CURRENT UPDATES ON IMMUNOTHERAPY AND THE SCOPE OF NANOMEDICINE IN CANCER THERAPY

Abstract

A brief history Cancer immunotherapy has brought significant improvements in survival and quality of life. It has established itself as a pillar of cancer care. We emphasize how advancements in cancer immunotherapy have been made possible by its history. The current drawbacks and restrictions of checkpoint immunotherapy are also highlighted. The formation of tumors has been demonstrated to be significantly influenced by immune infiltrates in the tumor microenvironment. The processes of cancer-immune evasion might be better understood with more research and discussion against immune cells that infiltrate tumors. We summarize the most current advancements in cancer immunotherapy, Monoclonal Antibody therapy, Dendritic Cell Cancer Therapy, checkpoint inhibition, CAR T cell therapy, and Oncolytic virus therapy, and in the field of nanomedicine is regarded as an innovational field with potential for improving cancer treatment Although the use of nanotechnology in medicine is still in its infancy, it is anticipated to have a transformative effect on the delivery of healthcare. In comparison to conventional medicines, nanomedicine has the potential to be more effective, bioavailable, dose-responsive, targetable, customizable, and safe. The design and development of multifunctional nanoparticles may be the most inspiring idea in nanomedicine research. (NP) complexes that are

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capable of simultaneously delivering therapeutic and diagnostic substances to specific areas. These characteristics are unmatched and signify a significant improvement in patient diagnosis, treatment, and monitoring.

Keywords: Cellular therapy, immunotherapy, treatment, nanomedicine, CART T therapy, cancer vaccines and Drugs design.

I. INTRODUCTION

The leading cause of death in the twenty-first century is considered to be cancer. The World Health Organization (WHO) reports that, in most countries, cancer was the first or second leading cause of death before the year 2015 reached the turning point of 70. It is anticipated to increase to 21.4 and 13.2 million annually by 2030. Globally, the incidence and death of cancer are both rising quickly. Although there are many complicated variables contributing to the rise in cancer cases, aging, population expansion, and changes in significant cancer risk factors, many of which are correlated with socioeconomic development, are the main culprits.

A set of disorders known as cancer are characterized by an abnormal cell proliferation that can infiltrate or spread to different bodily parts. As a result, by improving the prognosis of many patients with a variety of hematological and solid malignancies, immunotherapy has established itself as a pillar in the treatment of cancer. Cancer immunotherapy has expanded and is focused on developing effective treatment methods to increase the accuracy and potency of the immune system to fight malignancies. There are three primary types of immunotherapy treatments used today. The first method involves shutting down immunological checkpoints; the second involves adoptive cellular therapy; and the third involves vaccination. Immunotherapy seeks to stabilize the immune system in order to eradicate cancer cells and the disease. In this review article, we will provide a complete overview of nanomedicine- liposomes and drug delivery mechanism, advanced therapies – immunotherapy, Monoclonal Antibodies therapy, Dendritic Cell Cancer Therapy, checkpoint inhibition, CAR T cell therapy, Oncolytic virus therapy .

II. IMMUNOTHERAPY

Immunotherapy is a type of cancer treatment that boosts immunity and aids the body in locating and eliminating cancer cells. It is a biological therapy that can be used to treat many cancer kinds. The immune system is thought to stop or reduce the growth of many malignancies by identifying and eliminating aberrant cells. Cancer cells, however, are able to avoid being destroyed by the immune system. By inhibiting immunological checkpoints, enhancing T cells, or employing monoclonal antibodies, immunotherapy helps the immune system fight cancer more effectively. There are numerous routes to provide immunotherapy, including intravenously (IV), orally, topically, and intravesically T cells, B cells, cytokines, interferon, and NK cells are examples of immune system reaction cells [2].
Immunotherapy can be classified into three forms on basis mode of action:

1. **Active Immunotherapy**: Agents that induce acute infections have been successfully treated with active immunotherapy. Active immunotherapy targets the body's cells and elicits an immune response. Active immunotherapy is used for the treatment of neurodegenerative disorders person's prion disease multiple sclerosis, Alzheimer's disease, etc [1]. The categories of active immunotherapy are:

    - **Non-specific activity active immunotherapy** It generates immune response using cytokines and other cell signaling molecules Examples: cytokines, and BCG vaccines [4].

