CANCER STUDIES AND MOLECULAR MEDICINE
Openventio PUBLISHERS
ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-2-108

Letter to Editor

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Volume 2 : Issue 1
Article Ref. #: 1000CSMMOJ2108

Article History
Received: June 29th, 2015
Accepted: July 7th, 2015
Published: July 10th, 2015

Citation
Kumar A. Immuno-oncology: is it a new hope for cancer patients?. *Cancer Stud Mol Med Open J*. 2015; 2(1): 66-68. doi: 10.17140/CSMMOJ-2-108

Immuno-oncology: Is it a new hope for cancer patients?

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Cancer is the one of the leading causes of death, whose incidences is increasing day by day due to lack of understanding about its complete mechanism. Therefore, to understand complete mechanism of cancer, researchers started to move their focus from the cancer cell to the host and the environment in which the cancer grows, a very important component of which is the immune system.[1,2] The immune system comprises of innate and adaptive system which provides protection to the body against pathogens. The immune cell receptors recognize the foreign and activate the complex immune response signaling pathways which results in the elimination of pathogens.[3,4] The first problem with cancer cells is that they arise from our own cells, so some times unable to recognize as non self. Further, if they recognized, alters the immune response signaling pathways at various steps which results in failure of immune response. The cancer cells can avoid recognition and elimination by altering the immune response signaling pathways at various steps such as disrupting antigen recognition and presentation mechanisms, down regulates the MHC class I molecules or inhibiting the antigen processing mechanisms. Additionally, cancer cells may disrupt the pathways which are involved in controlling T-cell inhibition and activation, or by recruiting regulatory T cells (Treg) and Myeloid-derived suppressor cells (MDSC) which are immunosuppressive. Further, cancer cells may release of some of immunosuppressive immune factors such as adenosine and prostaglandin E2, and the enzyme Indoleamine 2,3-dioxygenase (IDO) which leads to progression of cancer.[5-7]

Immuno-oncology is the new and emerging field of cancer research that works to understand the interaction of the immune system with cancers cells and finds ways for harness of the patient's immune system to treat or prevent cancer. It targets only the immune system, not the cancer cells.[8] Researchers have been tried to understand this complex interaction for over a century, with tantalizing but unsustainable results. Recent advances in our understanding of antigen recognition, presentation and the molecules involved in T and B cell activation have provided new and excited immunotherapeutic strategies which can be used against the cancer cells. Some success in animal models has been observed and some molecules are now being under clinical trials. The interaction between our immune system and cancer is very complex process. Current strategies are based on agents that can break immune tolerance.[9]

Presently, numbers of immunotherapy having different mechanisms for cancer patients are under clinical trials. Toll like receptors (TLRs), recognize the conserved molecular structures found in pathogens called Pathogen-associated molecular patterns (PAMPs) which leads to the activation of innate immune signaling pathways. Members of TLRs are well conserved in both human and mouse, consisting of at least 11 members. The agonists of toll-like receptors (TLRs) have been actively pursued for their anticancer potentials, either as monotherapy or as adjuvants to vaccination or other therapeutic modalities.[10] The Bacillus calmette-guérin (BCG, an attenuated strain of Mycobacterium bovis initially developed as an anti-tuberculosis vaccine), have been shown to potently activate TLR2 and TLR4 and approved by the FDA for bladder carcinoma. Similarly, imiquimod act as TLR7 agonist and approved by the FDA for superficial basal cell carcinoma.[11] Further, TLR9 agonists are under clinical development phase. TLR9 agonists directly induce activation and maturation of plasmacytoid dendritic

ISSN 2377-1518 Open Journal http://dx.doi.org/10.17140/CSMMOJ-2-108

cells and enhance differentiation of B cells into antibody secreting plasma cells. The immune role of TLR9 has been studied most extensively in plasmacytoid Dendritic Cells (pDCs) and B cells, which may be the only human immune cells to constitutively express TLR9.[12] The other most recognized class of immunooncology agents are checkpoint inhibitors which modulate pathways that either switch off or stimulate T cell activity, results in anticancer responses. These agents are recognized as breakthrough treatments for advance stage cancer. The approval of sipuleucel-T (a therapeutic vaccine composed of recombinant antigen protein designed to stimulate T-cell responses) and ipilimumab, an antibody that blocks Cytotoxic T lymphocyte associated antigen 4 (CTLA 4) were the first immunotherapies to be approved for patients with cancer.[13] Similarly, treating patients with antibodies that block the Programmed Death-1 (PD1) receptor, or its ligand, PD-L1, has proved highly promising results in clinical trials.[14,15] Cytokines have the capacity to stimulate an immune response by activating T cells development and their differentiation into the effector cells. Interleukin-2 (IL-2), a cytokine that stimulates the growth, differentiation and survival of antigen-selected cytotoxic T cells, resulted in durable anticancer responses is the first Food and Drug Administration (FDA) approval cytokine for the treatment of patients with metastatic renal cell carcinoma.[16,17] IL21 and IL7 are the other cytokines which are under clinical development phase along with combination of other drugs.[18,19] Another promising immunotherapy approaches is the adoptive cell transfer technology which involves the collection of T cells from patients, the *in vitro* expansion and activation of T cells with reactivity to cancer antigens, and the subsequent reinject back to the patient, with the expectation that the cancer-specific T cells will attack the tumor.[20,21] These types of approaches are combining with other immunotherapies and are under preclinical and clinical phases which may further improve clinical efficacy.

Thus, the long term survival in cancer patients can be achieved by treating the immune system. Further, it is important now, how to use these new immunotherapies most effectively to achieve the best possible patient outcomes. Can we combine immunotherapies that target distinct immune pathways? Can we combine immunotherapeutic agent with existing treatment modalities such as radiotherapy, chemotherapy? What is the optimal dose, schedule of therapies in combination regimens? These are some important questions which have to be answered. At present, it is difficult to identify the best combination approaches, sometimes combinations leads to the unexpected toxicity (e.g. ipilimumab and vemurafenib). Thus, there is a need of more preclinical and clinical studies which will help to direct immuneoncology research.

The development of new immunotherapies against various diseases is based upon many years of researcher's hard work to understand the complex signaling pathways of immune systems. As that knowledge increases, researchers will hold the keys to developing new treatments that have the potential to change the ways in which we treat cancer. Although, the science of immuno-oncology is still evolving, and there are a number of important questions that remain unanswered but I hope, in future, immuneoncology will answer most of the questions and benefit the large numbers of cancer patients with minimum side effects.

ACKNOWLEDGMENT

Author gratefully acknowledges the Department of Science and Technology (DST), New Delhi, India for providing financial assistance in the form of a DST-INSPIRE fellowship (IF 120789).

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