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Checkmate with checkpoint inhibitors: New paradigm in immunotherapy

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Cancer immunotherapy is a form of biotherapy (also called biological response modifier therapy) that refers to a broad array of anti-cancer therapies targeted to activate and trigger the body's immune system against cancer.[1] This includes targeted antibodies to specific cell surface entities on cancer cells, anti-cancer vaccines like vaccines against HPV in cervical cancer, cytolytic virus, adoptive cell transfer, biologicals like cytokines and other small molecular agents, and the most explored immune checkpoint inhibitors.[2] Immunotherapies use immune modulatory materials from the same organism to fight disease, while some immunotherapy treatments use genetic engineering-based gene editing approaches to enhance the host immune system in an effort to eradicate the cancer cells and boost its cancer-fighting capabilities.[3] Used in combination with surgery, chemotherapy, and radiotherapy, cancer immunotherapy improves their overall effectiveness.[4,5]

WHAT IS AN IMMUNE CHECKPOINT

T cell activation involves the engagement of a number of signaling cascades, originating from the interaction between T cell receptors (TCR) with antigen-presenting cells (APC) that ultimately determine cell fate through regulating cytokine production, cell survival, proliferation, and differentiation.[6] TCR alone is not sufficient to generate an adequate response. It needs the participation of coreceptors.[7] Primary T cell activation involves the integration of three distinct signals (1) antigen recognition in the presence of APC, (2) costimulation, and (3) cytokine-mediated differentiation and expansion. To make sure that these activated T cells do not cross-react with self-antigens, these are rendered inactive by immune checkpoints. PDL on T cells and PDL1 on host cells engage in bringing about this. Programmed Cell Death Protein 1 (PD-1) inhibits immune responses by fostering a state of self-tolerance.[8] This is achieved by activating apoptosis, anergy, and avoidance of antigen-specific T cells. The functional counterpart of PD-1, the Programmed Cell Death Ligand 1 (PD-L1), is a trans-membrane protein that acts as a coinhibitory immune response factor. This is what the cancer cells hijack for their survival. PD-L1 expressed on cancer cells attenuates the host T cell response transmitting negative signals. Therefore, the PD-1/PD-L1 axis is the main driver of cancer immune evasion, which needs serious attention.[8]

WHAT IS IMMUNE CHECKPOINT INHIBITORS

These classes of molecules are designed to block the cross-talks between cancer cells expressing PD-L1 with T cells expressing PD-1 receptors. When the interaction is blocked, inhibitory influence on T-cells is circumvented, and an attack may be launched.[9]

Checkpoint inhibitors are used in cancer immunotherapy, including a wide range of cancers, such as melanoma, skin cancer, and lung cancer. Different drug classes block checkpoint proteins like CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors. Commercially checkpoint inhibitors include pembrolizumab (Keytruda), ipilimumab (Yervoy), nivolumab (Opdivo), and atezolizumab (Tecentriq).

RAYS OF HOPE AND CAUTION

Because checkpoint inhibitors stimulate the immune system and are immunomodulatory, their usage has significantly improved cancer treatment and management, extending the

life span for numerous patients. However, we need to be cautious as they may cause immune cells to attack healthy cells, causing side effects such as fatigue, nausea, high fever, flu-like symptoms, and inflammation.

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