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IMMUNO-ONCOLOGY OF CANCER THERAPY

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ABSTRACT: The four primary forms of cancer therapy used in the last ten years have been surgery, radiation, chemotherapy, and targeted therapy. Still, immunotherapy has emerged as an essential aspect of cancer treatment, offering patients a better quality of life and increased chances of survival when compared to prior medicines. A cancer surgeon by the name of Dr. William Coley made the initial discovery of cancer immunotherapy in the 1890s. He found that giving specific bacteria to cancer patients occasionally caused tumors to shrink or even completely disappear. Currently, 22 different cancer types and one tissue-agnostic cancer indication are treated with immune checkpoint inhibitors and two CAR-T (treatment to treat blood malignancies) products that have been approved for the market.

KEYWORDS: Monoclonal antibody, Cytokines, ICIs, TMB.etc

Introduction

The one of the biggest causes for mortality globally is cancer, and over the past ten years, a lot of investigation has been done to discover novel treatments that can lessen the negative effects of existing ones As tumors expands, tumors grow incredibly diverse, generating a mixed population of cells with different molecular traits and histories of response to treatment. This heterogeneity is observable at both the spatial and temporal levels, and it is the primary cause of the emergence of resistant phenotypes that are stimulated by a selective pressure during treatment delivery [1]. Typically, tumors are viewed as an entire cell population and cancer is treated as a single, universal disease. Therefore, a thorough comprehension of these intricate processes is essential for creating accurate [2].

Applying the immune system of the body to prevent, control, and ultimately eradicate tumor is a form of cancer treatment called immunooncology, also referred by the term cancer immunotherapy. Increasing the immune response's natural ability to protect the body from sickness

A comparatively new and expanding area, immuno-oncology (I-O) is the result of the century's many revolutionary advancements in immunology and cancer treatment. The historical debate over whether or not the body's immune system could even react to cancer at all accounts for this field's uniqueness. William Coley originally put up the concept in 1893 after observing the disappearance of cancer in individuals who had experienced severe bacterial infections [4]; Paul Ehrlich arrived next, suggesting in 1909 that the immune system must have a part in preventing the body from developing cancer [3].

However, their theories were contested by individuals who refused to accept a biological explanation and who insisted that lymphocytes could not tell cancer cells apart from healthy cells. When it was recognized that lymphocytes do, in fact, recognize precancerous cells through tumor-associated antigens (TAAs), they are continually removing them from the body in a process known as "immune-surveillance," which is what gave rise to modern I-O in the 1960s [5]. Over the past few years, the growth rate of cancer has been rising rapidly. There are already more than 200 variations, and that number is rising. Since its inception in the 1800s,

treatment has slowly evolved, giving rise to four major recognized types of treatment. Immuno-oncology methods based on pharmacogenomics and precision medicine [6].
The huge influence that precision medicine can have on survival, particularly in cancer types with a poor prognosis, was recently highlighted by retrospective research including 1,856 pancreatic cancer patients. In the field of IO, drug research and development are quickly moving toward a pharmacogenomic paradigm, in which tumor biopsies are examined for biomarkers to determine which treatments will be most successful for a particular patient [6].

What is immunology?

The natural defence mechanism of the body is the immune system. It is made composed of several organs, cells, and unique compounds that guard you against cancer, infections, and other disorders. The body's natural defence mechanism is the immune system. You are protected from infections, cancer, and other diseases by a group of organs, cells, and unique substances. When an alternate (foreign) organism, such as a bacterium, enters the body, the immune system detects it and launches an attack to stop it from doing any damage. Immune response is the name given to this process. Because cancer cells differ greatly from healthy cells in the body, the immune system will fight them when it can identify them. However, cancer cells frequently discover ways to pass for healthy cells, making it difficult for the immune system to identify them as harmful. They can also alter over time (mutate), just like viruses, which allows them to avoid the immune system's defences. Furthermore, the immune system's defence against cancer cells is frequently insufficient. Our immune system is stimulated by immuno-oncology treatments, which enables it to identify and eliminate cancer cells [23].

History of immuno-oncology Although it has long been understood, it is now more widely acknowledged that tumor cells can be identified and neutralized by the immune system. Early signs of spontaneous regression in some tumors point to the possibility that the immune system is able to identify and destroy early-stage tumor cells. The field of IO was established as a result of patient observations of spontaneous remissions. A spontaneous remission is described as the lessening or eradication of a disease's signs and symptoms without any discernible cause and in the absence of medical intervention. Patients who have recently experienced acute infections are more likely to notice this, especially if they experience fever, which seems to boost the immune system. It is now understood that the immune system can sometimes totally eradicate a tumor. Although recorded in breast cancer, neuroblastomas, certain sarcomas, and embryonal malignancies, spontaneous remissions have been seen in the majority of cancer types, but most frequently in advanced melanoma, renal cell carcinoma (RCC), and urothelial carcinomas [7]. The first person to look into the possibility of IO was William Coley, who successfully treated cancers in the 1890s via immune stimulation. He looked into using bacteria to activate and boost the body's immune system to combat cancer after noticing that cancer patients who had post-surgical infections appeared to recover more quickly than those who did not. Coley's toxin, which was based on attenuated bacteria and is regarded to be the first known IO therapy, was later produced by him as a result of these investigations [8].

