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Immune Checkpoint Inhibitors: New Drugs on the Horizon

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Editorial

Recent advances in the field of cancer immunotherapy have opened up the prospects of applying the body's own defense system to fight cancer. Until recently, cancer research was focused on finding drugs that targeted signaling pathways and molecular mutations. These drugs have produced remarkable clinical responses and have made targeted therapy the buzzword in cancer treatment. However, the genomic instability and heterogeneity of cancer cells leads to development of resistance to these drugs and invariably results in disease progression.

New developments in our knowledge of immune regulation has prompted research into the application of this knowledge towards treatment of various cancers. Their specificity, ability to produce memory cells, and their vast repertoire in recognition of tumor antigens make the T-cells are ideally suited to kill cancer. However, under normal circumstances, the T-cells cannot mount an unrestrained response due to the presence of inhibitory checkpoints. Two immune checkpoints that have been most actively studied in cancer chemotherapy are the cytotoxic T-lymphocyte-associated antigen (CTLA4) and the programmed cell death protein 1 (PD1).

CTLA4 is expressed exclusively on T-cells and counteracts the stimulatory effect of CD28, a T-cell co-stimulatory receptor. Once a T-cell recognizes the antigen presented by the antigen presenting cells (APC), CD28 amplifies the TCR signaling causing T-cell activation. CTLA4 competes with CD28 for its ligands, CD80 and CD86, on the APCs and causes inhibition of the T-cell response [1,2]. Ipilimumab, a monoclonal antibody against CTLA4, was the first therapy to show a survival advantage in metastatic melanoma. In a pivotal phase III randomized controlled trial of 676 patients with advanced melanoma, Ipilimumab therapy demonstrated a survival advantage of 3.5 months over gp100 peptide vaccine. More importantly, responses were durable with 18% of the patients in the Ipilimumab group surviving beyond 2 years [3].

PD1 is another immune checkpoint that is expressed on T-cells, B-cells and NK cells. It has 2 ligands, PD-L1 and PD-L2 which are commonly upregulated on tumor cells. On activation of the T-cell in response to an antigen, PD1 is expressed on the T-cell surface and it binds with its ligands and down modulates the T-cell immune response via TCR signaling [4]. PD1 and its ligands have been a focus of interest for the treatment of various malignancies. Pembrolizumab and Nivolumab, both anti-PD-1 antibodies, have shown to have improved responses in advanced melanoma as compared to standard chemotherapy [5,6]. This triggered the FDA approval of both drugs for advanced melanoma in September and December 2014 respectively. Since both CTLA-4 and PD1 have different mechanism of action, combination of both anti-CTLA4 and anti-PD1 antibodies are also being used in clinical trials.

The success of these immune checkpoint inhibitors has led to a spate of new immune checkpoints as well as co-stimulatory molecules that can be targeted to harness the immune response against cancer. Since the target for these inhibitors is on the T-cell rather than the cancer cell, these drugs could theoretically work on a wide variety of malignancies. They can also be used to enhance the effect of immune vaccines and can also be used in combination with genomic targeting agents. Finally, a new era in cancer therapeutics has dawned!

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