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Review Article

Revolutionizing Cancer Therapy with Newer Treatment Modalities: A Review

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Abstract

Non communicable diseases like Cancer is a leading cause of death group worldwide. The reason for every sixth death in the world is cancer, making it the second leading cause of death. Curing cancer is certainly one of the biggest challenges of the 21st century. In the last two decades, our knowledge of cancer and its treatment has greatly improved. This has revealed the huge variability that can be found between not only different types of cancer, but also between patients with the same type of cancer. It seems increasingly evident that there won't be a single method to 'cure' rather, each patient will be treated accordingly to their specific needs. But for individualized medicine to become a reality, we need a range of therapies wide enough to cover the broad spectrum of cancer. It has been found that cancer in one person doesn't always behave the same way in another person. Thanks to the innovative research that has fueled the newer treatment options available for cancer treatment that increases the individuals' survival rate. New approaches to cultivate the immune system in the fight against cancer are getting us closer to a future where cancer becomes a curable disease. Targeted therapies, personalized vaccines, gene therapy, microbiome treatments and stem cell transplantation are some of the technologies that will change the way of cancer treatment.

Keywords: Cancer, targeted therapies, gene editing, microbiome treatment, personalized vaccines.

INTRODUCTION

Cancer is one of the major causes of death globally. More than 11 million people are diagnosed with cancer and this rate has been estimated to increase to 16 million by 2020 [1]. For a better health management an early detection and treatment of the cancer is needed. Cancer therapy has been characterized by several ups and downs, not only due to the ineffective treatments and side effects, but also expecting complete remission and cure in many cases. There are more than 100 types of cancers, affecting various organs in our body. Cancers can be slow-growing or aggressive. There are some cancers which are more prevalent in specific age group or gender. They may also vary in the way they respond to therapy (drugs, radiation, hormones etc) and some of them may differ in their rate and primary site of metastasis too. Because of such a diverse nature, cancer treatment can never follow a "One treatment regime for all" approach. Several factors such as the type of cancer, the stage of cancer, the site or organ of location, the age and overall health of the patient at the time of diagnosis, the tumor pathology, immunohistochemistry etc influence the choice of treatment. Each of the treatments has its own side effects to the patient; then, it is always necessary for the doctor to discuss the treatment plans with the patient and their family and obtain their concurrence before proceeding with the treatment plan. In some cases, it is always safe for the patient and the doctor to go in for a second opinion for proceeding with any treatment plan. A complete removal of the cancer tissues without causing damages to the adjoining tissues is the required goal for any treatment plan. The complete removal of the cancer tissues is limited by property of the cancer tissues to spread to the adjoining tissues or spread to distant sites by microscopic metastasis. Treatment procedures such as chemotherapy and radiotherapy have negative side effects on the normal healthy tissues. The basic purpose of a cancer treatment plan is to have cure for the cancer and, when a complete cure is not possible, the treatment plan should be to suppress the cancer to a subclinical state and maintaining the normal state for the subject to lead a normal quality of life [2].

Types of Cancer Treatments

The cancer burden can be reduced through early detection of cancer and management of patients who develop cancer. There are alternative ways to treat a cancer patient ranging from the traditional methods of Chemotherapy, Radiotherapy and Surgery to advanced ones. The type of treatment that a patient receive will depend on the type of cancer that he/she have and how advanced it is. Since new information and understanding of biological process of cancer tissues are emerging regularly, new treatment procedures and plans are being developed and modified to have increased effectiveness and precision of the treatment, thereby enabling the survivability of the patients and improving their quality of life. These efforts include the development of more effective and less toxic treatments, such as targeted therapies, personalized vaccine therapy, gene therapy, microbiome treatment, stem cell transplantation as well as the improvement of therapies that have existed for decades, such as surgery, chemotherapy and radiation therapy. Some studies suggest better management of a treatment's toxic effects, thereby improving patient's ability for effective cancer treatment.