The different types of immunotherapies include:

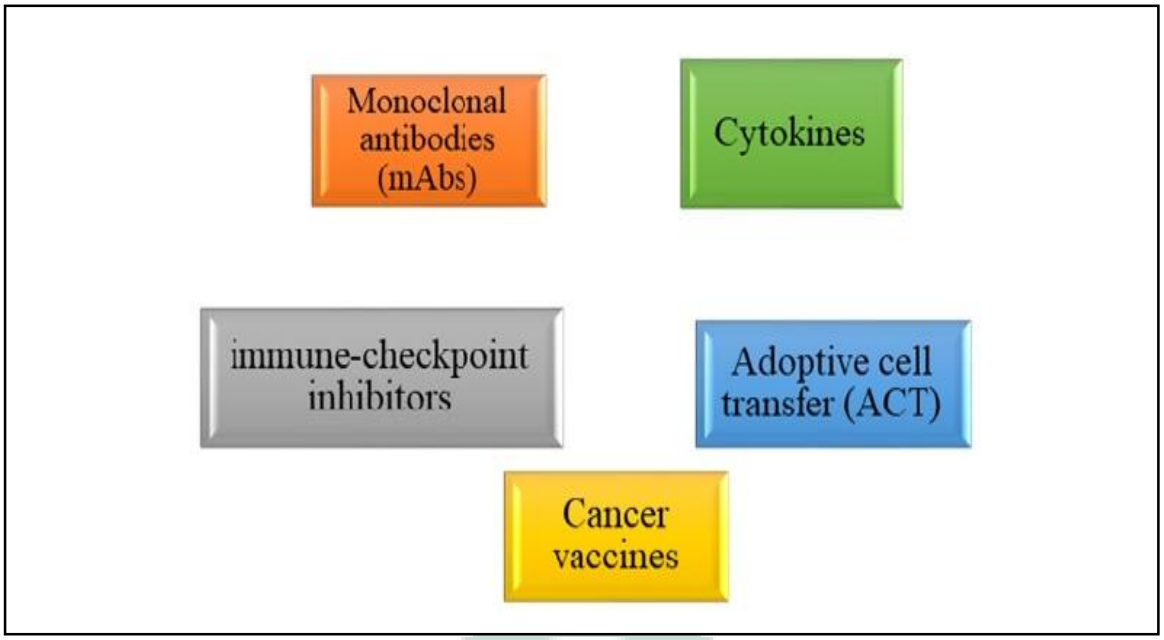

Fig., 1: Types of immunotherapies

Monoclonal antibodies (mAbs)

In the past 20 years, monoclonal antibody-based cancer therapy has emerged as one of the most effective therapeutic approaches for both hematologic and solid tumors [18]. In their 1890 research on animal models of diphtheria, Behring and Shibasaburo were the first to define antibodies as a neutralizing molecule found in blood. Uniquely, antibodies can activate host immune system to produce long-lasting effector responses against the tumor while also directly killing tumor cells. The ability of antibodies to induce potent anti-tumor responses while limiting toxicity & side effects distinguishes mAbs therapy from treatments like chemotherapy and combines a diverse mechanism of action with target selectivity [19].

