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A COMPREHENSIVE REVIEW ON CANCER IMMUNOTHERAPY AND VACCINES

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ABSTRACT

Cancer is identified by abnormal cells where cancer cells can easily infiltrate adjacent tissue and travel to other parts of the body through lymphatic and circulatory systems. Its primary features are proliferation and metastasis. Cancer is deadly if it is not controlled in the early stage. There are limited cancer treatment options available like radiation therapy, chemotherapy, and surgery but a new innovative cancer treatment has come which increases immunity and it is termed as the fourth form of treatment. The main drivers behind this immunotherapy treatment success are checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR) T cells, oncolytic virus therapy, and cancer vaccines. Cancer vaccines function by boosting the immune system's capacity to combat cancer. It has both therapeutic and preventive vaccines. Immunotherapy has proven to be effective, but only a small percentage of patients show signs of improvement after starting treatment. Biomarkers are useful in identifying patients who may respond to medication which gives better efficacy with immunotherapy. This review gives an idea of immunotherapy for cancer patients, types of immunotherapy drugs, advantages and disadvantages, new trends, and future predictions, and also gives a broad idea of side effects, mechanism of action, adjunct therapy, and Biomarkers.

KEYWORDS: Oncolytic viruses, Adoptive cell therapy, Tumor-infiltrating lymphocytes, T-Cell receptors, CRS, ICANS, etc.

INTRODUCTION

Cancer is characterized by abnormal and uncontrollably dividing bodily cells. Cancer cells can infiltrate adjacent tissues and travel to other areas of the body via the lymphatic and circulatory systems. Its two primary features are the human body's unchecked cell proliferation and the cells' capacity to move from their initial location and invade new areas (metastasis). Cancer can be lethal if it is not controlled in its spread.[1,5]

Radiation therapy, chemotherapy, and surgery are the three types of cancer treatment mostly available. However, in advanced or repeated stages of the disease, they are ineffective. An innovative treatment that boosts immunity is cancer immunotherapy. It also goes by the name “fourth form of treatment”.[6]

A. Immunotherapy

Immunotherapy has solidified its position as a cutting-edge cornerstone of cancer treatment, serving as a neoadjuvant and adjuvant in a variety of cancer types as well as in the metastatic stage. The main drivers behind this success are checkpoint inhibitors (CPIs) and chimeric antigen receptor (CAR) T cells, oncolytic virus therapy, and vaccines.[8]

TYPES

1. Oncolytic viruses (OVs)

Due to their ability to interfere with antitumor effects in multiple ways, oncolytic viruses (OVs) have demonstrated significant benefits in the treatment of cancer.[9,10] Oncolytic viruses are defined as naturally occurring or genetically modified viruses that specifically replicate within cancer cells to cause death while sparing healthy tissues.[11,12] When the immune system receives a warning from oncolytic viruses, it launches an attack on neighbouring tumor cells. Biological therapy is the recommended treatment option for cancer, despite its complexity and challenges.[13,15] Its effectiveness is high, its side effects are minimal, and its pain factor is lower for cancer patients. The drug of choice for treating cancer is chemotherapy, but its primary drawback is its long list of adverse effects.

Oncolytic viruses (OVs) present novel and exciting therapeutic options for patients whose cancer are resistant to traditional therapies. OVs, whether natural or

genetically engineered, are versatile tumour killers. In addition to indirectly enhancing antitumor immunity by releasing antigens and triggering inflammatory reactions in the tumour microenvironment, they directly lyse tumour cells while protecting healthy ones.[16,17]

Two groups of oncolytic viruses are available: Naturally occurring oncolytic viruses and genetically engineered oncolytic viruses.

- **Naturally occurring oncolytic viruses**

Viruses by nature proliferate more favourably in cancer cells and are not harmful to people, usually because they are dependent on oncogenic signalling pathways or have an enhanced sensitivity to innate antiviral signalling. These include Seneca Valley Virus (picornavirus), Newcastle disease virus (paramyxovirus), reovirus, myxoma virus (poxvirus), and autonomous parvoviruses.

