Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

A REVIEW ARTICLE ON IMMUNO-ONCOLOGY

S. Amrutha[1], Sk. Mohammed Rafi[1], S.Venkatesh[1], R. Mourya Sri[1], M. Sahithi[1],

[1]Pharm D students, Nirmala college of Pharmacy, Atmakur, Mangalagiri, AP, India-522503,
Affiliated to Acharya Nagarjuna University

***Corresponding Author**:

R. Mourya Sri,III Pharm D, Nirmala College of Pharmacy, Atmakur, Mangalagiri, AP, India – 522503, **Email ID:** mouryasriravi@gmail.com

ABSTRACT

Immuno-oncology, also known cancer immunotherapy that utilizes the strength of our own body's immune system to treat, prevents, control, and eradicate the cancer. Immunotherapy can, train the immune system to recognize and attack certain cancer cells. Strengthen the immune cells to help them get rid of cancer. Provide the body with additional nutrients to strengthen the immune response [1].

Unleashing the power of the immune system is a smart way to fight cancer:

The immune system is precise, so it can only fight cancer cells and protects healthy cells. Just like cancer, the immune system can adapt continuously and dynamically. Therefore, if the tumor escapes detection, the immune system can reassess and launch a new attack. The "memory" of the immune system allows it to remember what the cancer cell looks like in order to target and destroy it when the cancer recurs [2].

Cancer Immunotherapy has brought a significant changes and developments, in terms of patient survival and quality of life when compared to previous standards of care such as chemotherapy, radiotherapy and surgery. Researches in the Cancer treatment lead to arose of novel and more potential treatment approaches such as Immunotherapy, in which our body own immune system fights against cancer. Immunotherapy includes many treatment approaches such as, Check point blockades, Monoclonal antibodies, chimeric antigen receptor T cell therapy, Oncolytic viral therapy and vaccines.

Most of the early tumor cells were recognized and eliminated by host immunity, yet immunological checkpoints, represented by CTLA-4, PD-1, and PD-L1, pose a significant obstacle to effective antitumor immune responses. Intensity, Inflammation and duration of antitumor immunity are influenced by T-cell co-inhibitory pathways. Due to the immunosuppressive potential of tumor cells and their microenvironment, they can rapidly exploit and causes significant destruction to our immune system. Recent advancements (check point inhibitors) have shown durable responses in advanced stages of cancer (melanoma), proving the limitations and exposing the evidence of potential to replace conventional radiotherapy regimen. In this Review, we have highlighted and evaluated different treatment approaches in immunotherapy, and provided an overview on all of the approaches by giving a standard attention and awareness regarding the novel approaches in cancer treatment [3][4].

Keywords: Immuno-oncology, immune system, Checkpoint blockades, monoclonal antibodies, chimeric antigen receptor T cell therapy, Oncolytic viral therapy, cancer vaccines.

Introduction

Immunity:

Immunity refers to the body's ability to prevent pathogen invasion. Pathogens are foreign substances that cause diseases such as bacteria and viruses, and humans are exposed to them every day. Antigens attach to the surface of pathogens and stimulate the body's immune response.

Immuno-oncology:

Immunotherapy is a treatment in which our body's own immune system fight against cancer. Immunotherapy has the ability to boost or change how the immune system works to fight against cancer [5].

Therapeutical agents used in immune therapy of cancer [6]

- ✓ Check point inhibitors
- ✓ Chimeric antigen receptor T cell therapy(CAR-T cell therapy)
- ✓ Monoclonal Antibodies
- ✓ Oncolytic viral immunotherapy
- ✓ Vaccines

Checkpoint inhibitors

Check point inhibitors is one of the type of cancer immunotherapy. Immune check point inhibitors works by blocking checkpoint proteins from binding with their partner proteins. This allows the T cells to kill cancer cells [7].

Types:

CTLA-4: It is present on the T cell.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

PD-1: It is present on the T cell.
PD-L1: These are present on the cancer cells

- CTLA-4 is a drug that acts against a check point protein.
- Examples of checkpoint inhibitors are as follows:
  -Pembrolizumab (Keytruda)
  -Atezolizumab (Tecentriq)
  -Nivolumab (Opdivo)
  -Ipilimumab (Yervoy).

(Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors) [8]

Mechanism of action:

T cell is the main type of immune cells. Immune response is turned on by some of the proteins which are present on T cells and some other proteins are responsible for turn it off. The proteins that are present on T cells are called as Check point proteins. Hence some checkpoint proteins help T cells to be active and some for inactive. If T cells do not become inactive then it may kill healthy cells. High levels of proteins are present on the cancer cells which are against to T cells and try to inactive the T cells which are attacking the cancer cells. The cancer cells are pushing down the immune system so that the T cells cannot recognize and kill cancer cells. For this, Checkpoint inhibitors are more helpful by stopping the proteins on the cancer cells that are pushing down the T cell proteins. This Checkpoint inhibitor turns immune system active and helps T cells to find and attack the cancer cells [9].