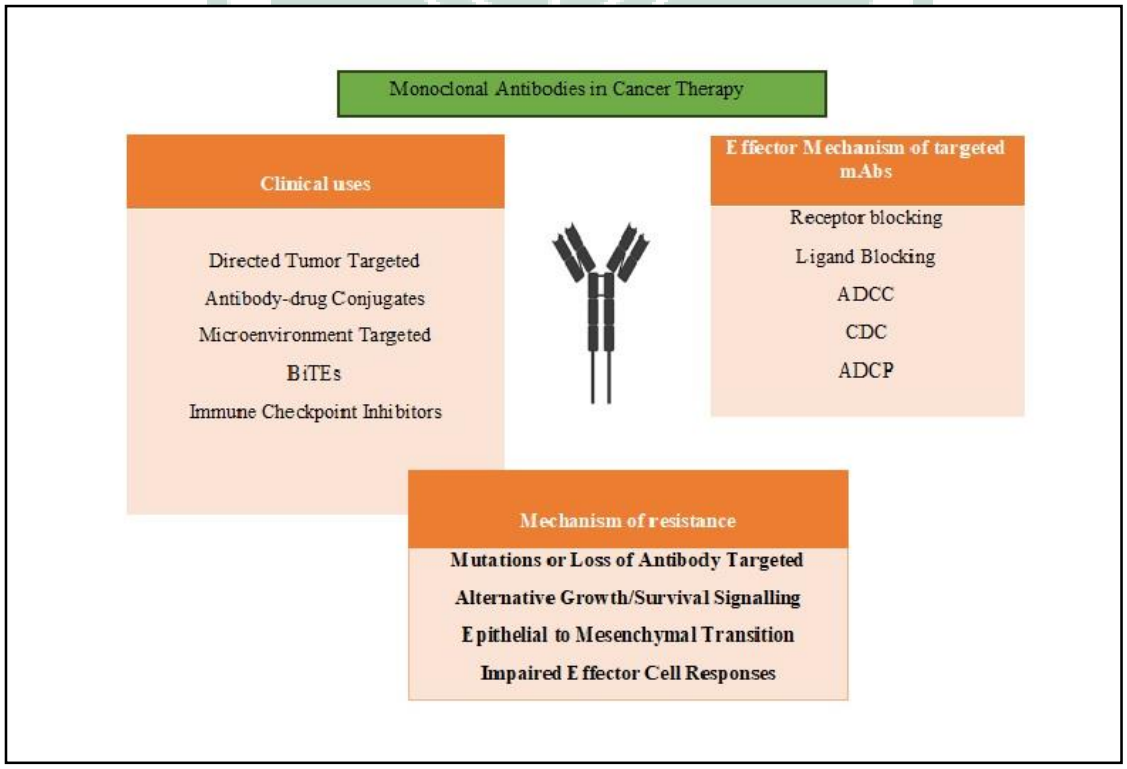

Fig., 2: monoclonal antibodies in cancer therapy

All monoclonal antibodies (mAbs) bind to distinct regions of an antigen, also known as an epitope, and are produced by clones of a single B cell. Schwaber discovered techniques to create human-mouse hybrid cells in 1973, and Köhler and Milstein exploited these techniques to manufacture human-derived hybridomas, which have since been a mainstay in the large-scale manufacturing of therapeutic antibodies [19].

Antibody Structure and Function

Large glycoproteins that are that are referred to as antibodies are member of the immunoglobulin (Ig) superfamily and perform an important role in the immune system by detecting foreign antigens, eliminating them, and triggering other immune system reactions. Their fundamental structure consists of two heavy chains and two light chains arranged in a Y configuration. The fragment of the antigen-binding (Fab) a part of the antibody, which is in charge of recognizing the particular antigenic substance, can be found at each point of the Y. The base of the Y structure's fragment crystallizable (Fc) region promotes interactions between the antibody and other immune system components [20].

Mechanisms of tumor cell killing by antibodies

Direct tumor cell killing
• Cell surface receptor agonist activity (leading to apoptosis) • Cell surface receptor antagonist activity (inhibit signalling, reduce proliferation, induce apoptosis) • Cell surface enzyme neutralization (leading to signalling abrogation) • Conjugated antibody, delivery of payload (drug, toxin, radio-isotope, leading to cell death)
Immune-mediated tumor cell killing
• Induction of phagocytosis • Complement activation • Antibody dependent cell-mediated cytotoxically (ADCC) • Target gene- modified T cells • Activate T cells (through inhibition of T cell inhibitory receptors, such as CTLA-4, or antibody-mediated cross presentation of antigen to dendritic cells)
Vascular and stromal ablation
• Vessel receptors antagonism or ligand trap • Stromal cell inhibition • Conjugated antibody, delivery of payload

Table., 1 mechanism of tumor cell killing by antibodies

Cytokines

Cytokines are molecular messengers that help immune system cells interact with one another in order to produce a well-organized, powerful, yet self-contained response to a specific antigen. An increase in attempts to describe cytokines and utilize their extensive signaling networks to create cancer treatments has coincided with the previous two decades' increased interest in using the immune system to fight cancer. The main cytokines used in cancer immunotherapy will be reviewed, along with their fundamental biology and therapeutic uses, in this paper. Additionally, the paper will discuss new cytokines that are in pre-clinical development, combinations of biological agents, cutting-edge delivery systems, and possible lines of inquiry for cytokine-based research in the future [21].