- **Genetically engineered oncolytic viruses**

Viruses that are genetically manipulated for use as vaccine vectors, including measles virus (paramyxovirus), poliovirus (picornavirus), and vaccinia virus (poxvirus), and those genetically engineered with mutations/deletions in genes required for replication in normal but not in cancer cells including adenovirus (Ad), herpes simplex virus (HSV), and vesicular stomatitis virus (rhabdovirus).[18,20]

Talimogene laherparepvec (T-VEC, also known as OncoVEXGM-CSF) was formally approved by the US Food and Drug Administration (FDA) on October 27, 2015, for use in patients with melanoma. T-VEC (marketed by Amgen, Inc. under the brand Imlygic®) becomes the first oncolytic virus authorised for use as a cancer treatment in the United States.[21,23]

Teserpaturev/G47Δ (Delytact®®), a GM HSV, was given conditional approval in Japan in June 2021 to treat glioblastoma.[24] A number of OV, meanwhile, have advanced to an advanced stage of clinical development and are being used in phase III clinical trials. These include the newcastle disease virus, which is being used to treat colorectal cancer, the vaccinia virus Pexa-Vec (formerly JX-594), which is being used to treat hepatocellular cancer, the Reovirus Reolysin, which is being used in combination therapy to treat squamous cell carcinoma of the head and neck, and the CG0070 Adenovirus, which is being used to treat non-muscle-invasive bladder cancer.[25,30]

Some of the clinical trials on OVs are as follow

Table 1: Genetic modification of oncolytic viruses.

Virus Classification	Oncolytic Virus	Genetic Modification	Indication
Herpes Simplex Virus-1 (DNA Virus)	T-VEC (talimogene laherparepvec, Imlygic®)	ICP34.5 deletion, ICP47 deletion, GMCSF insertion	Melanoma skin cancer
	HF10 (canerpaturev—C-REV)	Natural deletion and insertion led to loss of expression of UL43, Ul49.5, UL55, UL56, and LAT	Pancreatic cancer
	HSV1716 (Seprehvir®)	ICP34.5 deletion	Relapsed or Refractory extra-cranial solid cancers.
	OrienX010	ICP34.5 and ICP47 deletion, and GM-CSF insertion	Melanoma skin cancer
Adenoviruses (DNA Virus)	H101 (Oncorine)	E1B deletion and E3 partial deletion	Nasopharyngeal carcinoma
	ONYX-015	E1B-55 KDa gene deletion	Solid tumours
	ONCOS-102 (formerly named CGTG-102)	Adeno Δ24-RGD-GM-CSF insertion	Orphan drug status for soft tissue sarcomas.
	VCN-01	pRb-dependent; loaded with genes encoding PH20 hyaluronidase	Rare paediatric cancers such as PNETs
Reovirus (RNA Virus)	Pelareorep (Reolysin®)	Natural virus	Advanced Pancreatic Adenocarcinoma
Parvovirus (RNA Virus)	Parvovirus H-1 (ParvOryx)	Natural virus	Metastatic pancreatic ductal adenocarcinoma (PDAC)
Picornaviruses (RNA Virus)	CVA21 (Cavatak)	Natural virus	Advanced NSCLC.
	PVSRIPO	CD155/Necl5 dependent poliovirus. The internal ribosome entry site (IRES) of the poliovirus replaced with the IRES from human rhinovirus type 2 (HRV2)	Grade IV malignant glioma

The table includes the oncolytic viruses that were mentioned in this review.[30]

BARRIERS of Ovs

Even though OVs have a lot of potential, there are still a lot of issues that need to be resolved to increase their effectiveness in virotherapy. These consist of elements such as viral tropism, viral dissemination, delivery systems, dosage regimens, antiviral immunity, and oncolysis caused by the Ovs.[31]