- **Specific active immunotherapy**: It uses specific antigens as its therapy allowing the host to create antigen-specific response development against antibodies by helping in the recognition of cytotoxic t lymphocytes or malignant tumor cells in the case of Cancer Therapy [2].

2. **Effective immunotherapy**: is employed in the treatment of cancer or chronic infectious diseases to maximize the interaction between antigenic peptides, antigen-presenting cells, and T cells that disrupt the negative regulatory mechanism that prevents the immunotherapeutic effect from occurring [1].

3. **Passive immunotherapy:** It was created in (1888), when Emil Roux and Alexandre Yerson isolated the diphtheria toxin from the bacteria. They then administered modest doses of the toxin to animals to produce serum that included antibodies (antitoxin), which served as a passive treatment for diphtheria. It is also known as serum treatment; it has a successful track record in the clinic and employs monoclonal activities or receptor FC fusion proteins. Immunotherapy is used to treat a variety of cancers, including those of the bladder, brain, breast, liver, lung, lymph nodes, melanoma, ovary, stomach, and leukemia [1]**.**

Immunotherapy can be classified into two major categories on basis of site of action: Non **target immunotherapy** and **Targeted immunotherapy.**

III. TARGETED THERAPIES

Cancer can be treated using targeted therapy, by using medications to specifically target genes and proteins that aid cancer cells in surviving and expanding. The tissue environment and cells involved in the formation of cancer, such as blood vessel cells, can be impacted. Many different cancers can be treated with targeted therapy. It can also be used in conjunction with other cancer therapies like chemotherapy. Targeted therapies are currently not accessible for all malignancies, but this is an area of study that is expanding quickly, and numerous new targeted therapies are being tested in clinical studies.

1. **Monoclonal Antibodies Therapy**: In 1975, Köhler and Milstein's discovery of monoclonal antibodies sparked a wave of interest among medical professionals. Immune cells that are identical clones of their parent immune cell make up monoclonal antibodies, which are antibodies. The same epitope is the target of monoclonal antibodies' monovalent affinities. [3].

Monoclonal antibodies are used in diagnosing and treating various human disorders, including cancer and infectious diseases, by modulating immune responses. Recent advances include targeting cell-surface structures, genetic engineering, and using toxins or radionuclides to enhance their effectiveness. Recent advances in monoclonal antibodies (mAbs) have led to the approval of bevacizumab and cetuximab, which have shown significant benefits in oncology. These antibodies induce clinically significant anti-tumor responses, extend survival in metastatic malignancies, and decrease relapses in breast cancer patients when combined with conventional treatment. However,

administration challenges, toxicity issues, and inadequate tumor targeting continue to impede the development of radioimmunoconjugates [3].

2. Monoclonal Antibodies Approved by the us Food and Drug Administration [1]

- Muronomab- CD3 (Orthoclone OKT3) [1986]
  TARGET OF ACTION - CD3 antigen on T cells
  CONDITION- Transplant allograft rejection
- Abciximac (ReoPro) [1994]
  TARGET OF ACTION -Glycoproteins IIb and IIIa on activated lymphocytes
  CONDITION- cardiovascular disease
- Daclizumab (Zenapax) [1997]
  TARGET OF ACTION - CD25 (IL-2Rα, Tac) on activated lymphocytes
  CONDITION- Transplant allograft rejection
- Trastuxumab (Herceptin) [1998]
  TARGET OF ACTION - HER2 oncoprotein
  CONDITION- Metastatic breast cancer
- Alemzutumab (Campath 1H) [2001]
  TARGET OF ACTION - CD52 on B, T, and NK cells and monocytes
  CONDITION- Chronic lymphocytic leukemia
- Ibritumomab tiuxetan (Zevalin) [2002]
  TARGET OF ACTION - CD20 on B lymphocytes
  CONDITION- Non-Hodgkin lymphoma

3. Small Molecule Drug: These are Small-molecule drugs. Medicines called small molecule drugs can block a process that helps cancer cells multiply and spread. Some drugs mentioned are given in Table 1 given below.