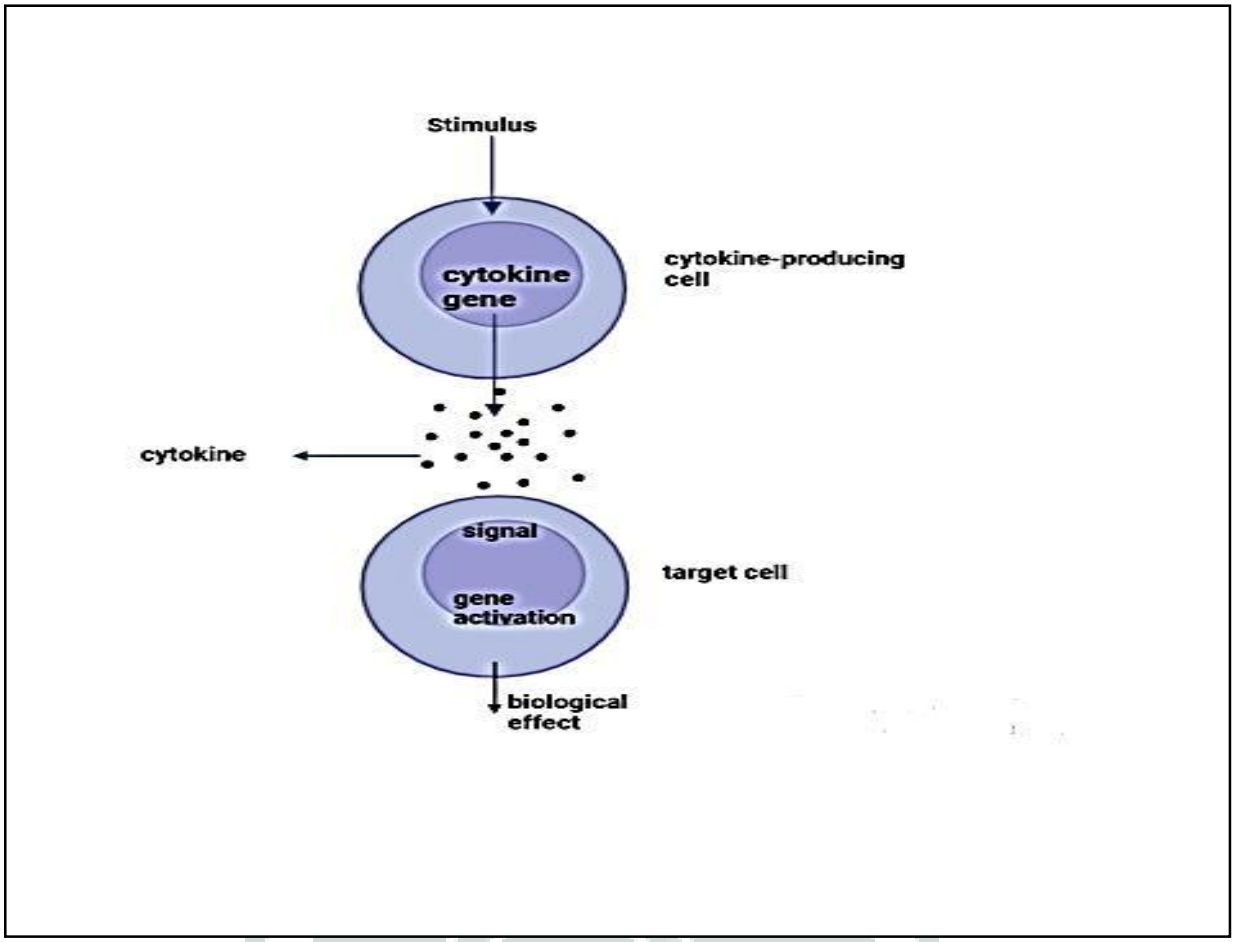

Fig., cytokines therapy

Immune checkpoint inhibitor

Immune checkpoint inhibitors also have fundamentally altered the landscape of cancer immunotherapy. Immune checkpoint inhibitors (ICIs) have revolutionized the field of tumor therapy. In a number of both solid and liquid malignancies, ICIs are now first-line therapies, but radiation therapy and chemotherapy are remains the mainstays of care for a variety of cancer types. ICIs work by releasing T cells' inhibitory restrictions, which activates the immune system aggressively and triggers efficient anticancer immune responses [22]. Over the past ten decades, cancer immunotherapy has advanced to previously unheard-of levels, and the most often used immunotherapeutic medications are blocking antibodies that target immune inhibitory receptors including CTLA-4, PD-1, and PD-L1. Although antibodies against a number of other immune checkpoints, including LAG3, TIGIT, TIM3, B7H3, CD39, CD73, adenosine A2A receptor, and CD47, are already FDA-approved treatments for a variety of cancer types, many of these antibodies and small compounds are still being studied in clinical settings [22].

PD-1/PD-L1 biomarker assays

In more than half of all ICPs that have received approval to yet, the PD-L1 ligand, which is expressed on the surface of several tumor cell types, is an important molecular target. This ligand suppresses the inhibitory activity of the T-cells' PD-1 receptors, which are expressed on their surface. Although PD-L1 is expressed by a variety of normal cells as well, it is up-regulated in tumor cells and immune cells that infiltrate them, shielding them from an immune response [10]. Thus, if patients are chosen for treatment with anti-PD-L1 drugs, evaluating them for tumor cell PD-L1 expression may result in improved clinical outcomes. Pharmacogenomic testing may be advantageous, as evidenced by early clinical studies examining PD-L1 expression and patients' subsequent responses to the anti-PD-L1 drug nivolumab (OPDIVO, Bristol-Myers Squibb); in PD-L1-positive patients, the objective response rate was 36%, while in PD-L1-negative patients, there were no responses [11]. Recent results from additional clinical trials, such as NCT01642004, NCT01668784, and NCT02008227, however, demonstrated that favourable responses and longer overall survival can occur in PD-L1-negative patients33–36 when compared to current standards of care. This makes

it clear that PD-L1 expression status alone is insufficient to decide whether patients should be administered PD-1 or PD-L1 therapy, according to the findings of meta-analyses of clinical trial data [12].