Side Effects:

The following are the most common side effects of checkpoint inhibitors are:

- Diarrhea.
- Pneumonitis (inflammation in the lungs)
- Rashes and itchiness.
- Problems with some hormone levels.
- Kidney infections.
- Myocarditis [10] [11]
- Type 1 diabetes
- Hypothyroidism
- Acute kidney injury
- Adrenocorticotropic hormone insufficiency.
- The most commonly effected system is the endocrine system due to the development of diabetic ketoacidosis or type 1 diabetes mellitus.
- Another major adverse effect of these inhibitors is pancreatic dysfunction. Pancreatic dysfunction may develop within 5 cycles of the therapy [12].

Therapeutic uses:

The 1st line treatment for several types of cancers is checkpoint inhibitors.

- Used in the treatment for advanced melanoma and renal cancers.
- Used in the treatment for breast cancer.
- Also in the treatment for some live cancer and lung cancer.
- For the treatment of urothelial cancer.

Checkpoint inhibitors are not only used for the above mentioned cancers but these are used for all types of cancers.

Chimeric antigen receptor T cell therapy (CAR-T cell therapy)

CAR T cell is a therapy in which a patient's T cells are transformed in the laboratory therefore they will attack cancer cells. T -cells are collected from a patient's blood. Formerly the gene binds to a particular protein for a specific receptor on the patient's cancer cells is included to the T cells in the laboratory. The specific receptor is known as chimeric antigen receptor (CAR). Greater number of the CAR T cells is developed in the laboratory and are imparted to the patient by infusion. Certain blood cancers are used to treat by CAR T cell therapy, and it is being considered in the therapy of other types of cancer

Chimeric antigen receptor T -cell therapy is an innovative novel therapy for cancer patients.

Chimeric antigen receptor (CAR) T -cell therapy is a technique to get immune cells known as T cells (a type of white blood cell) to fight against malignance by varying them in the lab so they can obtain and damage tumor cells. CAR T -cell therapy is also occasionally confessed about as a type of cell-based gene therapy, as it includes changing the genes inside T cells to aid them tackle the malignance.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

In 2017, the Food and Drug Administration (FDA) accepted two CAR T-cell therapies, one for the therapy of children with acute lymphoblastic leukemia (ALL) and the other for adults with progressive lymphomas [13].

As the term indicates, T cells are the mainstay of CAR T-cell therapy, which are frequently known as the workhorses of the immune system since their significant role in arranging the immune response and slaying cells affected by pathogens [14].

This treatment needs pulling blood from patients and distinguishing out the T cells. Followed by, the T cells are genetically persuaded to produce receptors on their surface by using a disarmed virus known as chimeric antigen receptors, or CARs.

These special receptors let the T cells to know and bind to a particular protein, or antigen, on cancer cells. Further along in growth the CAR T cell therapies target an antigen found on B cells known as CD19.

Once the T cells which are collected have been persuaded to express the antigen -specific CAR, they are "enlarged" into the hundreds of millions in the laboratory.

The infusion of the CAR T cells into the patient is the last step (which is headed by a "lymphodepleting" chemotherapy schedule). If altogether goes as planned, the persuaded cells further increase in the patient's body and, with the help from their persuaded receptor, recognize and slay tumor cells that protect the antigen on their surfaces [15].

How CAR T-cell therapy works

The immune system identifies irrelevant materials in the body by acquiring proteins known as antigens on the surface of those cells. T cells which are known as immune cells have their own proteins called receptors that bind to foreign antigens and help activate other parts of the immune system to damage the foreign substance.

Tumor cells also have antigens, but if your immune cells don't have the right receptors, they can't bind to the antigens and help to damage the tumor cells [16].

Getting CAR T-cell therapy

CAR T -cell therapy process takes many weeks.

Collecting The T cells

Formerly, white blood cells (which include T cells) are isolated from the patient's blood using a process called leukapheresis. During this process, patients mostly lie in bed or sit in a reclining chair. Two IV lines are required as the blood is withdrawn through one line, the white blood cells are separated out, and then the blood is place back into the body through the other line. At times a central venous catheter which is a special type of IV is used, in which both the IV lines put together.

All through this process the patient will need to remain seated or lying down for 2-3 hours. All through leukapheresis occasionally blood calcium levels can decrease, which causes numbness and tingling or muscle spasms. This can be simply cured by restoring the calcium, which may be provided by mouth or through an IV [17].

Making the CAR T cells

As soon as the white blood cells are withdrawn, the T cells are isolated, sent to the lab, and changed by enhancing the gene for the particular chimeric antigen receptor (CAR) and this creates CAR T cells. These cells are then developed and increased in the lab. It may take many weeks to generate the great number of CAR T cells which are needed for this treatment [18].

Receiving the CAR T cell Infusion

They will be given back to the patient when adequate CAR T cells have been made. The patient might be given chemotherapy a few days before the CAR T -cell infusion to decrease the number of other immune cells. This produces the CAR T cells a better chance to get triggered to fight against the malignance. CAR T cells work better than chemotherapy when there are few tumor cells to attack. Once the CAR T cells begin to attach with tumor cells, they begin to enhance their number and destroy even more tumor cells.

Possible CAR T-cell therapy side effects

CAR T -cell therapy can be very helpful against few types of tumors, however at times it can also cause serious or even life -threatening side effects. Since this is needed to be given in a medical centre where it is particularly trained in its use and patients are needed to be under supervision for few weeks after getting the CAR T cells.