Table 1: Approved some of the selective small molecule kinase inhibitors.

Sno.	CLASS	DRUG NAME	FIRST APPROVED
1	ABL	Asciminib (scemblix)	2021
2	KIT	Avapritnib (ayvakit)	2020
3	HER	Tucatnib (tukysa)	2020
4	ALK	Lorlatinib (lorviqua)	2018

IV. CELLULAR THERAPIES

1. **Dendritic Cell Therapy:** Professional antigen-presenting cells (APCs), of which dendritic cells (DCs) are a subset, can dwell in organs and move between lymphoid and other organs. MHC class I and II antigens are processed and presented by DCs simultaneously in the steady state. After being exposed to antigens, they continue to become activated. Recently, a number of strategies have been applied to boost the effectiveness of antigen presentation in order to trigger powerful immune responses against tumor cells [19]. DCs from the patient are extracted and modified ex vivo in DC-based cancer immunotherapy in order to entice the immune system to attack tumors. The long-term antitumor immune responses of DCs have been evaluated using a variety of methods. Contrarily, the combination of DC vaccinations with other cancer medications like chemotherapy and monoclonal antibodies can result in an efficient anticancer regimen [19].

2. **Checkpoint Inhibition:** Inhibitors of checkpoints are a kind of immunotherapy. They limit the immune system's ability to fight cancer cells by blocking specific proteins. Certain forms of treatment may not always be appropriate for cancer medications. The term "checkpoint inhibitor" can also refer to a particular class of monoclonal antibody or targeted treatment. Our immune system keeps us healthy and destroys viruses and bacteria. T cells are one of the key categories of immune cells that carry out this function [9]. T cells have proteins that both activate and deactivate the immune response. Checkpoint proteins are what these are known as. When an infection arises, for instance, some checkpoint proteins aid in the activation of T cells. T cells can, however, damage healthy tissue and cells if they remain active for an extended period of time. The other checkpoints therefore aid in the T cells dying off. Protein production is high in some cancer cells. These have the ability to stop T lymphocytes from attacking cancer cells when they ought to. Cancer cells work in this manner to activate the immune system's stop button. And T cells are no longer able to identify and eliminate cancer cells. Checkpoint inhibitors are drugs that suppress the activity of checkpoint proteins. The following lists a few medications Example PD-1 (programmed cell death protein 1), CTLA-4 (cytotoxic T lymphocyte-associated protein 4), PD-L1 (Programmed cell death ligand 1). They block cancer cell proteins from activating the halt mechanism. This restores the immune system, allowing the T cells to locate and attack cancer cells [9].

3. **CAR (Chimeric Antigen Receptor) T Cell Therapy:** By enhancing your T lymphocytes' (or T cells') capacity to fight cancer, chimeric antigen receptor (CAR) T cell therapy heals several malignancies. CAR T-cell therapy has been shown to be a highly effective method for treating some blood malignancies, even if researchers are still gathering long-term data. Your immune system's white blood cells are known as T cells. By searching for proteins called antigens, your immune system scans your body for invaders such as cancer (as well as infected or other aberrant cells). Invading cells have antigens on their surface. The proteins on your T cells are referred to as receptors. Your T-cell defense team uses its receptors to seize and repel intruders when they are identified by invasive antigens. Your T cells can also kill foreign cells. However, the invader genes have a line of defense. They can camouflage themselves to hide from your T cells. Your T cells will be able to pass through the masked or shielded form of the invasive antigen thanks to CAR T cell treatment [21].

It is used to treat diseases like Mantle cell lymphoma, Multiple Myeloma, and B cell acute lymphoblastic leukemia, which affects white blood cells and immature b lymphocytes growing in bone marrow and is treated with chemotherapy and bone marrow transplants [23].