Pembrolizumab (anti-PD-L1) is only licensed for use as first-line therapy for non-small-cell lung cancer (NSCLC) when patients have been tested for PD-L1 expression. Nivolumab (anti-PD-1) and Atezolizumab (anti-PD-L1) were both approved without PD-L1 testing. A threshold is established for the first-line clinical usage of the medicine and is determined by an immunohistochemistry (IHC) test to ascertain biomarker expression. Using the Dako 22C3 IHC assay, PD-L1 expression must be greater than 50%, but for second-line therapy, only greater than 1% expression is necessary. Patients with 5% or higher positive, however, do not benefit from regular treatment, according to a different study [13].

Response rates in PD-L1-positive and PD-L1-negative patients

Numerous cases of PD-L1-negative individuals responding to anti-PD-L1 IO medications exist, and tumor samples immunostained has provided a potential explanation for this [14] PD-L1 expression can vary significantly within a single biopsy, with some regions expressing the protein at very low or no levels and others at high levels [15]. Because of this, a patient might be classified as PD-L1-negative if the portion of a biopsy sample that was tested shows no staining, but additional tumor locations that the biopsy missed might show substantial PD-L1 expression. As a result, based on a single biopsy, it might not be possible to diagnose a patient's PD-L1 status with certainty. While PD-L1 expression levels have been associated with favourable response rates to anti-PD-1/PD-L1 drugs, another potential contributing aspect is that PD-L1 is a dynamic biomarker whose level of expression depends on a variety of biological processes rather than being a static biomarker. The expression of PD-L1, for instance, can be increased by the presence of T cells, but genetic pathways can also result in constitutive expression of PD-L1 [17]. As such, a tumor may initially be PD-L1-negative since there is no T-cell infiltrate, but this scenario may change due to an immune response that may be sparked by the administration of IO drugs. The stage of the disease, prior therapies (such as the type of chemoradiotherapy), tumor mutation status (e.g., PD-L1 expression in NSCLC is regulated by several oncogenic drivers, such as estimated glomerular filtration rate and anaplastic lymphoma kinase, that can alter expression levels), and concurrent drug use (such as corticosteroids) are additional factors that can contribute to biomarker heterogeneity of expression [18].

Emergent biomarkers

In the IO field, there are too many emerging biomarkers to list them all here; nevertheless, a few examples are included below. It has been demonstrated that a high tumor mutational burden (TMB), a measurement of the number of mutations within a tumor genome, is connected with a positive outcome for ICP. For instance, melanoma, NSCLC, and bladder cancer are only a few examples of malignancies that react to anti-PD-1 drugs and have a high mutational load [13]. It has been explored in several studies to link mutational load in NSCLC and melanoma with a response to ICP, but the results have not been able to demonstrate that a high mutational load alone promotes the response to therapy [19]. While PD-L1 expression (in particular tumor types) and high microsatellite instability (MSIH; independent of tumour type) are clinically validated biomarkers for predicting response to pembrolizumab, several newly emerging IO-related biomarkers associated with improved overall response rate (ORR) and progression-free survival (PFS) for ICP are being studied. T-cell-inflamed gene expression profile (GEP), TMB, and mutant mismatch repair (MMR) genes are a few examples of these. Although MSI-H and TMB are proximate indicators of tumor antigenicity generated from somatic tumor mutations, PD-L1 and GEP are both inflammatory biomarkers connected to a T-cell-inflamed tumor microenvironment. In an investigation conducted in 2018 of over 300 advanced solid tumor and melanoma samples collected from 22 cancer types from four KEYNOTE clinical studies, Cristescu et al. assessed the possibility for TMB and T-cell-inflamed GEP to jointly predict clinical response to pembrolizumab, with patients stratified into four biomarker-defined clinical groups of: GEP low/TMB low; GEP low/TMB high; GEP high/TMB low; and GEP high/TMB high [13].

