Review Article

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Newer Treatment Options and Ongoing Research in Oncology

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Abstract

In general, cancer can be broadly defined as an abnormal and uncontrolled proliferation of cells in the body. There are many different treatment modalities for cancer which are being developed and proving to be useful for cancer patients. In this review, the newer treatment options available for cancer treatment have been highlighted so that the healthcare fraternity can have a better understanding of all available treatment options before deciding on the right treatment choice for saving the lives of patients.

Keywords: Proliferation; Modalities; Healthcare fraternity.

Introduction

Cancer can be defined as the uncontrolled proliferation or multiplication of cells in the body. It happens when the normal growth control mechanism in the body stops functioning: as a result, the old cells do not perish, and grow into new, abnormal cells. These abnormal cells form a mass of tissue, called a tumor. Around 70% of all deaths due to cancer tend to happen in the low- and middle-income countries. In many developing countries, cervical cancer is the most common cancer.[1]

Types of Cancer

Cancer can affect any part of the body. One of the most common cancer in women is breast cancer, and in men, it's prostate cancer. Both genders are affected largely by lung and colorectal cancers.

Broadly, there are five main types of cancer:

- Carcinomas– Involve the skin or tissues lining the internal organs.
- Sarcomas– Affect the bone, cartilage, fat, muscle or other connective tissues.
- Leukemias– Begins in the blood and bone marrow.
- Lymphomas– Affect the immune system.
- Cancers affecting the CNS– Develop in the brain and spinal cord.[1]

Treatment modalities

Today, the most commonly opted types of treatment for cancer include chemotherapy, radiotherapy, surgery and hormonal therapy.[1]

A number of promising new experimental treatment modalities for cancer do exist like the following:

- Hyperthermia therapy,
- Tumor Treating fields & High-Intensity Focused Ultrasound,

- Gene therapy using tumor suppressor genes,
- Immunotherapy where the immuno-therapeutic vaccines are helpful, and
- Adoptive cell transfer therapies.[3]

Hyperthermia therapy

As the name suggests, hyperthermia therapy makes use of localized or whole-body administration of heat.

Application of intense heat will cause denaturation and coagulation of cellular proteins, i.e. the proteins will undergo structural alterations like losing the quaternary, tertiary and secondary structure, leading to cell disruption and cell death at a rapid rate.

Use of mild heat in combination with other stresses can also lead to programmed cell death or apoptosis, which is the cell dying and creating fragments called apoptotic bodies, which can be cleaned up by phagocytic cells. Phagocytosis or cell eating is a process wherein the phagocytic cells engulf the apoptotic bodies, rendering them unable to damage the surrounding cells.

Research on this therapy is still in its very early stages of development, because scientists need to assess as to how much heat is needed to destroy these cancerous cells.

The history of hyperthermia therapy to treat certain medical conditions, like possible tumours, has a very long history. The ancient usage of this therapy, the reported cases of shrinkage in tumors in the early 1900s and clinical trials carried out in the 1970's form the basis of today's treatment options using hyperthermia therapy.

Leading a healthy lifestyle could help in preventing cancer by more than 30%, like avoiding the use of tobacco, having a healthy diet, being physically active and limiting the use of alcohol can help in preventing cancer. In developing countries, up to 20% of deaths due to cancer could be prevented by immunization against the infections of HBV and HPV.[3]

Non-Invasive Cancer treatments

These are experimental treatments not requiring doctors to make an incision in a patient and doesn't require removal of any tissue. The recovery time for patients undergoing these treatments will be shorter.

A few examples of non-invasive cancer treatments include the following:

1. Use of Radio waves
2. Tumor treating fields
3. High-Intensity Focused Ultrasound (HIFU)

Radio waves were found to be helpful in heating up nanoparticles to be implanted into the cancerous tissue like gold nanoparticles or carbon nanotubes. The heat-conducting abilities and lower risk of causing metal poisoning make them the choice for use in cancer treatment. Currently, this is in pe-clinical trials, showing a lot of promise as a treatment option.

Tumor Treating fields– As the name implies, an electric field is used in this method. Electrodes external to the body help in the application of an electric field through a tumour. The efficacy of this method has turned out to be better than chemotherapy without any side-effects in clinical trials. Currently, this is in its early development stages for different cancers.

High-Intensity Focused Ultrasound (HIFU) is useful in treating tumours of bone, liver, breast, brain, pancreas, kidney, rectum, testes and prostate. Here, Ultrasound is used to deliver heat or agitation into the body which in turn can be used to target and kill cancerous cells. Advantage of HIFU is that it can increasetargeting to tumour sites by higher density anticancer drug load and nanomedicines by 20 times higher than the traditional targeted cancer therapy.[3]

Gene therapy

Another advancement in cancer treatment is the use of tumor suppressor genes or antioncogenes, which are used in gene therapy for cancer. These genes delay or stop the tumor growth once they are introduced into the cancer cells. Vectors are used in gene therapy to slow down the growth of the tumor, and the commonly used vectors are the adenoviruses, which represent the largest division of non-enveloped viruses.