Cytokine Release Syndrome (CRS): Because CAR T cells multiply, they can liberate great amounts of chemicals called cytokines into the blood, which can upgrade the immune system. Serious side effects from this release include:

High grade fever and chills

Trouble in breathing

Severe nausea, vomiting, diarrhea

Feeling dizzy or lightheaded

Headaches

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Tachycardia
Fatigue
Muscle spasms
As the doctors are getting more experience with this therapy, they are acquiring knowledge how to identify CRS as soon as possible and to treat it.
Nervous System Problems:
If you are getting CAR T-cell therapy, it's very important to report any side effects to your health care team right away, as there are often medicines that can help treat them.
This therapy may sometimes cause serious effects on the nervous system, which can develop in symptoms such as:
Headaches
Alter in consciousness
Confusion or agitation
Convulsions
Tremors
Trouble in speaking and understanding
Loss in balance
As the risk of these side effects, elderly patients are characteristically recommended not to drive, manage heavy machinery, or do any other possibly unsafe activities for at least some weeks after getting therapy.
Other side effects: Other likely side effects of CAR T cell therapy includes:
Allergic reactions during infusion.
Abnormal levels of potassium, sodium, or phosphorous levels.
A weakened immune system.
Low blood cell counts.
It is very important to report to your health care team right away in case of any side effects as there are often medicines that helps to treat them, if you are getting CAR T -cell therapy.

Monoclonal Antibodies
Antibodies are the proteins that are produced by plasma cells in response to an antigen. Each antibody can only bind to a specific antigen.
Monoclonal antibodies are produced in the laboratories which are similar to the antibodies produced in the body. Then they circulate to other parts of the immune system to fight against cancer [19].
Monoclonal antibodies are made by four different ways and they are named based on what they are made of:

- Murine: These are made up of mouse proteins and the names of the drugs end with -omab.
- Chimeric: These proteins are a combination of part mouse and part human and the names of the drugs end with -ximab.
- Humanized: These are made from small parts of mouse proteins attached to human proteins and the names of the drugs end with -zumab
- Human: These are fully human proteins and the names of the drugs end with -umab[20].

Monoclonal antibodies act by

- Weakening cancer cells
- Promoting cell membrane destruction
- Preventing cell growth
- Preventing blood vessel growth
- Obstructing immune system inhibitors
- Directly attacking tumors
- Proper delivering of radiation and chemotherapy
- Binding to cancer cells and immune cells [21].

Monoclonal antibodies work in three different ways they are

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Naked monoclonal antibodies- These antibodies are not attached to anything so they are called naked. These antibodies either boosts the person's immune system to fight against cancer or blocks the antigens that helps the cancer to grow and metastasize.

Conjugated monoclonal antibodies- These antibodies posses a chemotherapy drug or radioactive particle along with them and they attach directly to the tumour cells. These antibodies enhance the therapeutic effect of chemotherapy and radiations and helps to reduce side effects**.**

Bispecific monoclonal antibodies- These are called Bispecific antibodies because they are attached to two proteins at a time such as a cancer cell and an immune cell which boosts the immune cells to fight against cancer.

E.g. The leukaemia drug Blinatumomab (Blincyto) attaches to a protein on leukaemia cells, and to a protein on T cells [22].

FDA approved monoclonal antibodies:

Drug Name	Active Ingredients	Target	Indication
Rituxan	Rituximab	CD20	B-NHL
Herceptin	Trastuzumab	EGF	Breast Cancer
Mylotarg	GemtuzumabOzogamicin	CD33	AML
Campath	Alemtuzumab	CD52	B-CLL
Zevalin	Ibritumomab Tiuxetan	CD20	B-NHL
Erbitux	Cetuximab	VEGFR	MCC
Avastin	Bevacizumab	VEGF	Colon Cancer
Vectibix	Panitumumab	EGFR	Colorectal Cancer
Arzera	Ofatumumab	CD20	B-CLL
Yervoy	Ipilimumab	CTLA-4	Melanoma
Adcetris	Brentuximab Vedotin	CD30	HL
Perjeta	Pertuzumab	HER2	Breast Cancer
Kadcyla	Ado-Trastuzumab Emtansine	HER2	Breast Cancer
Gazyva	Obinutuzumab	CD20	B-CLL
Cyramza	Ramucirumab	VEGFR2	Gastric Cancer
Ketruda	Pembrolizumab	PD-1	Melanoma
Bexxar	Tositumomab; Iodine I 131 Tositumomab	CD19+CD3	ALL
Opdivo	Nivolumab	PD-1	Melanoma
Unituxin	Dinutuximab	GD2	Neuroblastoma
Darzalex	Daratumumab	CD38	MM
Portrazza	Necitumumab	EGFR	Lung cancer
Empliciti	Elotuzumab	SLAMF7	MM
Tecentiq	Atezolizumab	PD-L1	Urothelial Cancer

[23]

Side effects of monoclonal antibodies

The more common side effects caused by monoclonal antibody drugs include:

- Allergic reactions, such as hives or itching
- Flu-like signs and symptoms, including chills, fatigue, fever, and muscle aches and pains
- Nausea, vomiting
- Diarrhea
- Skin rashes
- Low blood pressure

Oncolytic Viral Immunotherapy:

