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# Overview Of Immunotherapy And Its Utilization In Oncology

## Introduction

Immunosuppressive therapy is otherwise known as Biological therapy is used in the treatment of several diseases such as cancer, auto-immune diseases, Inflammatory bowel diseases and in after transplantation procedures and in any other condition where there is a need to under activate or sensitize the body's immune system. Immunotherapy can be administered into the body in certain ways such as orally, topically, intravenously and through intra vesical route. (1)Chiefly Immunotherapy is divided into cancer vaccines, monoclonal antibodies and non-specific immunotherapies such as cytokines (Interleukins-IL and interferon).

Cancer vaccines and Monoclonal antibodies are used in the treatment of several kinds of carcinomas. IL-2 is used for treatment of malignant melanoma, while interferons are used in hepatitis C treatment. Immunotherapy is used in the investigation of obstructing the inflammation for diseases such as Inflammatory bowel disorders and Rheumatoid arthritis. The main aim of the Immunotherapy is to target and change the direction of tumour cells to refrain them from inactivating the T-cells and make the cancer cells to respond with increased capacity to the therapeutics. Biological response modifiers (BRM's) are materials that can increase the immune response and they can be derived externally such as nucleic acids, lipid proteins, polysaccharides and others. Polysaccharides are more in occurrence and widely used.

## Different Types of Immunotherapies (Selected)

- Colony stimulating factors (CSF)

These CSF are used in lymphoproliferative disorders where it over works in the bone marrow by creating immunity by producing blood cells.

- Monoclonal antibodies

They are developed in the body following the growth of cancer cells. They attach to the cancer proteins and destroys them. Monoclonal antibodies are made in the laboratory and they are directed upon the specific antigen.

- Cytokines

Cytokines are hormonal messengers produced as an outcome when there is a cell alteration or damage and stimulates the immunity to react towards cancer. Interferons and Interleukins are the 2 main types which aids in demolishing the cancer cells. Some examples of cytokines that are engineered in lab include interleukin-2 (IL-2), colony-stimulating factors CSF, G-CSF and GM-CSF and interferons. ALPHA Interferon is commonly used in the lab in treatment of cancers and ALDESLEUKIN (IL-2) is the interleukin generated in lab used in management of skin and kidney cancer.

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- Adoptive cell transfer

Adoptive cell therapy is a method which uses the patient's self-normal T-lymphocytes to regress the malignant cell activity. T-cells are grown in the lab and then injected back into the patient's body.

- T-cell therapy

CD-4 and CD-8 T-cells are aimed at the antigens of the tumour cells. T-cells are cultivated in the lab environment to preserve their maximum potential effect and given back the patient in the form of vaccines. Vaccination are used in clinical trials which can eliminate the small metastases in other parts of the body.

- Virus Oncotherapy

Viruses are genetically modified and then imposed into the blood stream where they enter the body and make several duplicates of itself which accelerate the anti-tumour immunity. Many oncolytic programs are undergoing phase III Clinical trials.

· Vaccines

Prophylactic vaccines – These vaccines are administered earlier to the evolution of diseases preventing the body against disease-causing pathogens.

Therapeutic vaccines – Type of immunotherapy where vaccines are applied in the body to boost the immunity and to fight-down the cancer. such vaccines even help in preventing and abolishing the reoccurring cancer cells.

## **Adverse effects of Immunotherapy**

There are so many adverse effects following Immunotherapy.

Some are as follows, Injection site side effects includes

- Signs of inflammation at the site such as pain, redness, swelling and soreness.
- 2nd grade - scratch reflex (pruritis)
- In advanced stage, ulcer formation in the site occurs. (11) Flu- like symptoms include
- Fever with chills
- Myalgia
- Nausea
- Dizziness
- Lethargy
- Headache

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- Diarrhea

Major Particularized adverse effects involve

- Eczema
- Colon inflammation
- Severe Liver infection
- Inflammation of thyroid, pituitary and adrenal glands
- Carditis (specifically myocardium)

## Background Of Immuno-Oncology

Sir William Coley postulated a concept about Immuno-oncology in 19th century stating that episodes of increased body temperature can be related to reduction in the malignant tumour size after noticing a case where there was an absolute abolition of tumour following few strikes of bacterial infection. Considering it Coley tried samples of bacterial toxins injected into patients and achieved more than 10% cure rates. (13) But this theory was not accepted by many other scientists until the discovery of Tumour associated antigens (TAA) that was detected by lymphocytes. Certain studies have shown that the genetically engineered lymphocytes are efficient at reducing the cancer rate.