The advantages in choosing adenoviruses include:

√ Their cell structure and behaviour

√ Their non-specificity for cells which are affected (both replicating and non-replicating cells)

√ Their ability to accommodate large transgenes

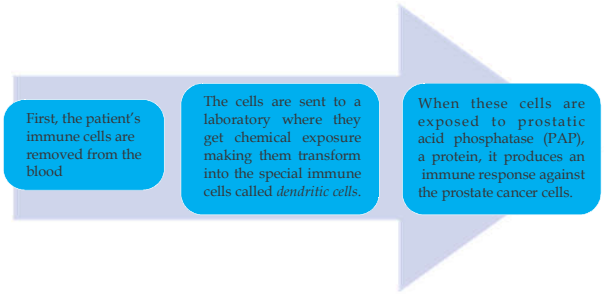
- √ Their use in protein coding without entering the host cell genome
- √ Use as a targeted therapy in the form of proteins or recombinant DNA

Gene therapy is expected to be highly efficacious, but it is still in its early stages of development.[3]

Immunotherapy

Among all treatment options available for cancers, immunotherapy is considered to be less toxic/ harmful and is well ahead in efficacy. This method takes help from the natural defence mechanisms in the body against the cancer cells.

The process is as follows:



Immunotherapeutic vaccines

The only immunotherapeutic vaccine that has received FDA approval so far is Sipuleucel-T (Provenge) for patients with advanced prostate cancer which is not responsive to hormonal therapy options.

Use of monoclonal antibodies (mAbs) represents another type of immunotherapy to treat cancer. They are antibodies designed in a way to have their action against specific antigens, like the cancer antigens. For using mAbs, the first step is identification of the right antigen to act on. This is not very easy, and investigations are still on for their action against a wide plethora of cancers.

Early detection and adequate treatment can help in the cure of cancers like breast cancer, cervical cancer, and colorectal cancer.[3]

Adoptive cell transfer therapies

Removal of cells from the immune system, usually white blood cells from the patient, followed by redesigning them to fight against particular types of cancer, and then re-infusing them back into the patient are the steps in adoptive cell transfer therapy. This kind of treatment should be specifically designed for each patient. Adoptive cell transfers help in improving a cell's functionality, particularly the immune function.

The fundamental principles of Adoptive cell transfer therapies were identified in the 1960's when the discovery of lymphocytes being mediators of allograft rejection in animals occurred.

In the 1960's, the discovery of lymphocytes to be the mediators of allograft rejection in animals occurred. Cultivation and manipulation of T-lymphocytes in cultures was needed to make use of T-cells to treat transplanted murine tumors. The first example of an Adoptive Cell Transfer (ACT) was the transfer of syngeneic lymphocytes from rodents which were profoundly immunized against the tumor to not allow the growth of small established tumors. Lymphocytes and Allografts form the basic building blocks for Adoptive Cell Transfer Therapies.[3]

Drug therapies

Drugs used for cancer therapy come from both man-made and natural sources which help in recovering from cancer.

Dichloroacetate (DCA)

Preclinical studies have shown the efficacy and mechanism of dichloroacetate (DCA) in lab rats, i.e. it was found to be through reactivation of the suppressed mitochondria in few kinds of tumor cells, which were starved of oxygen, thus helping in apoptosis. Since this drug has previously undergone testing for conditions like congenital lactic acidosis, now it is considered to be a comparatively safe, and not so expensive treatment option. But the lacuna is that this drug has gone through a pre-clinical trial in a very small patient population, with only five patients.

It works by inhibiting a kinase enzyme, namely pyruvate dehydrogenase kinase (PDK) which has been found to have increased activity in cancer cellsand causesdeprivation of adequate oxygen (hypoxic state). From pre-clinical trials, it has been observed that use of dichloroacetate inhibits the growth of cancers in animals in vitro. Administration of DCA can only happen in a carefully controlled laboratory environment, since, inappropriate use or dosage can be the cause of liver damage or other complications.[3]

Quercetin

Quercetin is an antioxidant that makes for an excellent free-radical-scavenging dietary supplement and it also supports programmed cell death (apoptosis) in cancerous cells. Laboratory

studies have proven its use to be anti-tumour proclivities in both oral cancer and leukaemia. Quercetin and ultrasound combination can significantly cause mortality of cultured skin and prostate cancer cells when compared with non-malignant cells. Natural sources of quercetin include most fruits, vegetables, grains and leaves. The topical ointment of quercetin is still in early stages of development, but the natural sources (food items) are available in the market.

