfunctional “exhausted” T cells. Exhausted T cells are actively suppressed by inhibitory signals that limit their effector functions and turn off their target cell-killing capacity. These inhibitory pathways resulting in T-cell exhaustion have been documented in mice, monkeys, and humans, highlighting their importance in modulating T-cell function.

Cancer cells express a variety of genetic and epigenetic alterations that distinguish them from their normal counterparts. These tumor-associated antigens can be recognized by the host immune system; antitumor T cells are generated, which then eliminate these transformed cells. However, tumors frequently develop immune resistance mechanisms that evade the host’s immune attack. One of these evasion strategies involves the manipulation of immune-inhibitory pathways or immune checkpoints. Tumors avoid being destroyed by actively stimulating these inhibitory receptors to turn off antitumor T cells. Figure 1 provides an overview of activating and inhibitory coreceptors and the drugs (monoclonal antibodies) that target them. In general, these antibodies work by releasing the brake on antitumor T cells and reinvigorating them to kill tumors. It is important to be aware that whereas some monoclonal antibodies block their respective target (PD1), others block the respective ligand (PD-L1). The therapeutic goal is to interfere with this inhibitory interaction that is actively suppressing T cells in the tumor microenvironment.

Figure 1:
Former nomenclature of therapeutic monoclonal antibodies. This older nomenclature, still in use by some workers, focused primarily on the source of the antibody (murine, human, chimeric, or humanized). Current nomenclature incorporates information on the target tissue as well. Fab, antigen-binding fragment; Fc, crystallizable fragment; CDR, complementarity-determining regions of the variable domains, also called hypervariable regions.
The two immune checkpoint receptors that have been the most extensively characterized in the context of cancer immunotherapy are CTLA-4 and PD1. These inhibitory molecules are highly expressed on antitumor T cells. When bound by their respective ligands (CD80/86 and PD-L1/PD-L2) on APCs or tumor cells, these inhibitory receptors dampen the T-cell response, albeit by different intracellular pathways. As antitumor T cells express PD1, tumor cells engage it through their expression of PD-L1. The tumor effectively inactivates the T cells and the tumor continues to grow2-3.

Immunotherapy to cancers holds great promise for treating patients with advanced disease, as evidenced by the success of clinical trials using this technology. Biologics to stimulate antitumor T cells have been rapidly approved by the FDA and have become the first line of treatment of cancers such as metastatic melanoma, non–small cell lung cancer, and renal cell carcinoma. In addition, anti-PD1, anti–PD-L1, and anti–CTLA-4 therapies are currently in clinical trials to assess their efficacy in head and neck cancers, breast cancer, small cell lung cancer, Hodgkin lymphoma, gastric cancer, hepatocellular carcinoma, bladder cancer, ovarian cancer, colon cancer, and Merkel cell carcinoma. It is important to note that only a small fraction of patients respond to checkpoint mono-therapy, and this frequency can increase when patients are given combination therapy, such as administering both anti-PD1 and anti–CTLA-4 antibodies. Furthermore, combination strategies that include checkpoint blockade paired with radiation or chemotherapy may further increase responsiveness in cancer patients.

PATIENT SAFETY

One consequence of checkpoint blockade is that autoreactive T cells are also unleashed after therapy. Patients can develop toxicities that include hepatic, pneumonitis, colitis, rash, vitiligo, and endocrine pathology. Greater immunotherapy efficacy will likely be achieved when drugs are developed to target other inhibitory pathways and are used in combination, but caution must be evaluated to ensure patient safety4.

CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

In addition to solid tumors, liquid tumors like CLL are also being targeted by immunotherapeutic approaches. Patient T cells are engineered to express chimeric antigen receptors (CARs) comprising antibody-binding domains connected to domains that activate T cells. In the case of CLL, CAR T cells recognize CD19 on B cells, and their chimeric receptor sustains T activation. CAR T cells are engineered from patient blood, expanded in vitro; then, millions are infused into the same patient. These cells then circulate in the patient and recognize all B cells expressing CD19 and destroy them. This cellular therapy has shown promise in patients with CLL with high durable objective responses5.
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