SYSTEMATIC REVIEW ON EFFICACY OF IMMUNOTHERAPY

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ABSTRACT

Compared with previous standards of care (including chemotherapy, radiotherapy, and surgery), cancer immunotherapy has brought significant improvements for patients in terms of survival and quality of life. Immunotherapy has now firmly established itself as a novel pillar of cancer care, from the metastatic stage to the adjuvant and neoadjuvant settings in numerous cancer types. In this review article, we highlight how the history of cancer immunotherapy paved the way for discoveries that are now part of the standard of care. We also highlight the current pitfalls and limitations of cancer checkpoint immunotherapy and how novel research in the fields of personalized cancer vaccines, autoimmunity, the microbiome, the tumour microenvironment, and metabolomics is aiming to solve those challenges.

Keywords: *Types of immunotherapy, Side effect of immunotherapy, Challenges in immunotherapy, Recent advancement in immunotherapy.*

INTRODUCTION-

Immunotherapy is defined as a type of biotherapy and is based on the sensitization of the patient's immune system to cancer, which increases selectivity and reduces side effects.Cancer is a complex disease characterized by uncontrolled growth of cells and expansion of these abnormal cells in the body, which caused over 9.6 million deaths worldwide in 2017 alone. Regarding the estimation of American Cancer Society for 2021, specialists consider that nearly 1.9 million people will be diagnosed with cancer and almost 608,570 people will die from cancer. The cancer-related mortality in the world is expected to reach 22 million by the year 2030.

Among the various approaches employed in cancer treatment, surgery is usually the first treatment of choice. The appropriate strategy for treatment is developed according to the type and stage of cancer. Other treatment methods in clinical practice are chemotherapy and radiotherapy and combinations of these approaches. Chemotherapy using various antineoplastic agents can be applied as first line treatment for therapeutic purposes, but also to prevent the proliferation of cancer cells after surgery or radiotherapy or to reduce the size of tumor tissue prior to surgery.

The main reason for this failure is the systemic toxicity and undesired side effects caused by the treatment strategy, particularly for chemotherapy. In order to overcome these side effects and provide more effective cancer treatment with lower doses of active ingredient, different treatment strategies have been developed. Immunotherapy, which has attracted attention in recent years, can be defined as the use of immune system features in cancer treatment.

HISTORY OF IMMUNOTHERAPY-

The field of immuno-oncology has been transformational in the care of cancer patients. William B. Coley, now widely accepted as the father of immunotherapy, first attempted to harness the power of the immune system for treating cancer in the late 19th century. As an orthopedic surgeon who operated on patients with bone sarcomas, he noticed that some patients with significant postoperative wound infections- a common occurrence when aseptic technique had not yet been optimizedwould undergo spontaneous regression of their unresected tumour.Beginning in 1891, Coley injected more than a thousand patients with mixtures of live and inactivated bacteria such as Streptococcus pyogenes and Serratia marcescens with the hope of inducing sepsis and strong immune and antitumour responses. His cocktail of bacteria became widely known as "Coley's toxin" and represents the first documented active cancer immunotherapy intervention. Coley achieved durable complete remissions in several types of malignancies, including sarcoma, lymphoma, and testicular carcinoma. However, the lack of a known mechanism of action for

Coley's toxin and the risks of deliberately infecting cancer patients with pathogenic bacteria caused oncologists to adopt surgery and radiotherapy as alternative standard treatments early in the 20th century.

MECHANISM OF ACTION-

The human immune system comprises various defense mechanisms against all potential threats including arising cancer cells. Immune surveillance continuously recognizes and eliminates any transformed tumor cells through numerous mechanisms. Cancer immunotherapy has been described as the fourth pillar of therapy against the tumor, which may surpass the effectiveness of conventional therapies such as surgery, radiotherapy, and chemotherapy. Zhang et al.classified the mechanisms of cancer immune therapies into five major groupsthe regulation of immune checkpoints, oncolytic virus therapies, cancer vaccines, cytokine therapies, and adoptive cell transfer.