V. ONCOLYTIC VIRUS THERAPY

This kind of treatment employs a genetically modified virus that is not pathogenic and aids the immune system in eliminating cancer cells without damaging healthy cells. The virus is directly injected into the tumor, where it can infiltrate cancer cells and grow out of control until the cancer cell erupts and dies. Cancer cells produce antigens during apoptosis, which causes the immune system to undertake a targeted attack against all cancer cells that share the same antigens. Talimogene laherparepvec (T-VEC) is an illustration of an oncology vaccine therapy authorized for the treatment of advanced melanoma skin cancer. It originates from a genetically modified herpes virus and is injected right into melanoma cells, where it keeps reproducing and eventually kills the tumor cells by bursting them. [30].

Viral vaccines: The viruses can be altered in the lab and used to deliver cancer antigens into the body. They alter viruses so that they can no longer be a major health threat. A viral vector is a modified virus. To introduce cancer antigens into the body, several vaccinations use viral vectors. The viral vector triggers an immunological response in you. This aids in the tumour antigen's recognition and response by your immune system. Viral vaccinations and the medication T-VEC (talimogene laherparepvec), also called Imlygic, are comparable. It makes use of a herpes simplex virus strain that causes colds. The virus was altered by altering the genes that direct the virus's behavior. This instructs the virus to target and kill cancer cells while sparing healthy cells. According to this procedure, the immune system is aided in locating and eliminating more cancer cells. When melanoma skin cancer cannot be surgically excised, T-VEC is now an option for some patients. In the study of head and neck cancer, it is also being considered. Melanoma or head and neck cancer was directly injected with T-VEC [32].

VI. NON -TARGETED THERAPY

1. **Cytokine Therapy:** In the etiology of cancer, the variety of cytokines secreted in the tumor microenvironment is crucial. The growth and spread of tumors can be slowed down by cytokines, which are proteins secreted in response to infection, inflammation, and immune responses. IFN regulates MHC class I surface molecules, encourages caspase-dependent apoptosis in some cancer types, inhibits angiogenesis in tumor vasculature, polarizes immune responses against Th1, boosts NK cell cytotoxicity and survival, stimulates the production and survival of CTL cells, memory CD8 T cells, and encourages dendritic cell (DC) maturation. A different possibility is that cancer cells react to cytokines produced by the host and that encourage proliferation, hinder apoptosis, and aid invasion and metastasis. Improved cancer immunotherapy is possible thanks to a deeper comprehension of cytokine-tumor-cell interactions. Examples are INTERFERONS and INTERLEUKINS [31].

2. **Bacillus Calmette Guerin (BCG):** The conventional treatment for bladder cancer that is non-muscle invasive and has a high risk of recurrence or progression is BCG immunotherapy. Preclinical and clinical research has demonstrated that a number of processes are necessary for a strong inflammatory response to BCG, including BCG fixation, internalization by established immune cells, healthy cells, and tumor urothelial cells, BCG-mediated induction of innate immunity arranged by the cellular and cytokine environment, and induction of BCG-mediated tumor-specific immunity [20]. Differences between clinical BCG strains can affect how tumor immunity develops, thus adding to the complexity. A deeper comprehension of the processes underpinning BCG-mediated tumor immunity can lead to new immune-based treatments that are more tolerable, more effective, and more effective. In fact, as targeted immunotherapies, such as checkpoint inhibitors, become accessible, interest in bladder cancer immunotherapy and the potential for combining BCG with other treatments is rising. BCG immunotherapy's mechanism of action has been better understood, but there are still many unanswered problems, and additional basic and clinical research is required to create new bladder cancer treatment regimens [20].

VII. CANCER STEM CELLS

CSCs can continuously divide & give rise to identical daughter cells, leading to the expansion of the CSC population within the tumor. CSCs can differentiate into various cell types present within the tumor, contributing to cellular heterogeneity and tumor plasticity CSCs can be isolated and identified on the expression of specific cell surface markers, such as CD44, CD133, ALDH1[6].