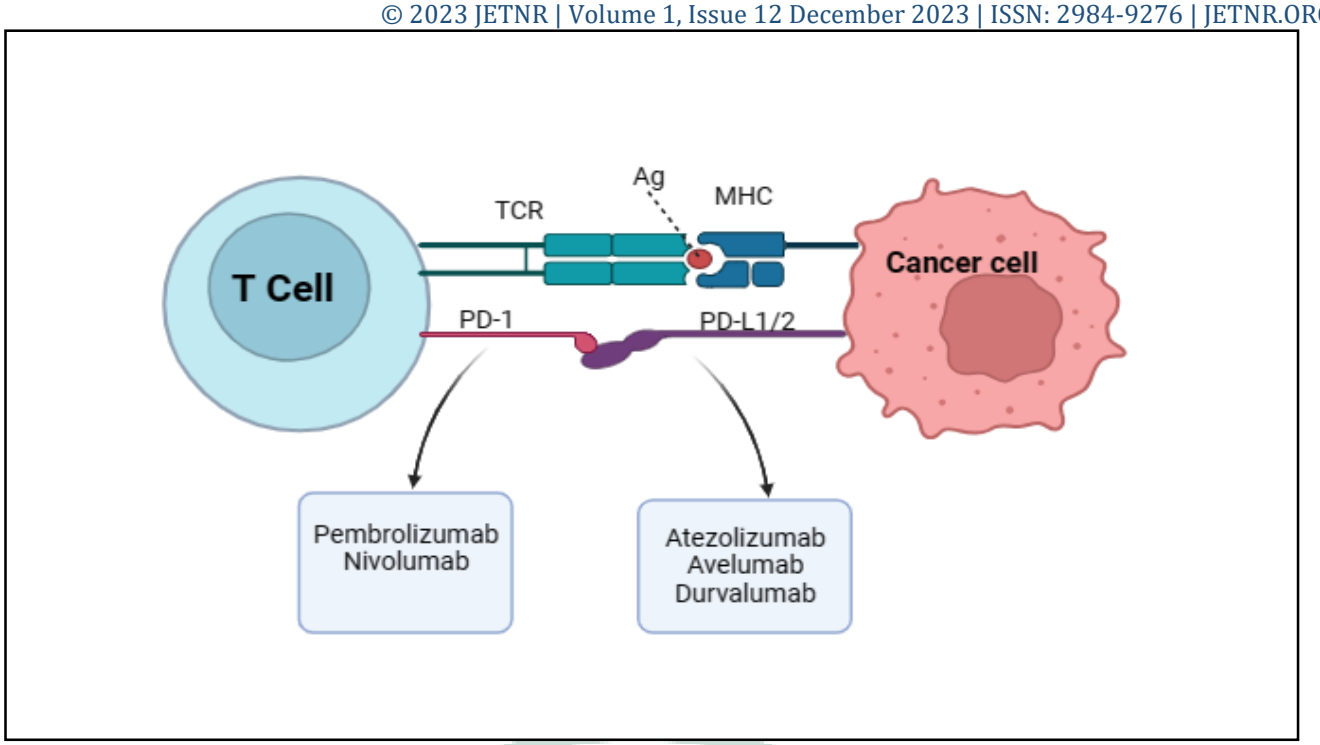

Fig.,Immune checkpoint inhibitor

Adoptive Cell Therapy

The uncommon anticancer immunotherapy technique known as "adoptive cell transfer" (ACT) relies on the ex vivo selection, multiplication, and activation of circulating or tumor-infiltrating lymphocytes before their reintroduction into patients. This treatment is usually often done in conjunction with immunostimulatory drugs and a lymphodepleting pre-conditioning regimen [26]. Adoptive cell transfer therapy has proven to be a productive and viable treatment option for patients with metastatic melanoma. The objective of the forthcoming trials is to raise the rate of constant responses and broaden the patient populations that are eligible for therapy. The administration and production processes for lymphocyte cultures are being improved by current research [24]. Using the patient's own immune system to target tumor cells is a regular aspect of contemporary immunotherapy, which is a common feature of the therapy. CAR T-cell treatment, which genetically alters a patient's own T cells to eradicate tumor cells, is the immunotherapy that is most frequently advised. Any immune system dysfunction could have a negative impact on a patient's future because tumor immunotherapy's success mostly relies on immune function. The substantially poorer success of CAR T-cell therapy in chronic lymphoblastic leukaemia (CLL) patients compared to B-ALL patients is assumed to be due to inborn T-cell abnormalities in CLL patients [25].