A Combinatorial Approach for Cancer Treatment:

Novel Scientific developments in the Research field, led to the enhanced treatments for Cancer. One of the Novel therapies is Oncolytic Viral Immunotherapy [24]. Doctors tend to be more interested in using viruses to treat cancer, for more than a century, and in recent years patients have begun to show some benefits from this approach [25]. Due

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

to poor tumor cell targeting, immunosuppressive status of tumor microenvironment (TME), large heterogeneity of cancer, combinatorial approaches or agents are necessary to obtain a more effective and consistent therapeutic responses. Oncolytic virus (tumor-specific virus) is a virus, selected or genetically engineered, that tends to be more preferential in infecting and breaking down (lysing) of cancer cells sparing normal cells. Cancer cells which are infected and lysed (Oncolysis), liberates new infectious virus particles called virions, which shows greater affinity in destroying the remaining tumors. Non-pathogenic viruses in humans such as myxoma virus, reovirus, have the ability to invade and selectively replicate within cancer cells. Many Oncolytic viruses have been used as genetic vectors for the augmentation of antitumor immune responses, such as herpes simplex virus type-1(HSV-1), adenoviruses, vesicular stomatitis virus (VSV), measles virus, poliovirus, New castle disease virus (NDV), reovirus etc., Noticeably, a major landmark achievement for Oncolytic viral therapies, H101(a genetically altered or modified adenovirus) has been approved in 2005 in China, which can be used as combination with chemotherapy, for the treatment of nasopharyngeal carcinoma, considering the H101 , world's first OV to be used on cancer patients. According to US Food and Drug Administration (FDA) in 2015, Talimogene laherparepvec (T-VEC) a genetically altered or modified HSV-1 encoding granulocyte-macrophage colony-stimulating factor (GM-CSF), was the first approved Oncolytic virus to treat patients with unresectable stage III and IV melanoma. Ongoing clinical trials have shown that Oncolytic virus alone or combination with immune adjuvants, treat conglomerate cancer types such as glioblastoma, colorectal cancer, Non-small cell lung cancer and pancreatic cancer etc., [26].

The cancer Immunotherapy approach with which we are familiar today, were mainly designed to activate innate (inborn) or adaptive immune cells, such as T (thymus) cells and NK (Natural killer) cells, in the tumor microenvironment (TME) to control tumor development and progression [27]. However, unsatisfactory results were obtained during the long-term treatment effects of multiple immunotherapy for solid tumors, which may be due to the immunosuppressive status in the TME arbitrated by negative immune cells (like T-regulation cells, Tumor associated macrophages and myeloid-derived suppressor cells etc.,) [28]. As the OVs are highly specialized or capable for replication in tumor cells and ingenerate systematic responses, combination with cancer immunotherapies has paved a way to overcome immune inhibitions in TME, and a massive improvement in the anti-cancer therapeutic effects[29] [30] .

Mechanism of Oncolytic virus Immunotherapy:

Selective tumor cell entry and induction of systematic immune response are the two main requirements for a successful OV immunotherapy approach. Inherent abnormalities in cancer cell stress responses, cell signaling, homeostasis, give an opportunity for the OVs with enhanced ability to selectively enter, replicate in, and destroy cancer cells but not normal cells. Viral clearance usually depends on several signaling pathways, including IFN, TLR (Toll-like receptors), JAK-STAT (Janus kinase-signal inducer and activator of transcription), and PKR pathways, that are lack or inhibited in the cancer cells, granting the OVs to enter for incorporation and survival in these cells. However, in addition to it, Cancer cells may also possess several surface receptors, that includes CD46, ICAM (CD54), DAF (CD55), CD155 and integrins, allow the OVs to enter tumor cells in TME.

Elicitation of systemic immune response, which can be either innate or adaptive, or both, eradicates or demolishes the cancer cells in the TME, that immediately occurs after the entry of OVs in to the tumor cells. Oncolysis liberates certain molecules called PAMP's (pathogen-associated molecular patterns) such as, viral nucleic acids and proteins, as well as DAMP's (damage associated molecular patterns), such as HMGB 1 (high mobility group box 1), HSP (heat shock proteins), which have a role in stimulation of innate immunity. PRRs (pattern recognition receptors), which are present on the surface of NK cells and macrophages provides an opportunity for the recognition of PAMP's and DAMP's within the Tumor microenvironment (TME), and secretes certain inflammatory cytokines such as IFN-alpha, IFN-gamma, TNF-alpha, IL-6, IL-12, responsible for inducing anti-viral and anti-tumor immune responses and for the recruitment of other innate immune cells from peripheral lymphoid organs. Antigen presenting cells (APCs) such as Dendritic cells recognizes TAAs (Tumor-associated antigens) or TSAs (Tumor-specific antigens), that are liberated during Oncolysis, and generates an adaptive immune response by the activation of antigen specific T cells such as CD4+ and CD8+ T cells, resulting in an T-cell mediated immunogenic cell death (ICD) in Tumor cells [31].

Nevertheless, OVs alone can produce significant positive outcomes in some clinical trials, but the major challenges are found to be the systematic viral clearance, poor tumor cell targeting and infectivity of OVs. So, this led to the development of combinatorial approaches that provides the patient an increase and a long-term benefit. Infact, in some cases, OVs turned out into an exhausted state, where they lose their ability to maintain continuous replication and lytic activity, in which the combinatorial therapy again serves as a best option [32].