Dietary sources of quercetin include: capers (canned or fresh), black plums, cranberries, radish leaves, dill, red onions, kale, sweet potato, blueberries, fennel, red delicious apples, broccoli and black or green tea. Popular treatment options involving quercetin are usually radiation therapy or Adoptive Cell Transfer Therapies that utilize a diet rich in quercetin as a complimenting supplement.[3]

Combination Opdivo and Yervoy

Clinical testing of the combination of Opdivo and Yervoy, products of Bristol-Myers Squibb showed the efficacy of the combination in treating melanomas. Studies conducted later in a larger cohort of patients (n=142) proved the same, with 22% patients showing a complete therapeutic response to the drugs.

Opdivo (Nivolumab), is useful in treating unresectable or metastatic melanoma and metastatic squamous and non-smell-cell lung carcinoma. It is also known as programmed death receptor

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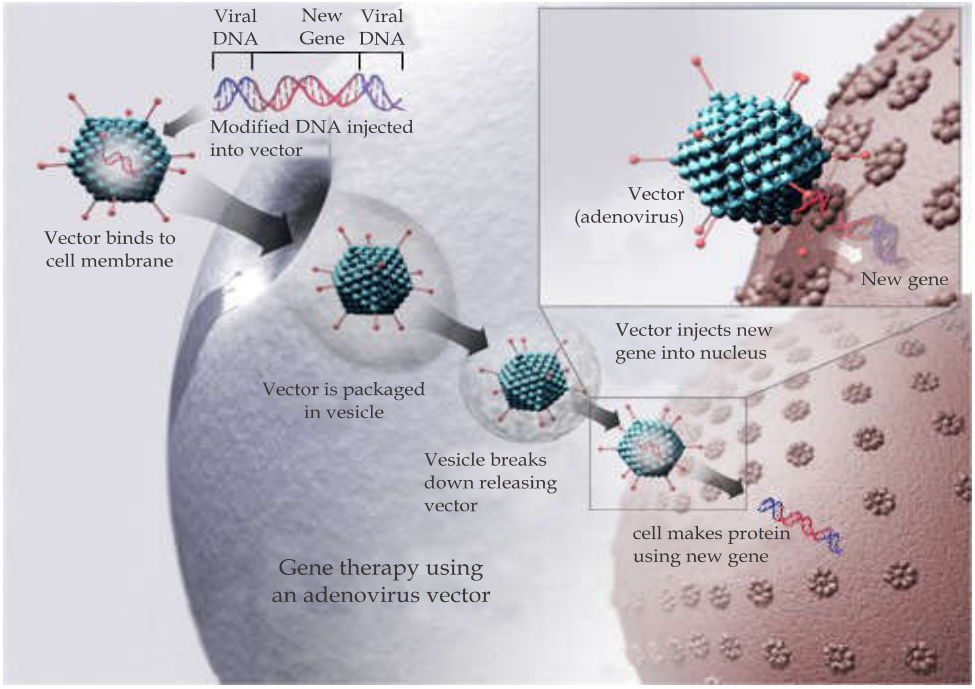