The most significant burden to the effectiveness of OV is neutralizing antibodies. The viruses chosen for oncolytic virotherapy can infect human cells, which has advantages and disadvantages for the course of treatment. Some of the naturally occurring viruses utilized in OV treatment have been exposed to or vaccinated against by many people, and as a result, they have neutralizing antibodies against the virus.[32]

2. Adoptive cell therapy

Adoptive cell therapy (ACT) is an immunotherapy modality in which tumor-fighting autologous cancer-cognate lymphocytes are increased, altered, and reinfused ex vivo.[33] Tumor-infiltrating lymphocytes (TILs), genetically modified T-cell receptors (TCRs), and chimeric antigen receptor (CAR) T cells are the three main ACT modalities at the moment. While TCRs and CAR T cells utilize the proliferation of a genetically altered T-cell targeted toward certain antigen targets, TIL treatment involves the expansion of a diverse population of endogenous T cells identified in a collected tumor.

2.1 Tumor-infiltrating lymphocytes (TILs), which are isolated from newly obtained tumour samples, as well as peripheral blood lymphocytes, which can be chosen and subsequently employed either in their native form or by genetic modification, are both utilized in T cell-based ACT. TILs are a component of the immune system's defence against cancer. They are able to recognize and combat cancer antigens that are thought to be external to the body.[34,38] CAR-engineered T cells have received Food and Drug Administration (FDA) approval for the treatment of patients with certain B-cell malignancies.[39] Tumor-infiltrating lymphocytes (TILs) in adoptive cell therapy (ACT) is a highly customized kind of cancer immunotherapy. Due to its remarkable clinical outcomes and capacity to produce full, long-lasting responses in patients who would otherwise be treatment-resistant, it has attracted attention.[40] Through a number of processes, CD8+ and CD4+ T-cell populations are thought to be essential for tumor suppression. While CD4+ T cells can encourage the development of plasma cells that manufacture antibodies and aid in the activation of CD8+ T-cell responses, activated CD8+ T cells can create proinflammatory cytokines and destroy tumor cells.[41,42,43]

TILs are T cells that are separated from tumor fragments, expanded ex vivo, and then reinfused into patients who have already undergone conditioning while receiving high doses of interleukin-2 (IL-2) as part of a non-myeloablative lymphodepletion chemotherapy. TILs have demonstrated remarkable outcomes for melanoma patients with metastases.[44,45]

2.2 Genetically engineered TCR

Adoptive immunotherapy with tumor reactive T cells derived from TIL has been mostly used to treat patients with malignant melanoma, but it has some exceptions, it is very difficult to isolate and expand pre-existing tumor-reacting T cells from patients with tumor types other than melanoma. To get around this restriction, patients' lymphocytes have been genetically modified to express TCRs specific to tumor antigens. These TCRs are made up of α and β chains of TCR genes that were taken from an allogeneic T-cell clone that reacts to tumors, resulting in genetically modified cells known as TCR-T cells.[46]

The foundation of genetically engineered TCR therapies is the modification of T-cell specificity via the expression of particular TCR α and β chains, which facilitate the process of antigen recognition. Tumor-specific TCR α and β chains are found, separated, and cloned into transduction vectors, which then induce T cells to produce T cells specific to tumor antigens.

It is necessary to determine an appropriate target sequence to successfully generate a tumor-specific TCR. This could be extracted from an uncommon tumor-reactive T cell, or in the event that this isn't feasible, highly potent anti-tumor T-cell antigens can be produced using different technologies.