Combining Oncolytic Viruses with Cancer Immunotherapies:

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Oncolytic virotherapy provides an ideal therapeutic platform when combined the cancer immunotherapies, as OVs have the potent capability to induce T cell priming and infiltration, activate local immune responses, and counteract cancer-mediated immune evasion in the TME.

Combining Oncolytic Viruses with Immune Checkpoint Blockades:

Interruption of immunosuppressive tumor signals and restoration of anti-tumor immune responses can be achieved by the administrating Immune checkpoint blockade therapy, by targeting specific checkpoint receptors or ligands, such as PD-1 and its ligand PD-L1, CTLA-4 (cytotoxic T lymphocyte-associated protein), LAG-3 (lymphocyte-activation gene 3) etc.,

Due to low levels of TILs (tumor infiltrating lymphocytes), lack of expression or presentation of TAAs/TSAs in the TME, a minimum patient recovering response rate was recorded. The combinatorial therapy of OVs with several ICBs (immune checkpoint Blockades) provided an assuring approach to overcome the confinements.

Synergistic therapeutic effects can be elicited by the concomitant combinations of immune checkpoint antibodies among metastatic or locally unresectable tumors with unmodified OVs or OVs girded with facilitated cytokines and chemokines, such as TNF-alpha, IL-2, IL-12, IL-15, GM-CSF and IFN-beta. Significant synergistic improvement of therapeutic activity has been observed, during the combination of Ipilimumab with T-VEC, led to the enhanced Objective Response Rates in both injected lesions and visceral lesions compared with Ipilimumab alone.

Recent pre-clinical studies have found that OVs which are genetically engineered has an ability to encode and secrete checkpoint antibodies within the TME, apart from direct combination of OVs with checkpoint antibodies. However, combining OVs with ICBs is an innovative approach; this combination may also have some antagonistic effects that should be considered.

Combining Oncolytic Viruses with Chimeric Antigen receptor - T cell Therapy (CAR-T):

Chimeric antigen receptor T-cell therapy, is a treatment in which the T-cells are Designed, Modified and amplified *in vitro* (in laboratory), to provide or grant them the ability to recognize tumor cell surface antigens with the help of transduced CAR structure on the T cell surface, which makes them allow to enter the TME and kill tumor cells with its respective corresponding antigens. In addition with ICB therapy, CAR-T cells have wide range treatments for patients with previously refractory hematological cancers such as acute lymphoblastic leukemia and chronic lymphocytic leukemia (CLL).

Although a novel technique, CAR-T therapy provided only a minor and a provisional Objective Response Rates (ORRs) in the patients with multiple solid tumors, due to poor penetration of CAR-T cells in to the TME and inefficient CAR-T cell effector function in “Cold tumors”.

As discussed above, the Immunogenic Cell Death of tumor due to OV-induced viral infection, make OVs a remarkable potential partner that tends to show a greater therapeutic action with CAR-T therapy. Certainly, different types of OVs are genetically engineered to release or to deliver appropriate immunostimulatory cytokines, T-cell attracting chemokines against immune checkpoints that could eventually enhance migration, proliferation and activation of CAR-T cells in solid tumors. Meanwhile, to understand the depth in this combinatorial therapy, an experiment was conducted recently. TNF-alpha and IL-2 (Ad-mTNFalpha-mIL2) which are expressing on Oncolytic adenovirus was combined with mesothelin-redirected CAR-T cell therapy to treat human PDA- (pancreatic Ductal adenocarcinoma)–xenograft immunodeficient mice. This has been found that Ad-mTNFalpha-mIL2 caused a massive increase in both CAR-T cell and host T cell infiltration into immunosuppressive PDA tumors, resulting in the alteration of TME, leading to M1 polarization of macrophages and increased dendritic cell maturation.

Combining Oncolytic Viruses with Bispecific T cell engagers (BiTEs):

DNA recombination technology is underlying principle to form Bispecific antibodies, in which a two specific single-chain antibody single-chain variable fragment (scFvs) linked together by a ligation peptide. One of the BiTE scFvs preferentially binds to Tumor associated antigens (TAAs) on the tumor cell surface, where the other scFv binds to T cell surface that eventually enhancing the targeting, proliferation and activation of tumor reactive T cells in the TME. In 2015, FDA approved, Blinatumomab, a Bispecific T cell engager antibody targeting CD19 and CD3, for the treatment of Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia.

BiTEs tend to show lower tumor penetration and reduced effects on the targets in Solid tumors. Synergistic therapeutic actions are elicited when BiTEs are combined with OVs (as genetic vectors), thus secreting the BiTEs within the TME and breaking down the tumor cell-mediated immunosuppressive status.

A pre-clinical study by Freedman, shown that adenovirus signifying EpCAM/CD3 (Epithelial Cell adhesion molecules/CD3)-selective BiTEs could enhance the penetration and activation of both CD4+ and CD8+ T cells, therefore amplifying the T cell mediated tumor killing in clinical tissue biopsy samples containing EpCAM-positive tumor cells.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Trispecific NK cell engager, was the most novel technique developed recently, proved to be more potent *invitro*.