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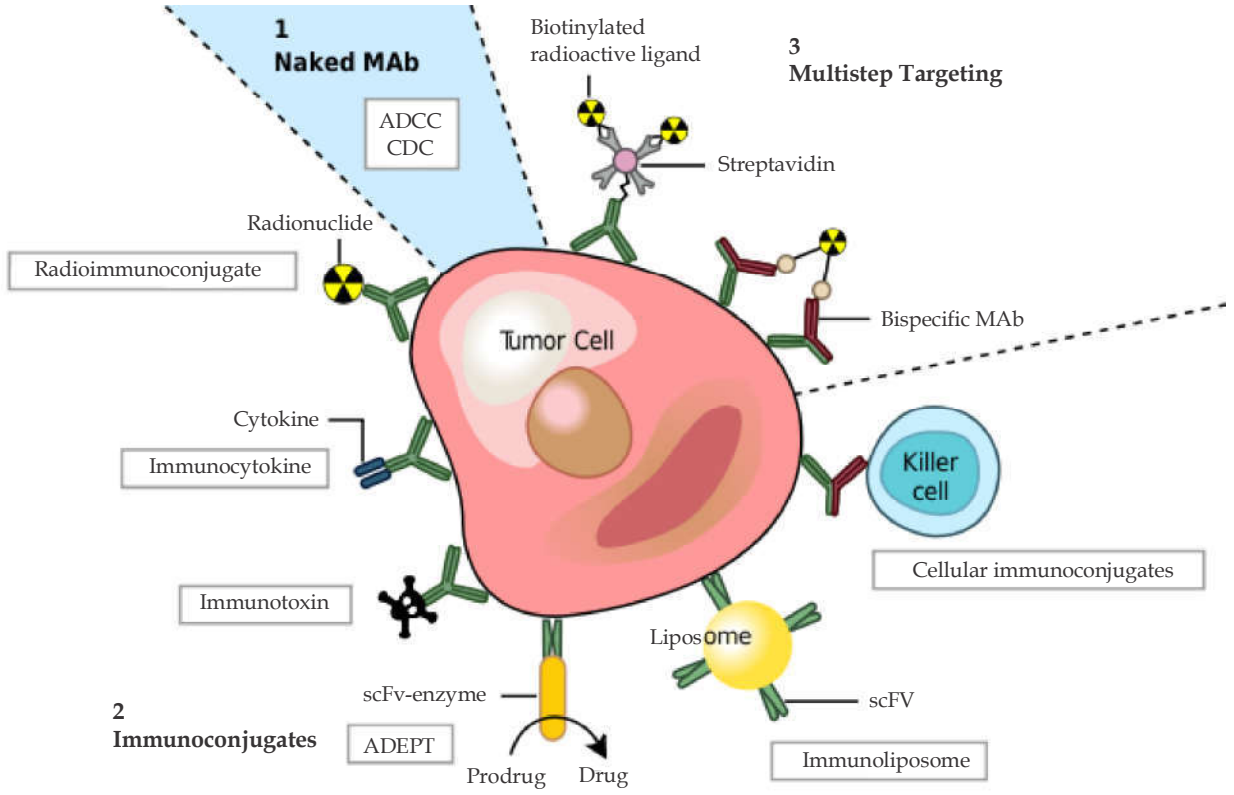

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which acts by blocking antibodies. Nivolumab is a drug designed to make the immune system of the patients act against the tumour cells killing them.

Yervoy (Ipilimumab) being a monoclonal antibody (mAbs) works by activating the immune system and making it target CTLA-4 which is a protein receptor. CTLA-4 causes downregulation of the immune system. The drug obtained approval from the U.S. FDA for melanoma (type of skin cancer) in 2011, and is undergoing clinical trials for use in small cell lung cancer, non-small cell lung carcinoma, metastatic hormone-refractory prostate cancer and bladder cancer.[3]

Bacterial therapies and Virotherapy

Clostridium novyi

Anaerobic bacteria, such as Clostridium Novyi, are useful in treating cancers by consuming the interior of oxygen-poor tumors in patients. The death of tumor cells happen because of the contact with the oxygenated sides. This method works because anaerobic bacteria do not require air or oxygen for their growth, so Clostridium novyi can grow in oxygen-poor tumors. Tumor-induced tissue hypoxia which leads to tissue necropsy can be the causative factor for more complications when compared with a normal tumor.

Utilizing anaerobic bacteria transformed with the help of an enzyme capable of converting a prodrug which is non-toxic into a toxic drug. The bacterial multiplication in the hypoxicand necrotic areas of the tumor happens when the enzyme is expressed in the tumor. Hence, a prodrug undergoes metabolism to the toxic drug only in the tumor. Clostridium sporogenes, a non-pathogenic anaerobe has helped in the demonstration of this and is also being studied to be used as a carrier for delivery of anticancer drugs into the tumors in patients.[3]

Genetically-modified poliovirus therapy

This therapy using genetically-modified Poliovirus samples is a very novel treatment strategy for cancer patients. Poliovirus was modified with the removal of the intrinsic disease-causing properties of the virus. The genetically modified version is called PVS-RIPO virus which works by direct infusion into the tumor like brain tumor. Inside the tumor, it infects and causes death of the cancer cells.

The cancer regression capabilities of PVS-RIPO have been remarkable, but itstrueadvantage is that it alerts the body's innate immune mechanisms in acting against the tumor cells as well. The immune system is programmed to act against viral infections and because of that, it identifies the infected tumorcells as being viral and attacks them. The human body normallydoesn'tact against cancer cells on its own because of the protective "shield" around the cancer cells which does not let the immune system to have a clear look at the tumor cells.

Glioblastoma multiforme (GBM), also called as glioblastoma or grade IV astrocytoma, is the most aggressive and common cancer that starts within the brain. Recovery is very rare in this cancer, but with PVS-RIPO, the patients may have a possibility to fight against this cancer.[3]

Conclusion

The experimental cancer treatments are medical options to supplement, improve, or replace the traditional cancer treatment options like surgery, radiation, and chemotherapy in order to lessen or eliminate cancerous growths and they have also been proved to be helpful in the survival of cancer patients for a comparatively longer period of time.

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