Immune checkpoint inhibitors
Physiology, clinical benefits and future challenges

John Hilton, MD, FRCPC, Medical Oncologist, Ottawa Hospital Cancer Centre

ABSTRACT

Immune checkpoint inhibitors have become standard of care for multiple tumour types. Two classes of agents have been approved for clinical use: CTLA-4 and PD-1/PD-L1. This article discusses the rationale behind why CTLA-4 and PD-1/PD-L1 inhibitors are beneficial for cancer therapy, their potential shortcomings, and why new agents and strategies are needed to broaden their therapeutic scope. 

Keywords: checkpoint inhibitors, immunotherapy, melanoma, NSCLC, immunoediting

The development of immune checkpoint inhibitors as an anticancer therapy represents one of the most exciting advances in cancer drug development in the past decade. Immune checkpoint inhibitors have become standard of care for multiple tumour types, such as metastatic melanoma and non-small cell lung cancer (NSCLC), and are currently being evaluated in a number of other cancer types, including head and neck cancer, and breast cancer. At present, the 2 classes of agents that have been approved for clinical use are inhibitors of either the cytotoxic T-cell lymphocyte-associated protein 4 (CTLA-4) or of the programmed death receptor 1 or its ligand (PD-1/PD-L1). Agents that target other aspect of the immune system are in development. This article will briefly discuss the rationale behind why CTLA-4 and PD-1/PD-L1 inhibitors are beneficial for cancer therapy, their potential shortcomings, and why new agents and strategies are needed to broaden their therapeutic scope.

OVERCOMING IMMUNE TOLERANCE

From a physiologic point of view, the PD-1/PD-L1 pathway evolved due to the need to control the degree of inflammation at sites expressing the antigen, in order to protect normal tissue from destruction. All activated T cells express PD-1 protein on the surface of their cells. When a T cell recognizes the antigen presented by the MHC complex on the target cell, inflammatory cytokines are released, starting the inflammatory process. These cytokines lead to PDL1 expression in the tissue, activating the PD1 protein on the T cell and resulting in immune tolerance, a phenomenon where the immune system fails to mount an inflammatory response, despite the presence of actionable antigens. In certain tumours, most strikingly in melanoma, this protective process is corrupted through overexpression of PD-L1, thus preventing the generation of an immune response to the tumour. PD-1/PD-L1 inhibitors pharmacologically prevent the PD-1/PD-L1 interaction, thus facilitating a generated immune response. While PD-1/PD-L1 inhibitors have clear, demonstrative benefit as anticancer agents, one limitation to their use is that activity is dependent on the generation of a population of T cells capable of recognizing the tumour via antigen-presenting cells. If this process has not taken place, inhibition of PD-1/PD-L1 is ineffective, as there is no immune response available to unleash on the tumour. While tumour expression of PD-L1 may be suggestive of a tumour that is subduing an immune response and thus could serve as a possible biomarker for clinical benefit, it is clear that not all PD-L1-expressing tumours respond to PD-1/PD-L1 inhibitors and, conversely, that PD-L1-negative tumours can respond to these agents. Further work on this question is ongoing.

ACTIVATING T-CELL PROLIFERATION

In contrast, CTLA-4 inhibitors promote increased T-cell proliferation in response to an antigenic stimulus, hopefully tumour specific, presented in lymphoid tissue. T-cell proliferation requires costimulation between the antigen-presenting cell (APC) and the T cell. Costimulation requires 2 successful interactions: 1) between B7 on the APC and CD28 on the T cell; and, 2) between the HLA-bound antigen and the T-cell receptor (TCR). When these interactions occur, the T cell is permitted to proliferate, generating the T-cell population necessary to produce a lymphocyte-mediated immune response. The size of this lymphocyte population is one key aspect which determines how strong an immune response will be, with a larger population resulting in a greater inflammatory response; therefore, it is essential for the immune system to develop an effective way to prevent the generation of too large a T-cell popula-

