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Development of immune checkpoint inhibitors for treating various cancer diseased conditions

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ABSTRACT

Cancer is a state which involves an abnormal increase in the number of cells, with a potentiality to invade or spread to other parts of the body and destroy their function. Every individual is born with an immune system that acts as a security checkpoint. The immune system does possess B and T lymphocytes, B -cells acts as the military intelligence and T-cells acts as soldiers it also possesses some receptors that scan normal cells and abnormal cells like a virus and some other cells. Abnormal cells are detected and removed by the T-cells, but in some conditions, T-cells fail to detect and eliminate cancer cells. This is because of higher mutations in cancer cells leads to a development of some of the receptors like PD-L1 which acts as the signal jammer of the T-cell. This leads to failure in the work of T-cells against the cancer cells not only this some other receptors like CTLA-4 of T-Cells acts as a type of "off switch" to keep the immune system in off. Immune checkpoint inhibitors are used by targeting PD-1, PD-L1 and CTLA-4 targets and drugs like pembrolizumab, nivolumab, ipilimumab and etc. are used to treat various types of cancer.

Keywords: Programmed cell death, Pembrolizumab, Ipilimumab, Cytotoxic T-lymphocyte-associated protein [4].

INTRODUCTION

Immunotherapy is a new kind of approach to treat cancer which works to harness the innate powers of the immune system and makes to fight against various diseases. This therapy is most efficient when compared to that of remaining therapies. Because it is based on targeted for systemic treatment and it has fewer side effects, When we compare this immunotherapy with that of chemotherapy .chemotherapy treatment is for curing of disease state and after stopping of this treatment may have a chance of reoccurrence of disease and possess lots of side effects like bone marrow depression and some other, were as immunotherapy cures cancer or any other disease and gives a life-long protection with less to no side effects.

Immune cells play an crucial role in identifying abnormal cells like bacteria, viral and any diseased cells or etc conditioned cells.

In normal conditions B-cells are like the body's military intelligence system, search targets and

sending defenses to lock onto them. T cells are like the soldiers, destroying the foreign agents that the intelligence system has identified. T-cells gets attached to the target cell, cytotoxic T cells do possess TCR(T-cell receptor) , CD8 and some receptors and target cells do possess MHC molecule ,when T-cell attaches to abnormal cells they do release some toxic materials like perforins and some others materials perforins are the proteins one of the main cytolytic proteins of cytolytic granules, and it is known to be a key effectors molecule for T-cell and natural killer-cell-mediated cytolysis because of this granules lead to pore in target cells and finally it leads to the dying of the target cells and cytotoxic T-cell gets released from the target cells [1].

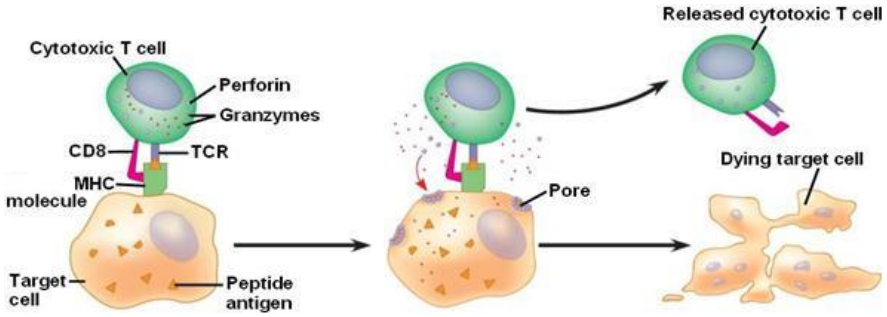

Fig: 1 Mechanism of T-cell how it attacks the abnormal cell

Whereas in cancer cells which are highly mutated in that condition T -cell does not show any of its action this is because T-cells possess PD-1 which acts as the signaling system, cancer cells possess PD-L1 molecule which acts as the signal jammer of the T-cell. and B7.1 or CD 80 that acts as the alarm when something is wrong which helps in the activation of T-cells by inhibiting the stimulus of T-cell finally, that leads to the escape of the tumor cells from the immune checkpoints, cytotoxic T-lymphocyte-associated protein 4(CTLA-4) receptor expressed on activated T-cells which function as an inhibitory receptor which inhibits T-cell activation not only this two receptors so many receptors are present which make cancer cells to live freely and T- cells are gets inhibited their activity. By triggering some of these sites may leads to the development of treatment for many cancer diseases like lung disease and some other disease.