1. Rationale for targeting cancer stem cells and tumor microenvironment in cancer therapy-

- **Tumor Heterogeneity:** Cancer Stem Cells (CSCs) contribute to tumor Heterogeneity by giving rise to different cell types within the tumor. Targeting CSCs allows for more effective elimination of cells responsible for tumor initiation, growth, and therapeutic resistance.
- **Tumor Initiation & Recurrence:** CSCs possess self-renewal and differentiation capabilities.
- **Metastasis & Invasion -** CSCs play a key role in Tumor metastasis and invasion by initiating the formation of pre-metastatic niches and promoting epithelial-mesenchymal transition (EMT). Targeting CSCs may prevent or inhibit these processes, limiting tumor spread [7].
- **Angiogenesis and Nutrient Supply:** Targeting TME can disrupt angiogenic processes, leading to tumor degeneration.
- **Synergistic Effects:** Simultaneous targeting of CSCs and TME can result in Synergistic Effects, as the interaction and crosstalk between these components greatly contribute to tumor progression and therapy resistance.

VIII. HYPOXIA- TARGET THERAPY

Low oxygen levels, or hypoxia, are a characteristic of solid tumors that frequently contribute to tumor growth and therapy resistance. By boosting tumor oxygenation and lowering therapeutic resistance, these therapies can increase the effectiveness of cancer treatments.ER and the hypoxia-inducible factor HIF-1 regulate a number of genes in an even-handed manner [28].HIF-1-conciliate hypoxia confers radio resistance and chemoresistance in colorectal cancer (CRC), hypoxia mediates self-renewal of glioblastoma stem cells (GSCs), maintains their phenotype, and is likely related to the HIF-2 factor, according to studies on MCF-7 xenografts. Hypoxic breast cancer cells might become more sensitive if the hypoxia-induced amino acid transporter SNAT2 is chosen and targeted [27].

1. **Advancement in TME Characterization Techniques:** Improvement in TME characterization techniques is crucial for better understanding the complex interactions between tumor cells, stromal cells, and extracellular matrix. Novel imaging technologies, such as Multiplex Immunohistochemistry, and Multiphoton Microscopy, enable high-resolution visualization of the TME components. Single-cell sequencing techniques allow to identification of various cell types within the TME and their gene expression patterns [29].

2. **CSC Inhibitors and Significance:** CSCs emerged from studies of Acute Myeloid Leukemia (AML) due to the isolation of hematopoietic cell surface antigens by flow cytometry. CD44 is a significant marker of cancer stem cells and it's a cell surface glycoprotein that is characterized by its numerous isoforms it acts as a sticking molecule that has a key role in signaling and migration.

3. **Therapeutic Approaches**

    - The most specific Treg marker is Forkhead box P3 (FOX P3).
    - An FDA-approved monoclonal antibody Daclizumab is raised against the CD25 receptor which is effective for decreasing circulating T cells.

4. **Preclinical & Clinical Trials Assessing the CSC Targeted Therapeutics:** Preclinical trials are carried out in the laboratory using animal models, or cell lines for the assessment of the potential of novel drugs. Advancement In the Characterization Techniques- Multiplex immuno-chemistry and Multiphoton Microscopy are novel imaging techniques that enable high visualization and high resolution of TME components.

5. **Cancer Stem Cell Markers in Common Cancers & Its Therapeutic Implications:** It has recently been shown that the hyaluronan receptor and stem cell markers like CD44 and MDR-1 have a molecular connection in breast and ovarian cells. Future Trends & Clinical Implications Bevacizumab is a drug. Target: Vascular endothelial growth factor-blocking antibody breast, ovarian, lung, and colon cancer Substance: Sorafenib Inhibition of Tyrosine Kinase Receptors as the Target, Renal Cell Carcinoma as the Cancer Type.

IX. NANOMEDICINE

Nanomedicine is one of the fastest growing areas in nanotechnology and is composed to revolutionize healthcare and medicine. Nanomedicine heralds a new opportunity for drug delivery to improve treatment indicators. Many biological hurdles affect drug delivery in cancer like renal, hepatic, etc. Nanoparticles loaded with drugs can be designed to overcome these hurdles [26].

1. **Nanoparticles:** Nanoparticles are defined as particles with one dimension less than 100 nm with different properties commonly not found in large samples of the same material.