Types of Immunotherapy-

1. Immune Checkpoint Inhibitors
2. Adoptive Cell Therapies
3. Monoclonal Antibodies
4. Oncolytic Virus Therapy
5. Cancer Vaccines
6. Immune System Modulators

1) Immune Checkpoint Inhibitors-

When your immune system attacks invaders like bacteria and viruses, it uses a system of "brakes" called checkpoints to stop it from attacking your own healthy cells. Cancer cells sometimes turn these checkpoints on or off so they can hide.

Immune checkpoint inhibitors are drugs that release the brakes on your immune system. Eight of these drugs are approved to treat cancer. They block the proteins PD-1, PD-L1, CTLA-4, and TF on the surface of immune cells, to let these cells go after the cancerous growth.

2)Adoptive Cell Therapies-

This group of treatments removes some of your own immune cells and either boosts their numbers or changes them in a lab so they can find and kill more cancer cells.

Tumor-infiltrating lymphocyte (TIL) therapy. T cells are powerful white blood cells that fight infections. In this treatment, doctors remove T cells that have started to attack your tumor. They grow a large batch of these cells, called tumor-infiltrating lymphocytes (TILs), in a lab. They then put these activated fighters back into your body.

Engineered T-cell receptor (TCR) therapy. This treatment removes T cells from your blood and reprograms them in a lab so they can find the cancer more easily. The engineered T cells look for tiny targets on the surface of your cancer cells.

CAR T-cell therapy. Doctors add special receptors to the surface of your T cells so they can lock onto and destroy your exact kind of cancer.

Natural killer (NK) cell therapy. These immune cells attack foreign invaders like cancer in your body. Adding CARs to NK cells helps them target the cancer even better.

3)Monoclonal Antibodies-

Antibodies are proteins your immune system makes. They find and stick to other proteins called antigens on cancer cells. Then they recruit other parts of your immune system to destroy the cancer.

Researchers can make antibodies in the lab. They're called monoclonal antibodies, and they work in different ways:

Cancers Treated By Monclonal Antibodies-

The FDA has approved more than a dozen monoclonal antibodies to treat these types of cancers:

A. Breast
B. Lung
C. Liver
D. Bladder
E. Head and neck
F. Colorectal
G. Stomach
H. Prostate
I. Melanoma
J. Certain types of lymphoma and leukemia

Naked monoclonal antibodies are the most common type used in cancer treatment. They're called naked because they're unattached to anything. These antibodies boost your immune system's response against the cancer, or block antigens that help the cancer grow and spread.

Conjugated monoclonal antibodies have a chemotherapy drug or radioactive particle attached to them. The antibodies attach directly to cancerous cells. This reduces side effects and helps chemotherapy and radiation treatments work better.

Bispecific monoclonal antibodies attach to two proteins at once. Some attach to both a cancer cell and an immune cell, which helps the immune system attack the cancer. The leukemia drug blinatumomab (Blincyto) attaches to a protein on leukemia cells, and to a protein on T cells.

4)Oncolytic Virus Therapy

Viruses like the flu infect cells and make us sick. Oncolytic viruses are a special type that infects and kills cancer cells without harming healthy cells. The FDA has approved one oncolytic virus, talimogenelaherparepvec (T-VEC, Imlygic), to treat metastatic melanoma.

Cancer Vaccines

These use your immune system to prevent or treat cancer. Cancer vaccines are made from dead cancer cells, proteins or pieces or proteins from cancer cells, or immune system cells.

Four vaccines are approved to prevent cancer:

Cervarix, Gardasil, and **Gardasil-9** protect against the human papillomavirus (HPV), which is linked to cancers of the cervix, throat, vagina, vulva, anus, and penis.

Hepatitis B (HBV) vaccine (HEPLISAV-B) protects against HBV infections that can cause liver cancer.