PROGRAMMED CELL DEATH

PD-1 (Programmed death- 1) is expressed on monocytes, T-cells, B-cells, dendrites' cells, natural killer cells and many tumor-infiltrating lymphocytes(TILs).PD-1 is expressed in regulatory T-cells and able to facilitate the proliferation of regulatory T cells and restrain immune response [3], PD-L1 (Programmed death-ligand 1)is expressed in various cancers cells , especially in Non-small cell lung cancer (NSCLC), gastric cancer, melanoma, hepatocellular, renal cell carcinoma as well as various leukemia's and so on [4].PD-L1 is induced by multiple proinflammatory molecules like TNF-α, LPS, Granulocyte-macrophage colony-stimulating factor and Vascular endothelial growth factor, as well as the cytokines IL-4and IL-10, with IFN-γ being the most potent inducer[5]. PD-L1 is regulated by oncogenes (a gene that has the power to cause cancer), also known as the inherent immune resistance in cells. And drugs against this are ANTI-PD-1 and ANTI-PD-L1 is effective.

ANTI-PD-L1

Durvalumab

MEDI4736 is a code name and its name is durvalumab human IgG1 antibody, Upon iv administration, durvalumab binds to PD-L1 of tumor, thereby blocking its binding to T-cells and activation of its receptor programmed death 1(PD-1) expressed on activated T-cells [6].

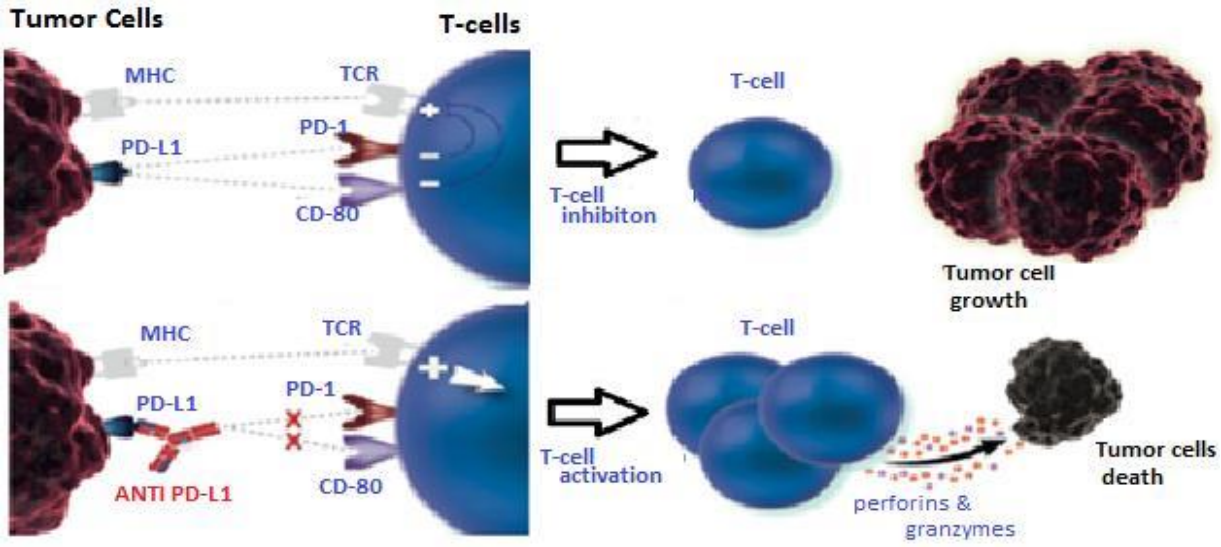

Fig: 2 Mechanism of action of anti-PD-L1 drugs. They block the PD-L1 receptors of tumor cell which leads to the activation of the patient's T-cells, mechanism of the T-cell starts as shown in above fig;1and finally destruction of tumor cell happens [7].