OVs tend to be more advantageous and can be fully exploited as genetic carriers in combination with BiTES, BiKEs or TriKEs *invivo*, to activate tumor-killing immune cells.

Combining Oncolytic Viruses with Cancer Vaccines:

To prevent or to control tumor growth, recurrence, long-term immune memory, Cancer vaccines are developed and designed to induce or amplify cellular and humoral responses which are already pre-existed, against target TAAs or TSAs *invivo*.

Due to the deficiency of MHCII epitope presentation on the Dendritic Cell surface in the lymph node, led to the failure in the recruitment of sufficient Th (T helper) cells, for the amplification of tumor-reactive CTLs (cytotoxic T lymphocytes), stands as a major obstacle for the development of vaccine based cancer therapies.

Therefore, the combination of OVs with tumor antigen targeting vaccines, have a remarkable activity in amplifying tumor reactive CTLs.

"Oncolytic Vaccine" is another more novel and a developed combination approach that encodes OVs with one or more TAAs.

At present, TAAs which are more expressed in tumor tissues and in normal cells are the major targets of OV-combined cancer Vaccines. Vaccines targeting tumor neo-antigens (TSAs) are detected only in tumor cells are highly efficacious. Recent publication studies have found that neo-antigen based vaccines in human glioblastoma treatment, shown a potential role by demonstrating their ability to turn "cold" tumors into "hot" tumors [33].

Side effects:

Occurrence of side effects for Oncolytic viral treatment depends on the type of virus we are treating with and its target, location and type of cancer, and patient's health status. As it is having a potent capability to infect healthy cells, stimulates overall immune activity, in some cases, Oncolytic viruses divert the immune system to attack healthy cells and their use may increase the risk of infection.

Currently approved side effects for Oncolytic viral therapy are: Chills, fatigue, flu-like symptoms, Nausea, fever, and pain at the injection site.

Vaccines

Novel developments in the scientific research field have paved its way for the development of Vaccines for cancers that prevent healthy individuals from getting cancers caused by viruses [34].

According to, US FDA there are 2 types of vaccines that are approved by them which have a role in the prevention of cancer.

HBV vaccine

HPV vaccine

There are some other vaccines which have a greater incidence in the prevention of cancer

Sipuleuce -T

Talimogene laherparepvec (T.VEC)

Bacillus Calmette Guerin (BCG Vaccine) [35]

HBV Vaccine:

HBV (Hepatitis B virus) has the incidence in the development of Liver Cancer. HBV vaccine provides protection against Hepatitis B Virus.

Some of the brand names of the Hbv vaccines are

Engerix-R

Heplisav -B

Pediarix

Recombivax

Mechanism

These vaccines increase the power of the immune system by combining with the surface antigen of the Hepatitis B by using the help of receptor and agonist.

HPV vaccine:

HPV contains lots of types like

Hpv types 6 &11 cause most of the genital warts.

HPV types 16&18 are high risk types which cause the cervical cancer

HPV type 31, 33, 45, 52&58 these are high risk viruses which cause most of the cancers like cervical, vaginal etc.

Human papilloma virus has the higher incidence in the development of Cervical, Vaginal, Anal, Vulvar cancer. HPV vaccine provides protection against Human papilloma Virus.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

There are three HPV Vaccines

1. **Gardasil® 9** - 9-Valent HPV Vaccine (9vhpv)
2. **Gardasil®** - Quadrivalent HPV Vaccine(4vhpv)
3. **Cervarix®** - Bivalent HPV Vaccine (2vhpv)

Mechanism of Action

Like all the immune agents these Hpv vaccines will also stimulate the body's immune system to produce antibodies. The present Hpv vaccines contains Virus like proteins (VLPs) which are in active in form due to the lack of DNA of the HPV which is synthesized from the HPV surface components. After the administration of these vaccines our immune system recognizes it as a antigen and develops the antibodies in our body. These antibodies will further use full for the prevention of virus that cause cancers.

Sipuleucel -T

Sipuleucel -T consists of the recombinant antigen protein that should be incubated with the patients' isolated antigen presenting cells from the blood collected from the patients. This sipuleucel-T is mostly used in the prevention of the prostate cancer.

Mechanism of Action

The accurate mechanism of Sipuleucel - is unknown. This is an autologous cellular immunological agent. This works through the APCs, stimulate T cell immune response that are targeted against the prostatic acid phosphatase which is highly expressed in the most of the prostate cancer cells.

Talimogene laherparepvec (T.VEC)

Talimogene laherparepvec (T-VEC) is a viral therapy used to treat cancer. This T-VEC is a strain of Herpes Simplex Virus (HSV).This HSV was genetically made to express granulocyte macrophage colony stimulating factor (GM-CSF).

Mechanism of Action

Talimogene laherparepvec is a live, attenuated HSV-1 that has been genetically modified to enable selective replication in tumor cells with a tolerable safety profile. Deletion of the ICP34.5 gene attenuates the natural neurovirulence of the virus, which enhances the preferential tumor-killing property of the HSV JS1 strain and diminishes infection of normal tissues, improving both safety and cancer specificity. Furthermore, deletion of the ICP47 gene permits antigen presentation and allows for up regulation and earlier and increased expression of US11, resulting in increased replication of ICP34.5-deleted HSV-1 in tumor cells without any loss of tumor selectivity. Last, insertion of a human granulocyte–macrophage colony-stimulating factor (GM-CSF) cassette allows for local expression to increase the activation of antigen-presenting cells.