1) Targeted Therapy: - It is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread. Tumors have the ability to develop their own blood supplies, manipulate the immune system to hamper immune responses, and recruit normal cells to help them grow. Even as vital, tumor cells will ignore signals that normally tell old or damaged cells to die. This new understanding has created opportunities to develop Targeted Therapies (TT)—cancer treatments that target the specific changes, most often in proteins, that underlie the growth and development of cancer. Molecular targeted therapy refers to a class of medication that block the growth and spread of cancer by interfering with specific molecules that are critical for tumor progression, for example Tyrosine Kinase [3]. Surgery, radiation therapy, and standard chemotherapy will continue to play an important role in treating cancer, but the emergence in recent years of targeted therapies has expanded the treatment choices available to patients with certain types of cancer. Unlike traditional chemotherapy, which simply interferes with all rapidly dividing cells by interrupting the essential cellular events like DNA replication and microtubule assembly, targeted therapy focuses on molecular abnormalities specific to cancer. They consist of small molecular drugs and monoclonal antibodies. The targeted therapy is given in the form of small-molecule drugs either in the form of pills or capsules that can be swallowed. Monoclonal antibodies are proteins also known as therapeutic antibodies are usually given through a needle in a blood vein. These proteins are designed in such a way that they attach to specific targets found on cancer cells. Some cancer cells are marked by monoclonal antibodies therefore they are better seen and destroyed by the immune system. Other monoclonal antibodies directly stop malignant cells from growing or cause them to self-destruct. Mostly targeted therapy help treat cancer by interfering with specific proteins that help tumors grow and spread throughout the body. Some targeted therapies can cause cancer cells to go through this process of apoptosis. They starve cancer cells of the hormones it needs to grow**.** Hormone therapies are a type of targeted therapy that work in two ways: some of them prevent the body from making specific hormones while others prevent the hormones from acting on the cells, including cancer cells. More than 30 targeted drugs are having been approved in clinical use. To name few molecularly target anticancer drugs are- Imatinib (Gleevec, STI571), Cetuximab (Erbitux), Axitinib (Inlyta, AG013736) etc [3]. The most advanced of these agents that has been approved for the treatment of AML is the humanized anti-CD33 antibody–calicheamicin conjugate Mylotarg [4].