Development phases	Research conditions of the drug
Phase- III	Bladder cancer, Non-small cell lung cancer ,Head and neck cancer
Phase- II	Breast cancer, Glioblastoma,Colorectal cancer, Hepatocellular carcinoma, Mesothelioma.
Phase- I/II	Cervical cancer; Diffuse large B-cell lymphoma; Gastric cancer; Malignant melanoma; Ovarian cancer; Solid tumours
Phase-I	Multiple myeloma[8]

Anti PD-1

Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody it is given as a targeted therapy which acts by blocking a negative regulator of T-cells. Binding of PD-L1 receptors of the cancer cells to the PD-1 receptor found on T cells lead to inhibition of T cell proliferation and cytokine production [9], Upregulation of the PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors so in order to prevent this nivolumab is introduced which used as iv injection and in combination with ipilmumab (Yervoy) to treat certain types of melanoma (a type of skin cancer) that has spread to other parts of the body or cannot be removed by surgery. Administrated for a treatment of patients with metastatic Non-small cell lung cancer (NSCLC a squamous cell carcinoma), on the condition of a continuance of the diseases during or after chemotherapy with platinum-based drugs like cis-platin and etc. This drug is been used and do possess fewer side effects than that of the remaining [10, 11].

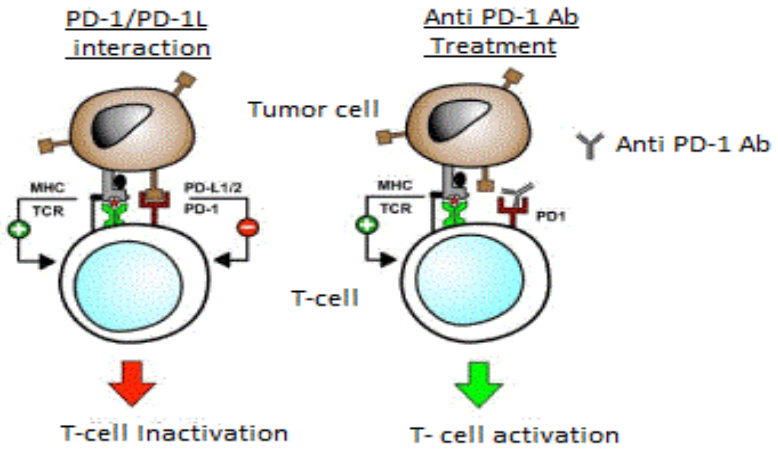

Fig: 3 Explains how the Nivolumab shows its action by inhibiting the PD-1 receptors on the T-cells.

Cytotoxic T-lymphocyte-associated protein 4

It is also known as CTLA-4 which is a member of the immunoglobulin super family and it is a co-stimulatory molecule expressed on T cells mainly. CTLA-4 or CD28, and both molecules bind to B7-1 (CD80) / B7-2 (CD86) on antigen-presenting cells. CTLA-4 transmits an inhibitory signal to T cells which lead to inhibition of the activation of cells, whereas CD28 transmits a stimulatory signal for the activation of T-cell [12].

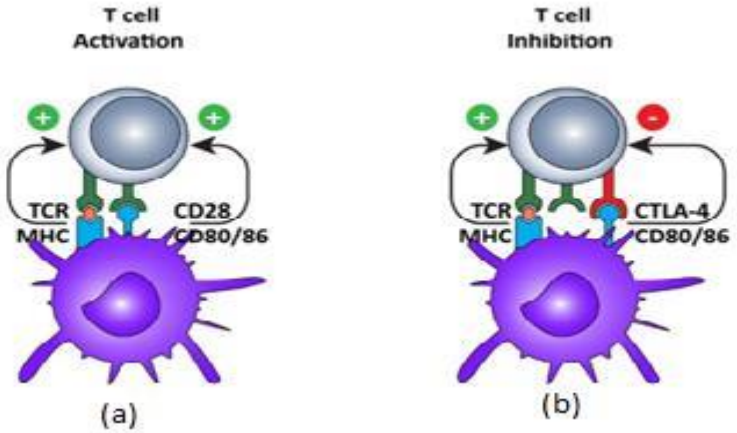

Fig: 4 (a) Explains normal activation of T-cell (b) Explains attachment of CD80 receptor to the CTLA-4 which leads to send the inhibitory signal to T-cell that leads to the inactivation of T- cell and finally surveillance of the tumor cell fails.