## Immuno - Oncology

For the past three decades several researches have proved that Immunotherapy serves as a strong tool in the management of cancer. The immune system acknowledges the tumour cells and their growth can be ceased or altered in a long run through a procedure named as Immuno-surveillance. Many immunotherapy trails have been carried out in field of cancer management implying that they have the higher capability in destroying and deep-rooted memory to avert reoccurrence.

## Cancer-Immunity Cycle

The series of events taking place in cancer-immunity cycle as follows-Dendritic cells coverup the neoantigens released by cancer-major histocompatibility class 2 and 3 bound neoantigens to T-cells. -(CD4+ and CD8+) T cells gets activated and recognizes the cancer antigens. -CD8+ -HELPER cells move and infiltrate the tumour and destroy it by immunological signals.

## Immuno-Oncotherapy

Interleukin-2 is a cytokine which activates the development and differentiation of antigen selected cytotoxic T cells that achieved success rates in 1985 and it exhibited consistent anti-tumour response which was approved by FDA for treatment in metastatic melanoma. Interleukin 2 and 12 are both vigorous immunoregulatory cytokines which when combined and administered resolved the tumour completely in primary as well as metastatic renal carcinoma. Next ipilimumab, a human monoclonal antibody was developed which targets against the cytotoxic T-lymphocyte associated antigen-4(CTLA-4) which improves the anti-tumour immunity. Determining the forward survival rate, it got approved by FDA with dosage rate of 3mg/kg.

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Few years later, anti-PD-1 molecules nivolumab and pembrolizumab exhibited greater results with higher survival rates and with less toxic effects. Also, combining ipilimumab and GM-CSF (granulocyte-macrophage colony stimulating factor) showed more favourable results. Nivolumab demonstrated effective prognosis in small cell-lung carcinoma than Docetaxel which was earlier considered to be secondary major treatment in lung cancer. Sipuleucel-T, a therapeutic cancer vaccine, composed of autologous peripheral nuclear cells trigger immune response over patient's own immunity. It has been commercially available and has been tested on hormone -resistant cancer patients. Nonvalent HPV vaccines were introduced which exhibited effects as like as the quadrivalent. A Study conducted with the nonvalent vaccines coating all 9 types of HPV evidenced 90 percent prevention to cervical cancers and 80 percent to pre-malignant lesions with decreased mortality rates and its cost-effective. (23) Moreover, cancer vaccines can also be used to override or boost the immunity by elevating the antigen-specific immune response.

## **History of Monoclonal Antibodies**

Monoclonal antibodies, monovalent produced from B-lymphocytes are specific in targeting the particular protein. The first successful monoclonal antibody was created in 1975 and licensed in 1986. By then so many new humanized antibodies are being developed. (24) Till date, more than 25 antibody-based therapies have been successfully approved. Nevertheless, these antibodies do not point against other many tumour antigens. New discoveries to take-aim at the non-uniformities of cancer genes are yet under trials.

### **Use Of Monoclonal Antibody In Breast And Ovarian Cancer**

Ovarian cancer is the leading cause of death in women in recent years and the major treatment of ovarian cancer depends on Monoclonal antibodies chiefly, Pertuzumab and Trastuzumab which is used in breast cancer as well. HER-2 is a tyrosine kinase receptor is an important biomarker in breast cancer. Pertuzumab and Trastuzumab are monoclonal antibodies which target the HER2 and inhibit the dimerization of HER2 receptor. After series of trials conducted on three ovarian cancer cell lines of varying aggressiveness ranging from low to high grade such as PEO4(low), OVCAR4 and SKOV3(high) Unquestionably, the combination Pertuzumab and Trastuzumab was considered to have pronounced effect on inhibiting the action of HER-2 receptor definitely ovarian cancer cells, besides that it also opens up the venue for sensitizing ovarian cancer cells for combination chemotherapeutic strategies for complete eradication of ovarian cancers in case of drug resistance to these antibodies.