Three vaccines are FDA-approved to treat cancer:

Sipuleucel-T (Provenge) treats advanced prostate cancer when hormone therapy doesn't work.

Talimogenelaherparepvec (T-VEC) treats melanoma skin cancer that has spread.

Bacillus Calmette-Guérin, or **BCG,** treats early-stage bladder cancer.

Scientists are studying other cancer vaccines in clinical trials

5)Immune System Modulators

Other types of immunotherapy boost the activity of your immune system in general. A more active immune system can better fight cancer. These drugs fall into a few classes:

Interleukins are a type of cytokine, a protein that some white blood cells make to control your immune system's response to cancer. A man-made version of the interleukin IL-2 increases the number of T cells and NK cells in your body. The IL-2 aldesleukin (Proleukin) is approved to treat advanced kidney cancer and metastatic melanoma.

Interferons are another type of cytokine that makes your immune cells more active against cancer. IFN-alfa treats cancers such as leukemia, sarcoma, lymphoma, and melanoma.

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Imiquimod (Aldara, Zyclara)

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Side effect of immunotherapy

Some side effects are common with all types of immunotherapy. For instance, you might have skin reactions at the needle site, which include:

- pain
- swelling
- soreness
- redness
- itchiness
- rash

You may have flu-like symptoms, which include:

- fever
- chills
- weakness
- dizziness
- nausea or vomiting
- muscle or joint aches
- fatigue
- headache
- trouble breathing
- low or high blood pressure

Other side effects might include:

- swelling and weight gain from retaining fluid
- heart palpitations
- sinus congestion
- diarrhea
- infection
- organ inflammation

Some types of immunotherapy may cause severe or fatal allergic and inflammation-related reactions. But, these reactions are rare.

Challenges in immunotherapy -

1] Efficacy Is Often Unpredictable-

A major challenge for cancer immunotherapies is the need to develop agents that are consistently effective in a majority of patients and cancer types. Dramatic results have been observed in some patients treated with cancer immunotherapies, indicating that it is feasible to restore effective antitumor immune surveillance. However, to date, many immunotherapy treatments have demonstrated efficacy in only a select group of cancers.

2] Difficulty Identifying Clinically Significant Biomarkers-

In tumor models, a single-driver mutation is capable of conferring distinct biological properties and powering oncogenic capabilities, making tumor cells strongly dependent on that genomic alteration for survival. Such driver mutations are found in small subsets of patients across different solid tumors. The immune system can control malignancies by targeting the genetic mutations that lead to oncogenic outgrowth. It is therefore important to develop cancer immunotherapies that enhance TSA-specific T-cell reactivity. Because TSAs are expressed only by tumors, this approach offers the potential of high specificity, which will likely enhance both efficacy and safety.

3] Need for More Predictive Biomarkers-

Clinical biomarkers may have diagnostic, predictive, prognostic, or pharmacogenomic value.Predictive biomarkers are the most useful in daily practice because they enable selection of patients who will obtain the greatest benefits from a treatment, as well as exclusion of patients who are unlikely to respond. Prognostic biomarkers are predictive of patient outcomes irrespective of treatment, and they are therefore used less frequently for treatment decisions. The successful development of clinically significant biomarkers depends upon three features: their biological role with respect to malignant transformation and tumor progression; the ability to detect them with robust, reliable, and clinically applicable analytical genomic tests; and their prognostic or predictive value, as validated in clinical trials.

Recent advancement in immunotherapy -

1]The Tumor Microenvironment-

Tumor and host interaction shapes local and systemic immunity to promote tumor development and the immunosuppressive tumor microenvironment . The TME is heterogenous and varies by patient, cancer subtype and stage. TME composition influences cancer immunotherapy patient responses . To improve immunotherapy efficacy, it is critical to understand TME cellularity and functionally. Tumor cells drive TME formation by forming physical barriers, inhibiting immune cells and recruiting immunosuppressive cells. Tumor cells secrete immunosuppressive cytokines (e.g., TGF-b, IL-10, VEGF), drive expression of inhibitory receptors and ligands (e.g., PD-L1/2, CTLA-4) and reduce tumorspecific MHC-I antigens.