Bacillus Calmette Guerin (BCG Vaccine)

Bacillus Calmette-Guerin (BCG), a live attenuated strain of *Mycobacterium bovis*, BCG reduces the risk of progression in patients with high-grade non–muscle invasive bladder cancer (NMIBC)

Mechanism of Action of BCG

The mechanism of action of bacillus Calmette-Guerin (BCG) therapy is incompletely understood. Some early studies purported that an immune response against BCG surface antigens cross-reacted with putative bladder tumor antigens, and this was proposed as the mechanism for the therapeutic effect of BCG; however, multiple subsequent studies refute this claim.

The most likely mechanism of action of BCG immunotherapy involves a combination of its direct effect on tumor cells along with the patient's immune response to the therapy. These effects are summarized by Kawai et al into three categories: infection of cancer cells, induction of immune response, and antitumor effects

The infection of cancer cells is mediated by the glycoprotein fibronectin, which allows the internalization of BCG, breakdown of proteins, and cellular changes (antigen expression) that trigger the immune system. This is similar to the immunologic reaction that occurs in patients with tuberculosis. This immune response comprises specific cellular changes including surface receptor changes and release of various cytokines. Interferon (IFN) is considered to be an important part of this process and has been used in the past to determine appropriate response to treatment. The immune response crescendos to antitumor activity in which cells (e.g., cytotoxic T lymphocytes, natural killer cells, neutrophils, and macrophages) recognize the cancer cells, target them for destruction, and subsequently decrease cancer burden[36].

Side effects

Fatigue
Head ache
Pain at the site of injection
Pyrexia
Flue like infection

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Chills

Conclusion

Immuno-oncology works by stimulating our body's immune system to destroy the cancer cells, to fight against cancer. In recent times the use of immuno-oncological agents has been increased widely. Combinational therapies like PD -L1/PD-1 pathway inhibitor in combination with other immune modulators has been in use to attain more therapeutic effect and more efficacies of these drugs [37]. Immunotherapy in cancer works better when it is given along with other cancer treatments like chemotherapy and radiation. However the research is still going on to overcome many challenges in immuno-oncology [38].

References

1. Koury J, Lucero M, Cato C, Chang L, Geiger J, Henry D, Hernandez J, Hung F, Kaur P, Teskey G, Tran A. Immunotherapies: exploiting the immune system for cancer treatment. Journal of immunology research. 2018 Oct;2018.
2. Oiseth SJ, Aziz MS. Cancer immunotherapy: a brief review of the history, possibilities, and challenges ahead. Journal of cancer metastasis and treatment. 2017 Oct 31;3:250-61
3. Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH. A review of cancer immunotherapy: from the past, to the present, to the future. Current Oncology. 2020 Apr;27(s2):87-97.
4. Kaufman HL, Atkins MB, Subedi P, Wu J, Chambers J, Mattingly TJ, Campbell JD, Allen J, Ferris AE, Schilsky RL, Danielson D. The promise of Immuno-oncology: implications for defining the value of cancer treatment. Journal for immunotherapy of cancer. 2019 Dec;7(1):1-1.
5. Kamta J, Chaar M, Ande A, Altomare DA, Ait-Oudhia S. Advancing cancer therapy with present and emerging immuno-oncology approaches. Frontiers in oncology. 2017 Apr 18;7:64.
6. FeDempke WC, Fenchel K, Uciechowski P, Dale SP. Second-and third-generation drugs for immuno-oncology treatment—the more the better?. European journal of cancer. 2017 Mar 1;74:55-72.b 1;54(2):103-22.
7. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nature Communications. 2020 Jul 30;11(1):1-3.
8. Chabanon RM, Rouanne M, Lord CJ, Soria JC, Pasero P, Postel-Vinay S. Targeting the DNA damage response in immuno-oncology: developments and opportunities. Nature Reviews Cancer. 2021 Aug 10:1-7.
9. Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors in cancer therapy: a focus on T-regulatory cells. Immunology and cell biology. 2018 Jan;96(1):21-33.
10. Lobenwein D, Kocher F, Dobner S, Gollmann-Tepeköylü C, Holfeld J. Cardiotoxic mechanisms of cancer immunotherapy–A systematic review. International Journal of Cardiology. 2021 Jan 15;323:179-87.
11. Tocchetti CG, Galdiero MR, Varricchi G. Cardiac toxicity in patients treated with immune checkpoint inhibitors: it is now time for cardio-immuno-oncology.
12. King GT, Sharma P, Davis SL, Jimeno A. Immune and autoimmune-related adverse events associated with immune checkpoint inhibitors in cancer therapy. Drugs of Today (Barcelona, Spain: 1998). 2018
13. Pan C, Liu H, Robins E, Song W, Liu D, Li Z, Zheng L. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. Journal of hematology & oncology. 2020 Dec;13(1):1-5.
14. Yofe I, Dahan R, Amit I. Single-cell genomic approaches for developing the next generation of immunotherapies. Nature medicine. 2020 Feb;26(2):171-7.
15. June CH, Sadelain M. Chimeric antigen receptor therapy. New England Journal of Medicine. 2018 Jul 5;379(1):64-73.
16. Yu JX, Upadhaya S, Tatake R, Barkalow F, Hubbard-Lucey VM. Cancer cell therapies: the clinical trial landscape. Nature Reviews Drug Discovery. 2020 Sep 1;19(9):583-5.
17. Peskov K, Azarov I, Chu L, Voronova V, Kosinsky Y, Helmlinger G. Quantitative mechanistic modeling in support of pharmacological therapeutics development in immuno-oncology. Frontiers in immunology. 2019 Apr 30;10:924.
18. Tang J, Shalabi A, Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. Annals of Oncology. 2018 Jan 1;29(1):84-91.
19. Zahavi D, Weiner L. Monoclonal antibodies in cancer therapy. Antibodies. 2020 Sep;9(3):34.
20. Davda J, Declerck P, Hu-Lieskovan S, Hickling TP, Jacobs IA, Chou J, Salek-Ardakani S, Kraynov E. Immunogenicity of immunomodulatory, antibody-based, oncology therapeutics. Journal for immunotherapy of cancer. 2019 Dec;7(1):1-9.
21. Mishra RK, Ahmad A, Vyawahare A, Kumar A, Khan R. Understanding the Monoclonal Antibody Involvement in Targeting the Activation of Tumor Suppressor Genes. Current Topics in Medicinal Chemistry. 2020 Aug 1;20(20):1810-23.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

