WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on: Biological Therapies of Cancer

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1. Introduction :-

There are about 200 different types of cancer.It can Start in any type of body tissue.What affects one tissue may not affect another for e.g.Tobacco smokes that you breath in may help to cause lung cancer.Over exposine of your skin to the sun could cause a melanoma on your legs.But sun won't give you lung cancer and smoking won't give you melanoma.

Cancer is a term used to describe a large group of diseases thet are characterized by cellular malfunction.Healthy cells are programmed to know what to do and when to do it.Cancerous cells do no have this programming and therefore grow and replicate out control,They also serve no physiological functions.These cells are now termed as neoplasmiccells.Biologicaltherapie is the main component of clinical cancer research effort .In 1962 and 1963 Dr.Freireich was visionary in the hypothesizing on the roll of tumor host interaction in the natural history of cancer and the response to the treatment.

Types of Cancer:-

1.Benign(Non cencerous)tumor

2.Malignant(cancerous)Tumor

Types of therapies :- Surgery,Radiationtherapy, Chemotherapy, Immunotherapy, Targeted therapy, stem cell transplant, Nano particle drug delivery system, Biological therapies.

This review material is based on the study of biological treatment as well as immune therapy used for the treatment of the cancer.(8)

2. Methodology

Biological therapies for cancer

2.1 Definition of biological therapies

The therapies that involve use of living organisam or the substance which are derived from living organism by there processing in the laboratories and there use in treatment of cancer is known as Biological therapies for cancer**.**It is also defined as modification and exploitation of cellular and molecular mechanism host defence and regulation of tissue proliferation,tissue differentiation and tissue survival for treatment of cancer.

Biological therapies which stimulate the immune cells also act against cancer this types of biological therapy is known as"**immunotherapy".**They do not target cancer cells directly but act indirectly.Biological therapies that interface with specific molecules which is involved in tumor growth and progression are also known as targeted therapies cancer cells.

For the patients suffering from cancer Biological therapy can be used to treat the cancer itself and or also the side effects caused by other cancer treatments.Although biological therapy have been approved by the U.S Food and Drug Administration(FDA).other therapies are still under experimental works and these are available to cancer patients by participating in clinical trials i.e. research studies/programs carried out using human being directly.(4),(8)

2.2 Immune System

The immune system can be defined as a complex network of cells,tissues,organs,andthe substances they make.These system helps body fight against the infections and other diseases.

Working of Immune System

- White blood cells play an important role in immune responses towards a specific type of infection.These cells carry out the many tasks which are required to protect the body against disease and the causing microbes and abnormal cells.

- Some type of leukocyctes look after the circulatory system,seeking foreign invaders.such as microbes and pathogens,and diseased,damaged,or dead cells.These WBC's provides a general or non specific type of immune protection.
- Other types of leukocyctes called as lymphocytes provide targeted protection against specific threats,that may be from a specific microbe or a diseased or abnormal cell.The most important groups of leukocyctes responsible for these immune responses are β cells and T cells.(10
- β Cells make antibodies,which are large in size,secreted proteins that bind to the foreign invader cell and helps to destroyforeign cells or abnormal cells.
- Killer T cells which are Cytotoxic T Cells kills the infected or abnormal cells by releasing toxic chemicals or by prompting the cells to self destoy and such processis known as apoptosis.
- Other types of lymphocytes and leukocyctes play supporting role to ensure that β Cells and killer T Cells does their job efficiently or not.These supporting cells includes helper T cells and dendriatic cells which help activate both β cells and Killer T cells and enable them to respond to specific threats like microbes or a diseased/abnormal cell.(1)(10)

2.3 Role of Immune System on cancer :-

The natural ability of the immune system is to detect and destroy abnormal cells which are likely to prevent or suppress the development of many cancer cells.Immune cells are sometimes found in or around tumor cell.These cells are known as tumor infiltrating lymphocytes or TILs are an indication that the immune system is responding to the tumor.(11)

The presence of TILs in a patient's tumor is often associated with a better outcome in the patient.

However,cancer cells have various ways to invade detection and destruction by the immune system.Forexample,cancer cells can

- Undergo genetic change that may cause the reduction of the expression of tumor antigens on their surface.making them less visible to immune system
- This have proteins on there surface inactive immune cells.

Immunotherapy use various approaches for strengthening immune system and help it overcome the cancer defence against immune system.the goal is to improve ability of immune system to detect and destroy cancer(12)(13)

Types of biological therapies used to treat cancer

There are several types of biological therapies especially immunotherapies are being used or developed for cancer treatment. These therapies fight against cancer in different ways.