John Hilton, MD, FRCPC, is Assistant Professor of Medicine, Division of Medical Oncology, University of Ottawa and Medical Oncologist at the Ottawa Hospital Cancer Centre. His research interests are focused on early drug development, breast, and head and neck cancer. The author reports no conflicts of interest.
tion, which could harm the host as it performs its function. The CTLA-4 protein serves as this critical protector; with the initiation of costimulation, the CTLA-4 gene is transcriptionally activated, and the protein accumulates on the surface of the T cell. The CTLA-4 protein then disrupts the B7-CD28 interaction, thus ending the costimulatory signal and halting T-cell clonal expansion. The importance of this disruption can be demonstrated in mouse models; mice in which CTLA-4 is knocked out rapidly die secondary to autoimmune-mediated end-organ damage caused by a hyperactive immune system. CTLA-4 inhibitors, such as ipilimumab, delay CTLA-4 disruption of the B7-CD28 interaction. This has 2 key effects. First, it permits the generation of a larger T-cell clonal population than what is normally possible under physiologic conditions. Second, it allows weak antigens, which would normally generate small T-cell populations, to act as stronger antigens.

**IMMUNE RESPONSE TO CANCER**

When considering these agents from a clinical point of view, it is worthwhile considering the mechanisms by which the immune system prevents cancer. First, the immune system protects the host against viral infections that can lead to malignancy. The best example of this is clearance of human papilloma virus (HPV), where chronic infection is associated with cervical, anal, penile, and head and neck cancers. Second, endogenous immune modulators limit the chronicity of inflammation, thus reducing the rate of tumourigenesis. Third, and possibly most important, the immune system eliminates early transformed cells due to the production of neoantigens generated by the emergence of oncogenic proteins that drive the neoplastic process.

The importance of immune-mediated elimination of these aberrant oncoproteins, and thus the prevention of transformation, is best demonstrated by a laboratory observation that immunocompetent hosts give rise to functionally different tumours than immunodeficient hosts. In these experiments, immunocompetent mice exposed to carcinogens gave rise to tumours that could subsequently be implanted into either immunocompetent or immunodeficient mice. In contrast, immunodeficient mice exposed to carcinogens gave rise to tumours that could only be implanted into other immunodeficient mice; implantation of these tumours into immunocompetent mice resulted in destruction of the implanted tumour. These observations reflect a process known as immunoediting. The transformation of cells results in the generation of neoantigens through the creation of oncogenic proteins. These novel oncogenic proteins are recognized by the immune system and thus eliminated; therefore, in an immunocompetent host, tumour cells are continually selected by the immune system for their development of weak antigens, while generating proteins capable of carrying out oncogenic processes. This phenomenon can be observed at the DNA level, where the mutation rate of coding sequences within a tumour is far lower than the rate observed in non-coding sequences. Eventually, the transformed cells become malignant and tumour growth occurs.

**IMMUNOE DITING**

Overcoming tumour escape from immune system recognition through immunoediting represents one of the fundamental challenges facing drug development in this area. One of the possible reasons why the combination of CTLA-4 and PD-L1 inhibitors have resulted in superior clinical benefit compared to either agent alone is that CTLA-4 inhibition creates a new, robust T-cell population against weak tumour antigens, which can then be unleashed through PD-1/PD-L1 inhibition. This is why tumours with higher mutation rates, such as in mismatch-repair deficient colorectal cancer, are more likely to benefit from immunotherapy, as in these tumours there is a greater probability of immunoediting failing to remove all of the generated neoantigens. Many concepts are currently being tested to try to overcome this issue, such as combining immunotherapy with chemotherapy or radiation therapy (modalities which increase the mutation rate in tumour cells), or by introducing novel immune checkpoint agents, such as OX40 activators or lymphocyte-activating 3 (LAG3) inhibitors, to further remove inhibitors to the immune response. Hopefully, over the next few years, one of these strategies will prove to be effective, thus broadening the clinical benefit of these agents.

**References**