2]Tumor-Associated Macrophages and Other Immunosuppressive Myeloid Cells-

TAMs constitute most of the non-tumor stromal mass in solid tumors and modulate tumor growth and immunosuppression within the TME . TAMs are protumoral and have M2-like functions . They promote tumor growth and metastasis via antiinflammatory cytokine secretion and immunosuppressive immune cell interactions and recruitment . Similar to TAMs, myeloid-derived suppressor cells (MDSCs) are pathologically activated, immature, potent immunosuppressive cells at various stages in differentiation . They are subdivided into mononuclear MDSCs (M-MDSCs), morphologically similar to blood monocytes, and polymorphonuclear (PMN-MDSCs), which are morphologically similar to neutrophils . Their recruitment from bone marrow to secondary lymphoid organs and TME by cancer-cell-secreted growth factors promotes overall protumorgenic activity by inducing NK and T-cell inhibition, allowing tumor immunoevasion . Poor prognosis and OS were correlated with solid tumor MDSC abundance . Tumor-associated neutrophils (TANs) also have critical functions within the TME. N1s instruct effector T cells to reject tumor cells and N2s dampen the immune system by enlisting M2s and Tregs . Shorter survival rates in HCC and poor prognosis for DLBCL have both been associated with TANs . Due to their abundance in blood and their immediate reaction to inflammation and injury, their influence in the TME can set the tone for other immunosuppressive cells.

3]Approaches to Enhance ICI Therapy-

Given the response rates seen thus far with currently FDA-approved ICI therapies, it is unlikely that one type of ICI will overcome the various mechanisms of resistance employed by different types of tumors. Targeting aspects of the TME to overcome tumor resistance has shown promise in enhancing ICI therapy Targeting the CXCR4/CXCL12 (SDF-1) signaling pathway can help overcome the physical barrier of the TME and enhance ICI. CXCR4 is upregulated on MDSC/TAMs, playing a role in intratumoral fibrosis, and is associated with poor prognosis in several types of cancer. Nanocomplex technology, polymer-based combinatory approaches and liposomal formation have been used to combine anti-PD-L1 agents and CXCR4 antagonists to overcome ICI resistance . Increased effector T-cell infiltration, decreased Treg and MDSC populations and inhibition of primary tumor growth and metastasis were all observed in several tumor models. Nanoparticle technology applying a CSF1R inhibitor in combination with ICI allowed for the development of a sustained codelivery method that successfully reprogramed TAMs to an antitumoral M1-like phenotype and enhanced their phagocytic capabilities in a melanoma model . In glioblastoma, overcoming the TME physical barrier is also being explored. One group combined brain-tumor-targeted peptide-coated extracellular vesicles, loaded with small interfering RNA (siRNA) against PD-L1, and then delivered them with bursts of radiation therapy .

4]**Strategies to Improve CART Therapy** –

CART efficacy has achieved a high degree of success in hematologic malignancies. However, certain patients with risk factors, such as tumor bulk and a highly immunosuppressive TME, have worse outcomes. CART in solid tumors, in particular, has been characterized by a lack of efficacy due to the highly immunosuppressive TME present, resulting in impaired CART trafficking and suppressed proliferation and activation within tumors .

CONCLUSION-

Although there are various alternative treatment regimens, cancer still remains as the second leading cause of death globally according to a 2021 WHO report. Many approaches are used in clinical settings to eliminate cancer, such as chemotherapy, radiotherapy and surgery. Immunotherapy is more recent than these therapies and includes cellular therapy, antibody therapy, vaccine therapy, and nonspecific therapy. Nanotechnology-based therapies have been launched as novel and more selective therapeutics for cancer treatment. For an eventual improved efficacy, nanoparticulate drug delivery system combined immunotherapeutics are being developed both in vitro and clinically.

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