1 Immune Check point Inhibitors:-

Working of Immune Check point Inhibitors :-

These type of immunotherapy releases a brake on the immune system that normally prevents overly strong immune response that might damage normal cells as well as abnormal cells.This brake involve proteins on the surface of T cells called Immune Check point Proteins.When Immune Check point proteins recognize partner of proteins on other cells an off signal is sent that tells the T cell not to mount an immune response against those cells.

Two widly studied immune checkpoint proteins are 1)PD-1 and 2)CTLA-4.Some tumor cells express high level of PD -1 partner proteins PD-L1 which cause T cells to shut down and help cancer cells to invade to immune destruction.Interaction between B7 proteins on antigen presting cells and CTLA-4 that is expressed on T cells prevent T cell from killing other cells including cancer cells. drug called immune checkpoint inhibitor prevent interaction between immune checkpoint proteins and their partner proteins.enabling a strong immune response.The target of current checkpoint inhibitors include PD-1,PD-L1, and TLA -4(6)(14)(15)

Use of immune checkpoint Inhibitors

Immune checkpoint inhibitors are approved to treat a variety of cancer Type include skin cancer ,non-small cells lungs,bladdercancer,head and neck cancer ,liver cancer.one immune checkpoint inhibitor,pembrolizumab(keytruda)is use to treat ant solid tumor that is microsatellite instability high or mismatch repair deficient and has spread or cannot be removed by surgery another immune checkpoint inhibitor nivolumab (opdiva)is used to treat mismatch repair deficient and microsatellite instability high meta statie coloreetal cancer that has progressed following treatment with a fluoropyrimidine,oxaliplatin,and irinotecan hydrochloride.(18) (16)(17)

2 Immune cell therapy

It also known as**"adaptive cell therapy"**or adaptive immunotherapy

Working of immune cell therapy

This approach make patient own immune cell have better able to attack tumors.there are generally two approaches to adaptive cellular therapy for cancer trearment.both involve collecting patients own immune cells growing large number og these cells ,growing large number of these cells in the laboratory and then influcing the cell back into patient.(22)(23)

.1 Tumor Infiltrating Lymphocytes(TIL's)

Thisapproach use T cells which is naturally found in patient tumor known as **Tumor Infiltrating Lymphocytes.**the TIL'S that are used to recognize the patient tumor cells in laboratory test are selected.and these cells are grown to large number in laboratory.the cells are activated by treatment with immune system signing proteins called **cytokines** and infused into patient blood stream.The idea behind this approach is that the **TILs** have already show the ability to target tumor cells but there may not be enough of them in the tumor micro environment to kill the tumor or to overcome the immune suppressive signal that the tumor is releasing introducing massive amount of activated TILs can help to overcome these barriers.(21)(19)(20)

.2 CAR T-cell Therapy

This approach is similar to the TILs but the patients T-Cell are genetically modified in the laboratory to express a protein known as chimeric antigen receptor or a **CAR** before they are grown and infused into the patient CARs are modified forms of protein known as T-cell receptor,which is expressed on the surface of T-cell.The CARs are designed to allow the T-cell to attach to specific protein on the surface of the patient's cancer cells improving their ability to attack the cancer cell.

Before receiving the expanded T-cells.Patients also undergo a procedure called Lymphodepletion which consist of round of chemotherapy and in some case whole body radiation Lymphodepletion get rid of other immune cell that can impede the effectiveness of incoming T-cell.(9)(24)(26)(25)

Uses of Immune Cell Therapy :-

Adaptive T-cell Transfer was first studied for the treatment of metastatic melanoma because it causes a substantial immune response with many TILs.This TILs has been effective for some patients with melanoma and has produce encourgingpositive finding in other cancer e.g.cervical squamous cell carcinoma and cholangiocarcinoma.Two CAR T-cell therapies have been approved.Tisagenleclcucel is approved for treatment of some adults and children with acute lymphoblastic leukemia that is not responding to other treatments and for treatment of adults with certain types ofβ –cell non-Hodgkin lymphoma.In clinical trials,many patients cancers have disappeared entirely.and several of this patient have remained cancer free for extend period. Axicabtageneciloleucel(yescarta)is approved for patient with certain type of beta call non-hodgkin lymphoma who have not respond to or who have relapsed after at least two other kind of treatment .both therapies involve modification of patient own immune cell (27)(28)

3 Therapeutic Antibodies :-

Working of Therapeutic Antibodies :-

Antibodies can provide therapeutics to target the disease-related molecules that have been discovered in genomic research because 1) the high level of specificity and affinity to the target molecule or antigen achieves a high level of efficacy and fewer adverse events, 2) their ability to target diverse molecules and the modes of action of the antibodies allow them to be applied to a wide range of therapeutic targets, and 3) modification and refinement by genetic engineering technology and the establishment of recombinant manufacturing technology has made industrial manufacturing possible.Cancer treatment vaccine may be made from a patients own tumor cell (i.e.they are custmised so that they mount a immune response against features that are unique to specific patients tumor)or they may be made from substance(antigen)that are produced by certain types of tumors e.g.they mount on immune response in any patients whose tumor produce the antigen.