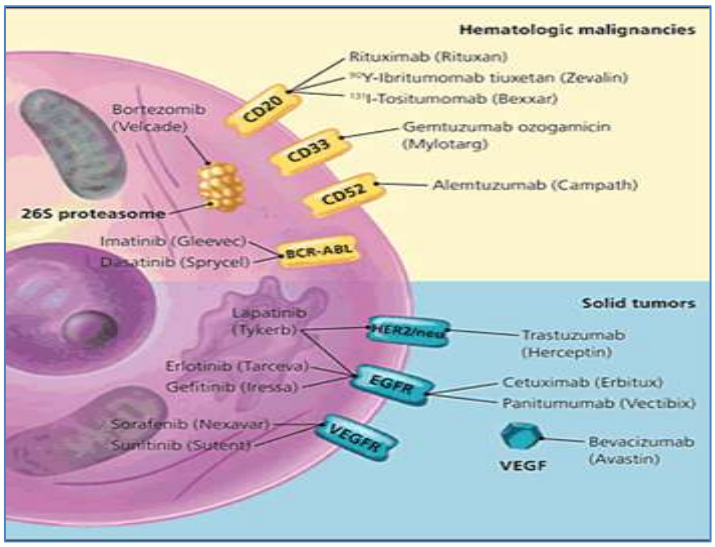

Fig-1: Available multiple agents used as anticancer drugs

2) Personalized Vaccine: - With the advancement in development of vaccines by emerging innovation of digital age, vaccinating a patient with individual tumor mutations may become the first truly personalized treatment for cancer. The first clinical trial of personalized vaccines on humans has shown the safety, feasibility and immunotherapeutic activity of targeting individual tumor mutation signatures [5]. To develop an individualized cancer vaccine, researchers needs to identify cancer-specific peptides that are known as neo-antigens, then use a cell, protein, or nucleic acid–based platform to deliver those neo-antigens to patients to prime the immune system to attack the tumor. Antigen-presenting cells like dendritic cells internalize the cancer-specific peptides selected for a personalized cancer vaccine and display them on their surface with the help of major histocompatibility complex (MHC) proteins. This triggers T cells with receptors that bind those neo-antigens to differentiate into effector, or killer, T cells that mobilize an immune reaction against cancer cells [Fig 2]. This activity in the cancer neo-antigen vaccine space is suggestive of the general concept of personalized cancer vaccines, which have thus far demonstrated highly specific immune responses against cancer cells without severe adverse events in patients. This excitement exists in spite of several remaining challenges that must be attended in clinical trials before taking the concept forward into mainstream cancer care [6].

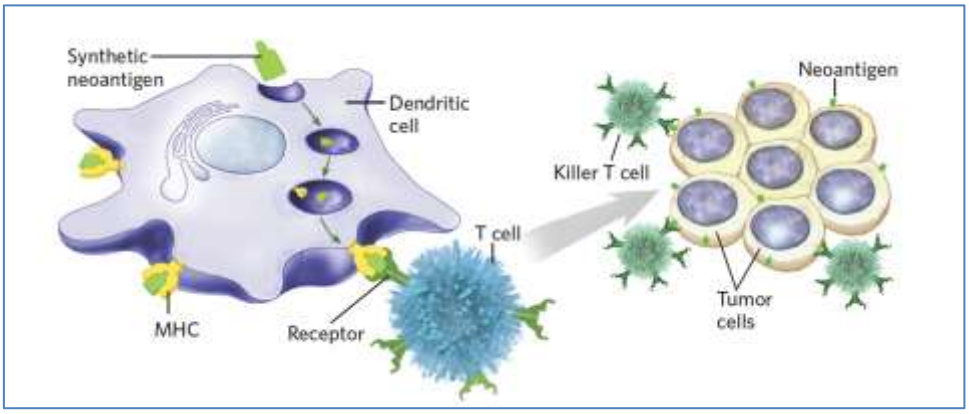

Fig 2: Personalized Cancer Vaccine Basics

3) Gene Therapies: - They are the newer treatment modality that introduces new genes into a cancerous cell or the surrounding tissue to cause cell death or slow the growth of the cancer [7]. There are many researchers around the world, conducting studies to test different ways by which gene therapy can help to treat cancer. Clinical trials include strategies involving augmentation of immunotherapeutic and chemotherapeutic approaches [8]. These strategies include *in vitro* and *in vivo* cytokine gene transfer, drug sensitization with genes for pro-drug delivery, and the use of drug resistance genes for bone marrow protection from high-dose chemotherapy. Inactivation of oncogene expression and gene replacement for tumor suppressor genes are among the strategies for targeting the underlying genetic lesions in the cancer cell [8]. According to Peng Wang et al, the type II bacterial clustered, regularly interspaced, short palindromic repeats (CRISPR)-Cas9 (CRISPR-associated protein) system (CRISPR-Cas9) is a powerful toolbox for gene-editing, however, the nonviral delivery of CRISPRCas9 to cells or tissues remains a key challenge. They explained a strategy to deliver Cas9 protein and single guide RNA (sgRNA) plasmid by a nanocarrier with a core of gold nanoclusters (GNs) and a shell of lipids. By altering the GNs with HIV-1-transactivator of transcription peptide, the cargo (Cas9/ sgRNA) can be delivered into cell nuclei. This strategy is utilized to treat melanoma by designing sgRNA targeting Polo-like kinase-1 (Plk1) of the tumor. Gene therapy can be used to complement traditional treatment methods and create a more advanced and personalized approach to cancer treatment. Current trials have shown promising results in improving the survival rates of cancers such as glioblastoma and pancreatic cancer.

