Immunotherapy For Skin Cancer

In recent years there have been several advancements in medical technology for treatment of skin cancers. However, the therapies developed for the treatment such as hedgehog inhibitors exhibits risk of developing resistance or recurrence of the disease. (2) Skin cancers were found to be highly immunogenic because of the mutations and tumor associated antigens. Both the CD4+ and CD8+ T- cell immunosuppression in skin cancer results in less survival rate and increased risk in skin cancer. (10) Antigenicity of skin cancer arises from tumor associated antigens, viral oncoproteins and neoepitopes. Melanomas were found to overexpress tumor associated antigens such as MAGE antigens, MART1. This makes immunotherapy as the promising approach for treatment of skin cancer. (22) It was found that the immunotherapy for melanoma exhibited low response rates. This was found to be due to more time required for response after immunotherapy. During this time the condition of patients in stage IV worsened to a great extent. (12) The various approaches by which immunotherapy is provided are immune checkpoint inhibitors such as CTLA-4 inhibitors and PD1 inhibitors, use of cytokines, adoptive T-cell therapies, cancer vaccines. (12)

Immune Checkpoint Inhibitors:

Cell surface membrane proteins such as Programmed cell death-1 receptor is expressed on T-cells. It belongs to B7 family of checkpoints. Tumor cells express programmed cell death protein ligand-1 which attaches to the PD-1 receptor present on T-cell. This inactivates T-cells and hinders tumor destruction caused by T-cells. Researchers have developed several anti PD-1 antibodies and anti PDL-1 that blocks these receptors and avoid inactivation of T-cells.

Chen et al studied the combination of cetuximab and nivolumab for treatment of cutaneous squamous cell carcinoma of auricle. It is quite challenging to treat cutaneous squamous cell carcinoma of head and neck regions. Immunotherapy is one of the treatment approach used to treat such cancers. Cetuximab is the epidermal growth factor inhibitor antibody and nivolumab is the programmed cell death 1 antibody. The results indicated that dual treatment with cetuximab and nivolumab caused complete remission of the squamous cell carcinoma of auricle. (23)

Wolchok et al. reported that nivolumab and ipilimumab combination is effective in treating advanced melanoma. Ipilimumab acts as CTLA4 inhibitor and prolongs survival whereas nivolumab acts as PD1 antibody and was responsible for tumor regression. Rapid and deeper tumor responses were observed on administration of the combination. (24)

Cannon et al. reported a case study in which a man with age around 50 years had basal cell carcinoma on shoulder. The carcinoma was removed 5 years ago. Block resection was required for the recurrence observed in the skin layers of sternum and clavicle. After one year CT scan revealed nodules on lungs with basal cell carcinoma. The patient was advised to take vismodegib. Disease progression was observed immediately after 3 months. Then he enrolled in clinical trial in which he was given taladegib but again clavicle BCC recurred. The patient then started off label use of pembrolizumab, PD1 inhibitor. He took 2mg/kg every 3 weeks. After 6 weeks lung lesioms were resolved. After 16 weeks the person reported severe back pain. He had to take opiod analgesics. CT scan revealed mass on T8 vertebral body. The patient did not

stop pembrolizumab. However, the patient was relieved on radiation therapy to vertebrate. This illustrates that PD1 inhibitors reduced the lung metastasis but failed to treat bony metastasis. The reason for this is unkonown but it is assumed that tumor cells escape the immune cells while adapting to bony microenvironment. (3)

CTLA-4 also known as CD152 is widely expressed in CD4+, CD8+,NK and FOXP3+ cells and regulates the T-cell mediated immune response. B7-1 (CD80) and B7-2 (CD-86) ligands are present on antigen presenting cells with which CTLA-4 associates and negatively regulates T-cell activation. This suppresses the T-cell dependent immune response. Hence, scientists have developed agents that block CTLA-4 and activate the T-cell dependent immune response. But it was reported that CTLA-4 inhibitors have more side effects as compared to PD-1 inhibitors. Ipilimumab was the first CTLA-4 inhibitor for melanoma.

Tremelimumab is an CTLA4 inhibitor which has shown activity in phase 1 and 2. No advantage was observed over chemotherapy in phase 3 trial. (25)

Cytokines:

Malignant cell growth was found to be inhibited by interferons including IFN-?2a and IFN- ?2b. Basal cell carcinoma cells were found to produce CD95 ligand. On treatment with IFN- ? cancer cells were found to express CD95 ligands as well as CD 95 receptors. Their interaction is responsible induction of apoptosis. Treatment with this interferon also increased the IL-2 productiona and inhibited IL-10 production. IL-10 has inhibitory action on cell-mediated immune responses. Limitations of these therapy include systemic side effects, more frequency and cost and time of treatment. (12)

Yanelda et al. conducted a retrospective study for combination of IFN alpha 2b and gamma (heberPAG) to treat periocular non melanoma skin cancer. Results indicated that combination can serve as an alternative to surgery when all other treatments are not possible. (27)

Cancer vaccines:

They increase the cell mediated immune response or humoral response. Two classes of vaccines are available including treatment vaccine and prevention vaccine. Treatment vaccine include DNA vaccines, peptide vaccines, and dendritic cell based strategies. They offer several benefits including less adverse effects and high specificity. (12)

Vinzon et al. reported human papillomavirus vaccine to be used for prevention of skin cancer. (28) In 1970’s it was reported that BCG vaccine can be used for treatment of melanoma metastases. Due to the high toxicity exhibited by this approach it was no more used for treatment. (10)

Adoptive cell Therapies:

In this approach the T cells are extracted from peripheral blood or tumor environment and injected in patient. They also include therapy with tumor infiltrating lymphocytes. Recent advances modify these cells to enhance the immune response. Example for this kind of approach is use of CAR-T cell therapy for treatment of melanoma. Chromosome is integrated

with CAR gene and directs T-cells to decode new genes and generate CARs. These genetic modifications make T-cells more specific towards cancer cell antigens.

Deniger et al. studied the effect of combination of vemurafenib and adoptive cell therapy in patients with metastatis melanoma. The results indicated that the combination generated desired results in small pilot clinical trials. (29)

Mullinax et al. studied the combination of ipilimumab and adoptive cell therapy with tumor infilterating lymphocytes for treatment of metastatic melanoma. The results indicated that the treatment is feasible and well tolerated. It serve as model for further improvement of efficacy.