The first FDA approved cancer treatment vaccine Sipuleucel-T(provenge)is customized to each patien .it designed to simulate immune response to prostatic acid phosphatic(PAP).A antigen that found on most prostate cancer cell.the vaccine is created by isolating immune systemcell called Dendritic cell,which are a type of antigen presenting cell (APC)from patientsblood.These cells are sent to vaccine manufacturer where they are cultured in the laboratory together with protein called PAP-GM-CSF this protein consist os PAP link to protein called granulocyte macrophage colony stimulating factor which stimulate immune system and enhance antigen presentation Antigen-Presenting cell culture with PAP-GM-CSF are the active componants of Sipuleucel-T these cell are infused into the patients although the precise mechanism of action of PAP-GM-CSF stimulate in T-cell of the immune system to kill the tumor cellsexpressPAP.the first FDA approval oncolytic virus therapy .

Talimogenelaherparepvec T-VEC, or Lmlygic,is also considered ane type of vaccine it based on herpes simplex virus types I,and includes a genes that codes for GM-CSF, Although this oncolactic virus infect both cancer and normal cell,normal cells have mechanism to kill the virus where as cancer cell do not .T-VEC injected directly into the tumor as the virus replicate it cause cancer cell to burst and destroy the destroid cell release new viruses GM-CSF .and a variety of tumor specific antigen that can stimulate immune response against cancer cell throughout the body.

Drugs Used :- Rituximab ,Cetuximab, Trastuzumab.

Uses of Therapeutic antibodies:-

Many Therapeutic antibodies have been approved to treat wide variety of cancer like chronic lymphocytic lymphoma (CLL),Hodgkinlymphoma. Advance bowel cancer ,head and neck cancer,breast cancer and stomach cancer.(29)(31)(30)

4 Therapeutic Vaccines:-

Working of Therapeutic Vaccines:-

Cancer treatment vaccines are designed to treat cancers that have already developed by streghtning the body's natural defences against the cancer.They are intended to delay or stop cancer cell growth:to cause tumor shrinkage:to prevent cancer from coming back:or to eliminate canvcer cells that have not been killed by other forms of treatment.

Cancer treatment vaccines may be made from a patient's own tumor cells(i.e.they are customized so that they mount on immune response against features that are unique to a specific patient's tumor),or they may be made from substances that are produced by certain types of tumor.

The first FDA-approved Cancer treatment vaccine ,sipuleucel-T.is customizes to each patient.it was designed to stimulate an immune response to prostatic acidphosphate,an antigen that is found on most prostate cancer cells.The vaccine is created by isolating immune system cells called dendritic cells,which are a type of antigen presenting cell,from patient's blood.These cells are sent to the vaccine manufacturer,where they are cultured in the laboratory together with a protein called PAP-GM-CSF.This protein consists of PAPlinked to protein called granulocyte-macrophage colony-stimulating factor,which stimulates the immune system and enhance antigen presentation.

Antigen presenting cell culture PAP-GM-CSF are the active componants of sipuleucl-T.these cells are infused I to the patients.although the precise mechanism of action of sipuleucl-T is not known,itapprears that Antigen presenting cell that have taken up PAP-GM-CSF stimulate T-cell of immune system to kill tumor cell that express PAP.The first FDA approved oncolytic virus therapy talimogeneLaherparepvec(T-EVC or lmlygic) is also considered as type of vaccine.it based on herpes simplex virus type 1 and include a gene that code for GM-CSF.Although the oncolytic virus can infect both cancer and normal cell.normal cell have mechanism to kill the virus where cancer cell do not.T-VEC is injected direct into the tumor.As the virus replicate it cause cancer cell to burst and destoy.the dying cell release new viruses e.g.GM-CSF and a variety of tumor specific antigen that can stimulate a immune response against cancer cells thoroughout the body.(32)(33)(34)

Uses of Therapeutic Vaccines:-

Sipuleucl-T is used to treat prostate cancer that has metastasized in main who have few or no symptoms and whose cancer is harmonerefractory(does not respond to harmone treatment).T-VEC is used to treat some patients with metastatic melanoma that can not be removed by surgery.(35)

5 Immunomodulatory drugs(also called biological response modifier):-

This drugs strongly modulates the body's immune system.They include Thalidomide (Thalomid), Lenalidomide (Revlimid) and Pomalidomide (Pomalyst), derivatives of Thalidomdethat have asimilar structure and function and Imiquimod(Aldara,Zyclara).