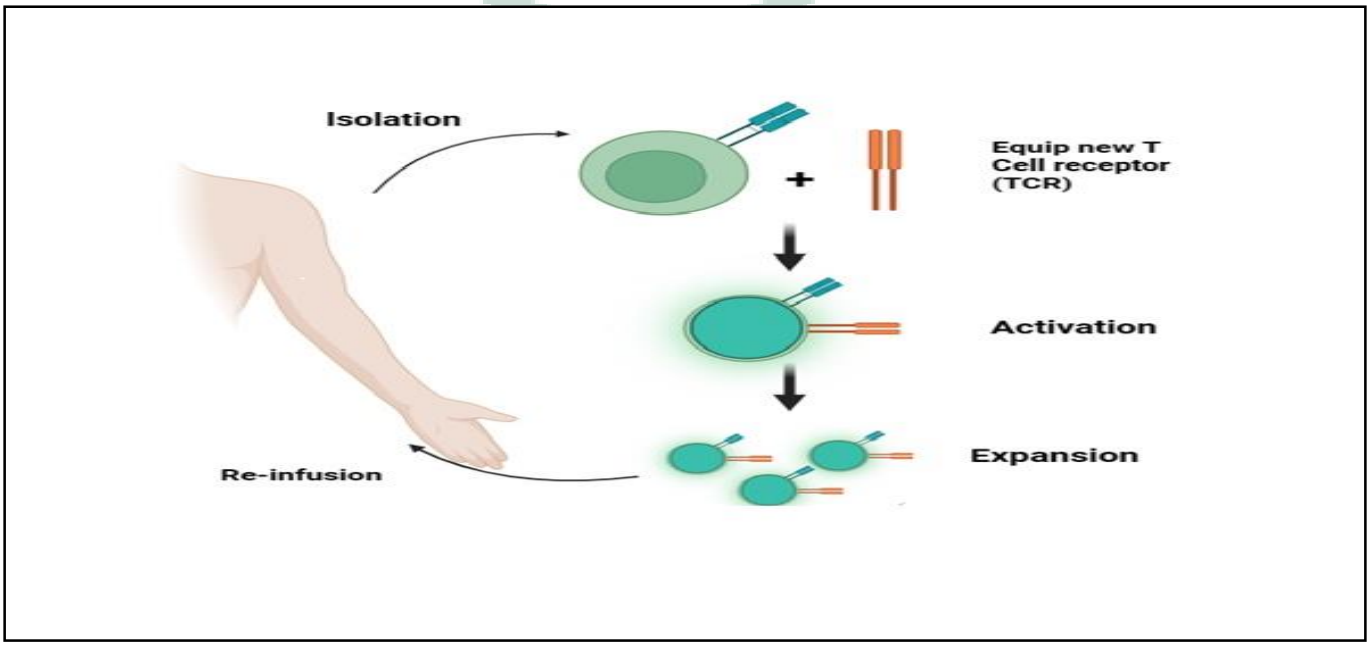

Fig., Adoptive cell transfer therapy

Cancer vaccines

Therapeutic vaccinations are an effective alternative for cancer patients undertaking active immunotherapy, which aims to cure advanced disease by stimulating the patient's own immune system. The U.S. Food and Drug Administration recently approved the first therapeutic cancer vaccination as a result of the clinical studies' encouraging outcomes. This remarkable development sets the standard for rational development and optimization of future vaccines with enhanced anticancer activity in addition to offering a new treatment option for cancer care [27].

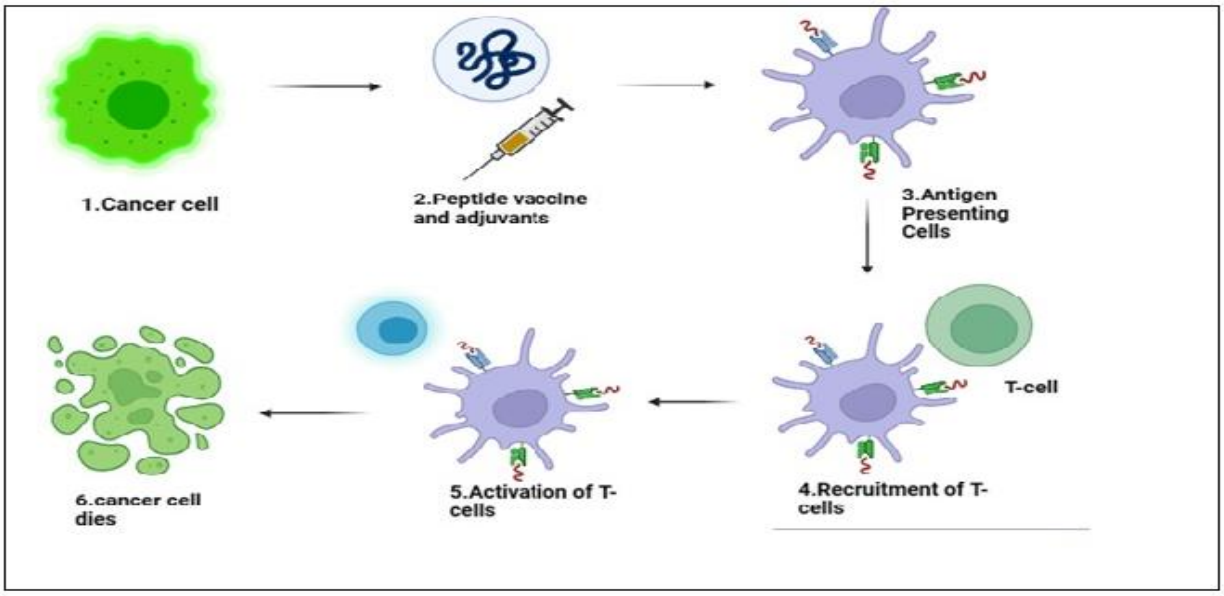

Fig., Cancer vaccines Therapy.

Discovery of specific epitope markers, preferably expressed exclusively on the surface of cancer cells, is necessary for the development of anticancer vaccines. The development process for a carbohydrate-based vaccination against metastatic breast cancer is described in this account [28].

As vaccines depend on foreign non-self-antigens, which are very effective at activating an immune response, vaccines that target diseases are generally effective and protective. In contrast, the effectiveness of therapeutic cancer vaccinations continues to be disappointing. The difficulty of locating tumor-specific target antigens, which should be specific to tumors or, at the very least, overexpressed on tumors compared to normal cells, is one of the main causes of such a poor outcome, among other factors [29]. To get around peripheral immunological resistance and generate a non-toxic immune response, this is the only approach available. To find specific tumor-associated antigens for the creation of cancer vaccination techniques aimed at inducing focused anti-tumor cellular responses, new and more effective methods are now accessible. This issue has received attention in recent years, and numerous therapeutic vaccination techniques based on either complete tumor cells or particular antigens have been and are now being tested in clinical studies. This study provides an overview of the state of cancer vaccines, primarily emphasizing antigen-specific methods [29].