Allogeneic TCR gene transfer is an alternate strategy wherein reactive TCR sequences are transferred to T cells from a patient who shares the disease but is non-responsive, using tumour-specific T cells that have been isolated from a patient undergoing tumour remission. Finally, by strengthening the interaction (avidity) between a weakly reactive tumor-specific TCR and target antigen, in vitro technologies can be used to modify the sequence of TCRs, improving their ability to kill tumors.[47,50]

2.3 CAR T cell

Chimeric antigen receptor (CAR) T-cell therapy is a significant breakthrough in personalized cancer treatment. It involves genetically modifying a patient's T cells to express a synthetic receptor that binds a tumor antigen. Then, the patient's T cells are expanded for clinical use and reinfused into the body to combat and eradicate chemotherapy-resistant cancer. When CAR T-cell therapy is used to treat B-cell malignancies, significant clinical responses and high rates of complete remission have been recorded.[51] CAR T cells are associated with unique side-effects, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and cytopenias are common.[52] CAR T cells are unique as they are “living drugs,” that is, gene-edited killer cells that can recognize and kill cancer. Tisagenlecleucel was the first gene therapy to receive approval from the FDA for any indication.[53,54]

3. Immunologic checkpoint blockade

Immune system checkpoints are a typical component. Their role is to keep the immune system from overreacting which can destroy own's the body's healthy cells. The activation of immune checkpoints occurs when T cell surface proteins identify and bind to partner proteins on other cells, including certain tumor cells. We refer to these proteins as immune checkpoint proteins. The partner proteins and checkpoints work together to send a "off" signal to T cells. This may block the immune system's ability to eradicate the cancer. Immunotherapy medications, as immune checkpoint inhibitors function by preventing checkpoint proteins from attaching to their corresponding partner proteins. As a result, the T cells can eradicate cancer cells by blocking the transmission of the "off" signal.[59] In several cancers, immunologic checkpoint blockade using antibodies that target the programmed cell death protein 1 pathway (PD-1/PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) has shown promise.[58] The US Food and Drug Administration has approved pembrolizumab (PD-1) and ipilimumab (CTLA-4) for the treatment of advanced melanoma.

Immune checkpoint blockade can have important antitumor effects, but because it also boosts immune responses specific to tumors, it can also have unique side effects due to nonspecific immunologic activation. Immune-related adverse events are the term used to describe side effects from these agents.[55] Immune checkpoint blockade, also known as immune-related adverse events (IRAEs), promotes the emergence of autoimmune manifestations by throwing the immune system out of balance. Steroids can be used to counteract lymphocyte activation and manage the majority of these adverse events. The antitumor response may be compromised by the immunosuppression that comes with steroid use, even though it causes the IRAEs to regress. For IRAEs to be detected early and managed appropriately, understanding them is essential.[56]

4. Cancer vaccines

Cancer vaccines are immune system modifiers that work by enhancing or strengthening the immune system's ability to fight cancer. There are vaccines for both preventive and therapeutic purposes.[60] Preventive vaccinations aim to stop the development of cancer.[61-62] They are based on antigens that are easily recognized by the immune system as foreign invaders and are carried by infectious agents.[63] The FDA has authorized vaccinations against the human papillomavirus (HPV) and the hepatitis B virus (HBV). Tumor antigens, peptides, or entire cancer cells can be used to activate the immune system.[64,65] The process entails using targeted T cells to stimulate the immune system to eliminate specific cancer cells. Medicinal vaccines broaden the immune system's assault on cancer cells by first attacking the immune system directly. Moreover, an expansion of the immune response could observe as it might attack additional tumor-specific antigens (antigen spread).[66,67]

4.1 Dendritic vaccines

DCs are an essential component of vaccination through their capacity to capture, process, and present antigens to T cells.[69] Sipuleucel-T, the first Food and Drug Administration (FDA)-approved DC vaccine (Dendreon Corp.) has been found to be somewhat effective in the treatment of human prostate cancer.[70] In DC-based immunotherapy, the patient's DC is extracted and activated outside of the body to stimulate the immune system to eradicate the tumor. Novel approaches have the potential to archive long-term immune responses against tumors. Numerous investigations have been conducted regarding the role of DC in various domains of the immune response.[71]