It is not totally clear that how thalidomide and its two derivatives stimulate the immune system,but they promote the IL-2 secretion from cells and inhibit the ability of tumors to form new blood vessels to support their growth.Imiquimod is a cream that is applied to the skin.It causes cells to release cytokines,mainly INF-alpha,IL-6,and TNF-alpha(a molecule involved in inflammation).

Uses of Immune modulating agents:-

Most immune modulating agents are used for treatment of advanced cancer.Some are used as part of a supportive cararegimne. E.g. recombinant and biosimilar forms of GM-CSF and G-CSF are used in combination with other immunotherapies to streghten anticancer immune response by stimulating the growh of WBC. (36)(37)

Side effects of biological therapies for cancer :-

The Side effects of biological therapies mainly reflect the stimulation of immune system and can defer by the type of therapy and by how individual patients react to the therapy.Pain,Swelling,Soreness,Redness,Itchiness and rash at the site of injection are fairely common side effects with these treatment.They can also cause a array of flu like symptoms including fever,chills,weakness,dizziness,nausea or vomiting,muscle or joint pain,fatigue,headache,occasional breathing difficulties and lower or higher blood pressure.Some immune therapies that provoke an immune system response also pose a risk of saver or even fatal hypersensitivity(allergic)reaction.Long term side effect of immunotherapies which occur particularly in immune checkpoint inhibitors include autoimmune syndromes and acute –onset diabetes.(38)(39)

Serious side effects of specific agent used for cancer therapy :-

.1 Immune Ckeckpointinhibitors :-

Side effects :- Oragan damaging immune mediated reaction involving the digestive system ,liver,skin,nervous system and heart and in the harmone producing glan.These reaction can cause immune mediated Pneumonitis colitis,hepatitis,nephritis and renal dysfunction.Myocarditis (inflammation of heart muscle) and hypothyroidism and hyperthrodism.(40)

.2 Immune cell therapy:-

Side effects:-

.1 CAR T-Cell Therapy:- Causes Cytokin release syndrome.(41)

.2 TIL Therapy:- Causes Capillary Leak syndrome**.**

.3 Therapeutic Antibodies or other immune cell molecules:-

Side effects:-

.1 CytokinreleseSyndrom-Infusion reaction,capillary leak syndrome and loss of visual acuity.(42)

.2 Therapeutic Vaccines:-

Side effects:-

Flu-like Symptoms,Severe allergic reaction,Stroke(Specially by Sipuleucel-T),Tumor lysis syndrome,herpes virus infection(T-VEC) (43)

Clinical trial of immune therapies:-FDA approvedand experimental immune therapies for specific type of cancer clinical trials are being studied.Descriptions of ongoing clinical trials that atr testing types of immune therapies in patients suffering from cancer can be accessed by the NCI's which consists of the list of cancer clinical trials

Drugs,Their actions and uses:-

Sr.no	Mechanism of action	Drugs	Uses	Side effect
1	Immune checkpoint inhibitors	1.Ipilimumab 2.nivolumab 3.Atezolizumab 4.Avelumab 5.Durvalumab 6.Cemiplimab	CTAL4-Melanoma Lung cancer Pancreatic cancer.PD1 Melanoma Lung cancer,Kidneycancer,Bladder cancer	Adverse effect on the immunology.Diverse effect on most of the organ system
2	Immune cell therapy	Drugs used are similar to immune checkpoint inhibitor	Acute lymphoblastic leukemia,bile duct cancer,cervical cancer	Fatigue,fever,chills,nausea,flu like symptoms,pain at the injection site
3	Therapatic Antibodies	TrastzumabCetuzimab Panitumumab	can repress or alter the endogenous responses to specific cell or molecule Cancer treatment,inflammatory and auto immune disease	Allergic reactions, chills,weakness,diarrhea,nausea,vomiting,rash,itching
4	Therapatic vaccine	Hepatitis B vaccine HPV vaccine	Cervical cancer and liver Cancer .Brest,Lungs,colon,skin,kidney,Prostate	HIV and Influenza Skin rashes,flu like symptoms,muscleache,headache,weight gain.

3. Conclusion

The new and advance treatment for cancer have created a totally different design and way that how to treat cancer.This advance studied have created a deeper understanding of molecular basis of cancer.The earlier treatment are still valuable and a great use but they were found to be having lots of drawback. e.g. surgery and radiation are effective but they treat only the local area of cancer. Chemotherapy can treat the cancer cells that spread all over the body but this was found to be toxic and had very long term side effect.all the old therapies are still in use today they are not outdated but this will be probably they will not be only use for treatment of cancer.The news molecular based therapies are in near stage of discovery. Use of vaccine and immunoligical are the first advancement toward cancer. How so ever this is great deal toward the research that will be necessary in order to improve these treatment to there full potential.

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