Allogeneic Tumor-Based Vaccination Strategies

Irradiated cells as a whole or lysates of cells can be used to create and give allogeneic or autologous tumor vaccines to patients. These vaccine delivery methods enable the generation of a repeatable, secure vaccine product that prevents the growth of tumor cells after injection [30]. The cellular immune responses of cancer patients, particularly those with melanoma, to autologous tumor cells have been seen. Cancer-testis antigens, differentiation proteins, altered gene products, broadly expressed proteins, and viral proteins are among the antigens identified by tumor-specific T lymphocytes [31].

In addition, irradiated cells naturally express and exhibit a significant amount of TAAs, obviating the requirement to isolate and purify TAAs and encouraging the start of an immune response targeted against the tumor [30]. Lysates are used of tumor cells have also been employed as vaccines to elicit an immune response that fights the tumor [31]. Despite allowing for the presentation of several TAAs, some of these vaccinations have been demonstrated to be entirely useless and to have poor immunogenicity. Immune suppressive substances may play a role in the immune system's incapacity to respond to tumor cell lysates in a sustained manner [32].

Approaches of cancer vaccination

Recent times included the development and clinical validation of numerous cancer vaccine strategies. The ultimate goal is to create vaccines with the ability to boost tumor immunogenicity, improve tumor death without causing harm to healthy cells, and also offer long-lasting anti-tumor immunity. The tumor-associated antigens (TAAs) that are overexpressed in tumors are the target of conventional cancer vaccines, but there is a danger of toxicity to normal cells that also express TAAs as well as of low immunogenicity, which results in subpar vaccination efficacy [34].

Therapeutic cancer vaccines

Ex-vivo activated immune cells, immune modulators (including cytokines), or tumor-specific antibodies are all used in passive immunotherapy. Up to now, antibody-based therapy has proven to be more effective than other immunotherapy techniques, leading to complete regression of tumors in a good majority of treated persons when paired with chemotherapy, while not typically being associated with the development of immunological memory [35]. When targeted at growth factor receptors, certain antibodies can either act directly by inhibiting signal transduction pathways or indirectly by activating NK-mediated killing (ADCC; antibody-dependent cellular cytotoxicity). The active ingredient can also be delivered in a highly precise manner using antibodies that have been coupled to radioactive compounds, chemotherapeutic medicines, or toxins. Other passive immunotherapies based on the selection of the patient's unique anti-tumor T cells and reinfusion in the same patient following in vitro multiplication with cytokine mixtures and/or transduction with highly specific TCRs for tumors also show promise [36].

Dendritic cell-based tumor vaccine

Dendritic cells (DC) that have been transfected with tumor RNA have recently been employed as a cancer vaccine. Examining the effectiveness of a cancer vaccination using DC transfected tumor RNA. The effectiveness of a vaccination using DC transfected with recrudescent tumor RNA for the treatment of a regrowing tumor following earlier immunotherapy was of particular interest. Additionally, the efficacy of co-transfecting granulocyte macrophage colony-stimulating factor (GM-CSF) mRNA to improve the DC vaccination was investigated. Mice injected subcutaneously with DC-CT26 that had been transfected with CT26 mRNA served as vaccines against CT26 tumors [36]. A special system of cells called dendritic cells (DC) is responsible for the induction, maintenance, and control of immune responses. Distributed throughout the body as sentinels, DC are ready to acquire antigen (Ag), travel to draining lymphoid organs, and, following a maturation process, choose Ag-specific lymphocytes to which they deliver the processed Ag, evoking immune responses [38].

The Use of DC in Cancer Therapy

One of the most important variables that must be taken into consideration when developing cancer vaccination strategies is the type of antigen used to load the DCs. This is because it greatly impacts the antigen's ability to access the MHC class I and MHC class II presentation pathways and, consequently, to induce CD8+ and CD4+ T cell responses, respectively. There are still other factors that must be taken into account, such as the amount of antigen to load, the effectiveness of loading, the duration of the antigen's persistence and presentation, and any potential negative effects of the loading approach [39].

Application of DC vaccine in clinics

Experimental evidence has demonstrated the safety and effectiveness of DC-based vaccines for PC immunotherapy in eliciting tumor-specific immune responses. The clinical results of DC vaccination, a possible immunological treatment for PC with metastatic spread, are frequently encouraging. Studies that target metastatic PC have looked into the effects of DC vaccination. For instance, in a phase I pilot study on the MUC1-peptide DC vaccine in metastatic PC patients, Rong et al. discovered that the vaccine improved the immune response to the tumor antigen MUC1 in metastatic PC patients without significantly increasing toxicity [42]. According to Mehrotra et al., poly-ICLC and peptide-pulsed DCs are a possible therapeutic combination for PC immunization that can prevent metastasis by inducing CD8+ T cells. By stimulating CD8+ T cells, Mehrotra et al. discovered that vaccination with peptide-pulsed DCs and the toll-like receptor (TLR)-3 agonist poly-ICLC is a viable therapeutic approach for preventing PC metastasis [40]. Liang et al. investigated the cytotoxic T lymphocyte (CTL) responses caused by DC vaccination for PC with the long-term evaluation of therapeutic responses and showed that DC vaccinations can effectively increase CTL response and prevent the migration of PC [41].

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