## **Immunotherpies In Inflammatory Bowel Disorders(IBD)**

In Autoimmune such as RA and Inflammatory bowel syndrome such as crohn's and ulcerative colitis, the immune system attacks itself and that leads to the hyper activation of Tumour necrosis factor that in turn leads to the inflammation of joints in RA and intestine in IBD's. Cytokines has an important role in inflammatory bowel diseases such as crohn's diseases and ulcerative colitis. (27). Presently, Infliximab - chimeric monoclonal antibody (TNF alpha antagonists ) has showed spectacular results in healing the mucosal lining and reduced fistular complications in patients with crohn's disease. (28) The implementation of other anti-cytokine derivates and other agents inhibiting leucocytes and blocking T-cell activation are into look up.

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## Allergen-specific Immunotherapy(AIT)

Allergen immunotherapy is used as a curative solution in allergic conditions such as allergic rhinitis, asthma, dermatitis and hyperallergic reactions. (30) Though the exact behind this is unknown yet the process in AIT is desensitizing the basophils and mast cells, yielding the responses of T and Breg cells and regulating the IgE and IgG4, decreasing the eosinophils. Studies have shown the induction of IL-2 imparted positive results in suppressing the allergic responses.

## Newer Forms Of Immunotherapy In Development

There are newer immunosuppressive drugs which are brought into experiment for treating several immune related diseases mainly cancer. The use of monoclonal antibody and adoptive cell therapy has proven to reflect good outcomes, yet their benefits are limited because of its toxicities and adoptive cell therapy being expensive and procedure being multiplex. Cancer vaccines showed favourable out-turn but only in the virus-related cancers. (32)

GLIOBLASTOMA is a fast-growing malignant type of brain tumour with nearly less than 5 percent survival rate with non-specific symptoms. The histopathological finding of GLIOBLASTOMA showed microglia surrounded with macrophages. The immunotherapy in glioma should hit at the TGF-Beta by setting off NK cells, cytotoxic T cells, dendritic cells and under-influencing the Treg cells which through the leukaemia inhibiting factor, SOX4-SOX-2 and DNA binding inhibition leads to the destruction of glioma stem like cell Trabectedin (antisense TGF-beta) has positive outputs in Phase II-b clinical studies. The approaches to accelerate the anti-tumour effect has undergone several researches includes applications of checkpoint-inhibitors which point out the compounds that assists the check responses. CTLA-4, PD-1 are crucial checkpoints in cancer and nivolumab and bevacizumab are currently In phase III trials and combinational therapy of nivolumab and ipilimumab are even under trials. (33) A combined therapy of Bevacizumab, radiotherapy and humanized PD-L1 mAb are currently under investigation. Adoptive T-cell therapy inducing chimeric antigen receptors (CARs) for tumour suppression in recurrent glioma patients are being studied and expected to exhibit high results with low toxicities. (34) CAR T- Cell therapies are now tested in breast cancer, acute myeloid leukemia, Hodgkin's lymphoma and pancreas cancer.

## Conclusion

Immunotherapy is one such treatment where various advances and alteration has been done continuously to produce efficacious and desired regimen to increase the survival of the patients and reducing the complications and in some cases even complete resolvment of carcinogens are aimed at. Immunotherapy serves as a pillar for diseases and cancers and it comprises of a variety of pre-clinical and clinical trials for the better understanding of the many strategies to combat cancer and other diseases and to identify and substantiate targets for treatment regimens and complex establishments. Several kinds of cancer vaccines such as tumour cell vaccines, vector-based vaccines, dendritic cells and antigen vaccines are already into practice and is being under studies. Monoclonal antibodies are salient type in the treatment of cancer yet numerous antibodies are being made with high shielding effect as it does not cause any ill-effects to the body (35). Immunotherapies together with other therapies like radio therapies, chemotherapy, use of biomarkers and various other combination regimens are being trailed and

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under research programmes to keep the life-deteriorating cancer and other diseases at bay.

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