So this leads to the development of the anti-CTLA-4 drugs in order to inhibit the co-stimulatory of the CTLA-4.

TREMELIMUMAB

Tremelimumab is a selective human antibody which is against cytotoxic T-lymphocyte-associated protein- 4(CTLA-4). By blocking the activity of CTLA-4 of T-cells, tremelimumab "releases the brakes" of T cell activation and boosts the immune response against cancer cells [13]. It is being investigated in a various clinical trial programmed, as in monotherapy or in combination with durvalumab, in NSCLC, bladder, neck and head, pancreatic, blood cancers, and gastric [14].

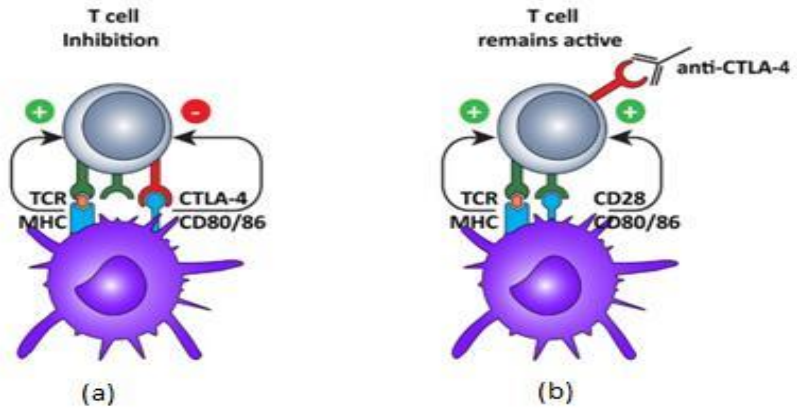

Fig:5 (a)Explains attachment of CD80 receptor to the CTLA-4 which leads to send the inhibitory signal to T-cell that leads to the inactivation of T- cell. (b)Explains attachment of anti-CTLA-4 drugs to the CTLA-4 receptors of T- cells leads to the usual attachment of the CD28 with that of CD-80 leads to the activation of the T-cell this is the mechanism involved in the Anti-CTLA-4 drugs.

PD-L1 and CTLA-4 immune checkpoints inhibit antitumor T-cell activity. Combination treatment with the anti-PD-L1 and the anti-CTLA-4 antibody tremelimumab might provide greater antitumor activity than either drug alone.

Complications in current and distant research about the drugs of PD-1/PD-L1 or CTLA-4

Even though much known about the treatment of cancer based on the immune therapy but many questions were unexplained properly or solved unclearly. Those includes inpatient concerned how to choose a correct therapy either to take PD-1/PD-L1 or CTLA-4, chemotherapy or combinational therapy or radiotherapy or others does may change of disease condition? Whether PD-1/PD-L1 or CTLA-4 inhibitors to be used as first-line therapy? Does blockade of the PD-1/PD-L1 or CTLA-4 pathway leads to the activation of only a tumor-reactive T cells or also T-cells that are auto reactive to non-tumor antigens which may cause undesirable autoimmunity? Thus, a need for additional basic immunology studies on this way of treatment to cancer disease and larger clinical trials are essential [15].

CONCLUSION

Research in immunotherapy gives a new wide space for the treatment of various cancer disease like myeloma, NSCLC and etc, when we compare this immunotherapy with that of radiotherapy, chemotherapy this give a wide range of results with relatively safer, less toxic, effective and etc conditions anti-CTLA-4 monoclonal antibody therapy has shown promise in a number of cancers, particularly melanoma and also antiPD-1/PD-L1 this therapy has shown an effect on patient with the NSCLC has been benefited. With the elaborated studies on biological marker and combined treatment in the PD-1/PD-L1 or CTLA-4 will make a new sense in development of immunity against cancer diseases and which make a new revolution in the treatment of cancer disease.

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