4.2 DNA vaccine

Tumor antigen (TA) vaccinations offer a viable means of eliciting a targeted and durable immune response. Immune system manipulation through DNA vaccination is a potentially effective approach. The purpose of DNA vaccines is to activate or boost the immune system's response to tumor cells that carry TAs by delivering plasmids containing TA-encoding genes.[72]

4.3 Anti-idiotype Vaccines

Idiotype antibodies can function as antigens in specific situations, inducing an immune response. To combat the idiotypes in this situation, the immune system will create anti-idiotype antibodies. It is possible to create a vaccine that can be injected to treat cancer by mass-producing anti-idiotype antibodies.[73]

4.4 Antigen Vaccines

These work by stimulating the immune system with proteins found on tumor cells, or tumor-specific antigens. By injecting these antigens into the patient's cancerous region, the immune system will boost the production of antibodies or cytotoxic T lymphocytes, popularly referred to as killer T cells, which will target the cancer cells that are harbouring that particular antigen. This kind of vaccine can contain several antigens to alter the immune system's reaction.[74]

4.5 TUMOR CELL VACCINE

Autologous and allogeneic tumor cell vaccines: One of the first kinds of tumor vaccines to be used was made using autologous and allogeneic tumor cells. The primary benefit of tumor cell vaccines, in theory, is that they contain all the pertinent tumor antigens required for the immune system to mount a potent antitumor response. This is especially true in the case of using autologous tumor cells as opposed to allogeneic tumor cells. Another benefit of tumor cell-based immunization is that it makes it possible to develop cancer vaccines without having to identify the precise antigens.[75]

B. Biomarkers in cancer immunotherapy

Immunotherapy has shown to be successful, but after beginning treatment, very few patients exhibit improvement. As such, identifying patients who might benefit from medication and understanding the underlying mechanisms are critical. Some of the biomarkers used are as follows

Mutational Load

A valuable predictive biomarker for treatment response could be mutation load. Progression-free survival (PFS), durable clinical benefit (DCB), and enhanced objective response are all correlated with higher mutation loads. Nevertheless, whole-exome sequencing, which is required to determine the mutation load, is too expensive and time-consuming to be used as a routine clinical test. As a result, research was done on the use of next-generation sequencing (NGS) gene panels for accurate mutation load estimation and treatment response prediction.[76,77]

PD-L1 expression

One of the first biomarkers to be examined in clinical immunotherapy trials was PD-L1. Immunohistochemistry-based PD-L1 protein expression detection can be used to screen for responses to anti-PD-(L)1 blockade in a range of tumor types. Immunohistochemistry (IHC) detection of PD-L1 (B7-H1) on patient tumors is currently the most frequently used clinically detected biomarker for predicting patient response to anti-PD-1/PD-L1 therapy.[78,79]

Table 2: Benefits of Biomarkers in Immunotherapy.

Biomarker	Benefits in Immunology
Mutational load	In general, the higher the number of mutations the better the response to immunotherapy; not the case for all tumors
Lymphocyte infiltrates	The presence of lymphocyte infiltrates is related to improved survival
PD-L1 expression	PD-L1 expression on tumor cells may potentially serve as a useful predictive biomarker for response to anti-PD1/PDL1 therapy; not the case for many tumors
Genetic profiling	Patients with higher baseline expression of immune-related genes generally respond better to ipilimumab

DISCUSSION

The review provides a comprehensive overview of types of Immunotherapy and vaccines which will be the new trends for Cancer Treatment. Also gives a broad idea of FDA-approved immunotherapy drugs along with side effects, mechanism of action, adjunct therapy, and biomarkers. Cancer immunotherapy is the fourth form of cancer treatment which gives better efficacy and safety to cancer patients. The current focus of cancer immunotherapy is on effective ways to stimulate and strengthen the immune response against cancer.

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