2. **Types of nanoparticles**
   - Polymeric nanoparticles (polymer-drug conjugates): A linker is used to conjugate these pharmaceuticals to the side chain of a linear polymer. They are biodegradable and water soluble. e.g., Abraxane, which targets malignant cells specifically
     Polymeric micelles: -
   - Amphiphilic copolymer joins together and forms a micelle with a hydrophilic shell and hydrophobic core. They are carriers for water-insoluble drugs. ex- PEG Pluronic DOX (targeting ability) [16].
   - Dendrimers: --Spiral appearing highly branched synthetic polymer with regular design and repeated unit. ex- PAMAM- MTX (multifunctional, controlled degradation) [17].
   - Liposomes: --Self-build closed colloidal structure consisting of the lipid bilayer. ex- Pegylated liposomal DOX (targeting potential) [15].
   - Viral nanoparticles: - Protein cage with polyvalent, self-assembled structure. Surface modified by mutagenesis. ex-HSP-DX (specific tumor targeting)
   - Carbon nanotubes: - These are carbon cylinder collections of benzene rings. Organic functionalization. ex-CNT-MTX [1].
   - Gold nanoparticles: - Safer cancer agent. Excellent drug and anti-cancer agent carrier in cancer therapy [25].

3. **Liposomes:** They are spherical bilayer vesicle which has one or more lipid layer, known as liposomes. That can be used to insert both hydrophobic and hydrophilic drugs. Liposomes have been considered accomplished drug vesicles. Liposomes display great features like site targeting, lower toxic side effects, sustained or controlled release, high therapeutic effect, and protection of the drug from decay [15].

4. **Structure and main components of liposomes:** The main components of liposomes are phospholipids and cholesterols.
   Liposomes can be categorized into 3 types
   - Unilamellar vesical (ULVs)
   - Oligolamellar vesicle (OLVs)
   - Multilamellar vesicles (MLVs) [15]

5. **The process of drug delivery by liposomes includes:** Methods determine how MLVs or ULVs are prepared.
   - The film hydration technique is useful for loading hydrophilic drugs.
   - The double emulsification method: this technique produces solvent extraction, microfiltration, water-in-oil and water-in-oil-in-water emulsions.
   - Water-miscible organic solvent is used to combine lipid material and hydrophilic substance before being injected into the aqueous buffer.
   - Liposomes that are prepared in situ are those that are created prior to clinical use.
   - Size reduction: Several techniques, including sonication by bath or probe, extrusion, and French press, are available to reduce the size of liposomes. Extrusion and high-pressure homogenization (HPH) are two often employed techniques [14].

6. **Drug targeting:** Drug loading: high drug loading is required to minimize the number of additives to reach a therapeutic agent. The two drug targeting methods are active and passive targeting [13].

   - **Active targeting**: Active targeting targets the cancerous cell by direct interaction between receptor and ligand. The ligand on the nanoparticles is chosen to target the molecule that is highly expressed in the cancerous cell, which differentiates between Targeted cell from the healthy cell [13].

   - **passive targeting**: Passive targeting is designed to differentiate tumor and normal tissue. The drug is reached to the target site to act as a therapeutic. A high increase of cancerous cells prevails upon neovascularization and huge pores in vascular wall led to bad imbibition of tumor vessels in comparison to normal vessels [13]
     - Buffer exchange and concentration
     - Therapeutic molecule is loaded in liposomes to tumor cells
     - Particle size and size distribution
     - Surface modification
     - Lyophilization if needed packaging.

X. CONCLUSION

The focus of treatment, or "cancer-immune arrangement," has shifted as the field of cancer immunotherapy has developed, from the hospital's treatment to the specific biological properties of the tumor and its interaction with the patient's innate immune system. Since the immune system has a memory and because immunotherapy is always employed to identify and eradicate tumor variations when they emerge, it has inherent advantages over other treatments that do not have these two crucial components. Cancer immunotherapy must specifically develop strategies to influence the immune system in (perhaps most) patients who have little or no immune response to their tumors, right down to the tumor the microenvironment is a "immune desert" lacking tumor-infiltrating T cell. To continually advance, novel discoveries are required.

XI. AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as fellow: A.R., A.M., R., A.M., DATA collection and manuscript preparation; D.D. DEAN: study conception and design, and critical analysis. All authors reviewed the result and approved the final version of the manuscript.

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