22. Bayer V. An overview of monoclonal antibodies. InSeminars in oncology nursing 2019 Oct 1 (Vol. 35, No. 5, p. 150927). WB Saunders
23. Krishnamurthy A, Jimeno A. Bispecific antibodies for cancer therapy: a review. Pharmacology & therapeutics. 2018 May 1;185:122-34.
24. Li Z, Song W, Rubinstein M, Liu D. Recent updates in cancer immunotherapy: a comprehensive review and perspective of the 2018 China Cancer Immunotherapy Workshop in Beijing. Journal of hematology & oncology. 2018 Dec;11(1):1-5.
25. Salama AK, Moschos SJ. Next steps in immuno-oncology: enhancing antitumor effects through appropriate patient selection and rationally designed combination strategies. Annals of Oncology. 2017 Jan 1;28(1):57-74.
26. Allard B, Aspeslagh S, Garaud S, Dupont FA, Solinas C, Kok M, Routy B, Sotiriou C, Stagg J, Buisseret L. Immuno-oncology-101: overview of major concepts and translational perspectives. InSeminars in cancer biology 2018 Oct 1 (Vol. 52, pp. 1-11). Academic Press.
27. da Silva JL, Dos Santos AL, Nunes NC, da Silva FD, Ferreira CG, de Melo AC. Cancer immunotherapy: the art of targeting the tumor immune microenvironment. Cancer chemotherapy and pharmacology. 2019 Aug;84(2):227-40.
28. Cesano A, Warren S. Bringing the next generation of immuno-oncology biomarkers to the clinic. Biomedicines. 2018 Mar;6(1):14.
29. Zhang JY, Yan YY, Li JJ, Adhikari R, Fu LW. PD-1/PD-L1 based combinational cancer therapy: Icing on the cake. Frontiers in Pharmacology. 2020 May 15;11:722.
30. Marshall HT, Djamgoz M. Immuno-oncology: emerging targets and combination therapies. Frontiers in oncology. 2018 Aug 23;8:315.
31. Russell L, Peng KW. The emerging role of oncolytic virus therapy against cancer. Chinese clinical oncology. 2018 Apr;7(2):16.
32. Tan AC, Bagley SJ, Wen PY, Lim M, Platten M, Colman H, Ashley DM, Wick W, Chang SM, Galanis E, Mansouri A. Systematic review of combinations of targeted or immunotherapy in advanced solid tumors. Journal for immunotherapy of cancer. 2021;9(7).
33. Barbari C, Fontaine T, Parajuli P, Lamichhane N, Jakubski S, Lamichhane P, Deshmukh RR. Immunotherapies and combination strategies for immuno-oncology. International Journal of Molecular Sciences. 2020 Jan;21(14):5009.
34. Zhang H, Chen J. Current status and future directions of cancer immunotherapy. Journal of Cancer. 2018;9(10):1773.
35. Düwell P, Heidegger S, Kobold S. Innate immune stimulation in cancer therapy. Hematology/Oncology Clinics. 2019 Apr 1;33(2):215-31.
36. Schlom J, Gulley JL. Vaccines as an integral component of cancer immunotherapy. Jama. 2018 Dec 4;320(21):2195-6.
37. Salama AK, Moschos SJ. Next steps in immuno-oncology: enhancing antitumor effects through appropriate patient selection and rationally designed combination strategies. Annals of Oncology. 2017 Jan 1;28(1):57-74.
38. Baik CS, Rubin EH, Forde PM, Mehnert JM, Collyar D, Butler MO, Dixon EL, Chow LQ. Immuno-oncology clinical trial design: limitations, challenges, and opportunities