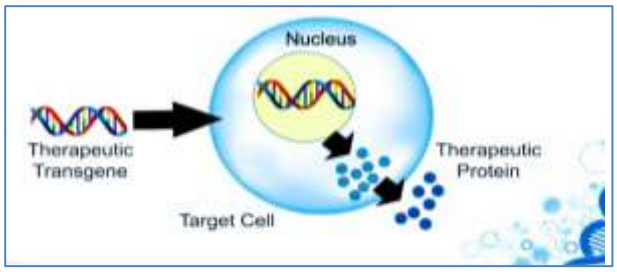

Fig-3: Gene Therapy

4) Microbiome Treatment: - The millions of organisms that make up the human microbiome play an important role in both health and disease. The effect of the human microbiome on cancer treatment is just the beginning to be explored. Recent studies have highlighted the importance and potential impact of microbes on disease recovery [9]. Remarkably, the microbiome can support the immune system in the fight against cancer. For example, cyclophosphamide (a drug used to treat leukemia and lymphomas) was found to

influence the microbes living in the gut. These gut microbes responded by promoting the creation of immune cells, which seems to enhance cyclophosphamide efficacy [10]. As we know, microbes have been shown to promote cancer development by inducing inflammation. This inflammatory response can also have a beneficial impact on cancer treatments [9]. Some therapies, such as platinum chemotherapy and CpG-oligonucleotide immunotherapy, are dependent on inflammation [9]. Mice that were treated with antibiotics (which killed the gut micobiome) did not respond as well to platinum chemotherapy or CpG-oligonucleotide immune therapy compared to mice with intact gut microbes [9]. These results suggest that the gut microbiome enhances the effects of therapies that are dependent on inflammation [9]. Resistance to cancer treatments has been linked to the presence of specific kinds of bacteria in the gut. Researchers watching at drug resistance in colorectal cancer patients found an increase in Fusobacterium nucleatum in the gut. The bacterium was shown to block death of the cancer cells and trigger autophagy, a survival tool for the cancer cells. The role of microbes in promoting immunity and affecting cancer development and treatment responses is still being investigated. It is clear, however, that the microbiome can play an important role in both the development of cancer and treatment responses. Ultimately, researchers hope to identify microbes that can fight cancer and develop ways to eliminate those which promote cancer development.

5) Stem Cell Therapy: - As the name suggests it involves the replacement of old and affected stem cells by new healthy ones. It may be used to treat some cancers such as leukemia, lymphoma, multiple myeloma and neuroblastoma. It may also be used after chemotherapy and high-dose radiation to treat the cancer. There are two main types of stem cell transplantation: (a) autologous transplantation; where the stem cells from the patient are collected, followed by a strong dose of chemotherapy or even radiation therapy. Once the rest period after the treatment is complete, the collected stem cells are retrieved and introduced back into the body intravenously. The stem cells reach the bone marrow in about 24 hours where they start growing and multiplying. (b) Allogeneic transplantation; where stem cells of another person are used for the transplantation. Allogenic grafts initiate immune reactions that are related to histocompatibility [11]. It is important to find an exact match for this, as there are proteins called antigens that need to match to those of the donor to avoid complications (Fig 4). Siblings of the patient are most likely to be the best match, if not, a close family member may work too. As chemotherapy or radiation therapy is a part of the transplantation process, many side effects of those treatments can be seen in this treatment method also but advances in cancer treatment can make them easier to live with. Stem cell transplants do not usually work against cancer directly. Instead, they help to recover body's ability to produce stem cells after treatment with very high doses of radiation therapy, chemotherapy, or both. But in cases of multiple myeloma and some types of leukemia, the stem cell transplant may work against cancer directly. This happens because of an effect called *graft-versus-tumor* that can occur after allogeneic transplants. Graft-versus-tumor occurs when white blood cells from the donor (the graft) attack any cancer cells that remain in the body (the tumor) after high-dose treatments. This effect improves the outcome of the treatments. Stem cells helps with a critical process needed for eliminating cancer by regenerating bad cells and tissues, and supporting the immune system for improving the chances of full recovery, however it is not an automatic cure.

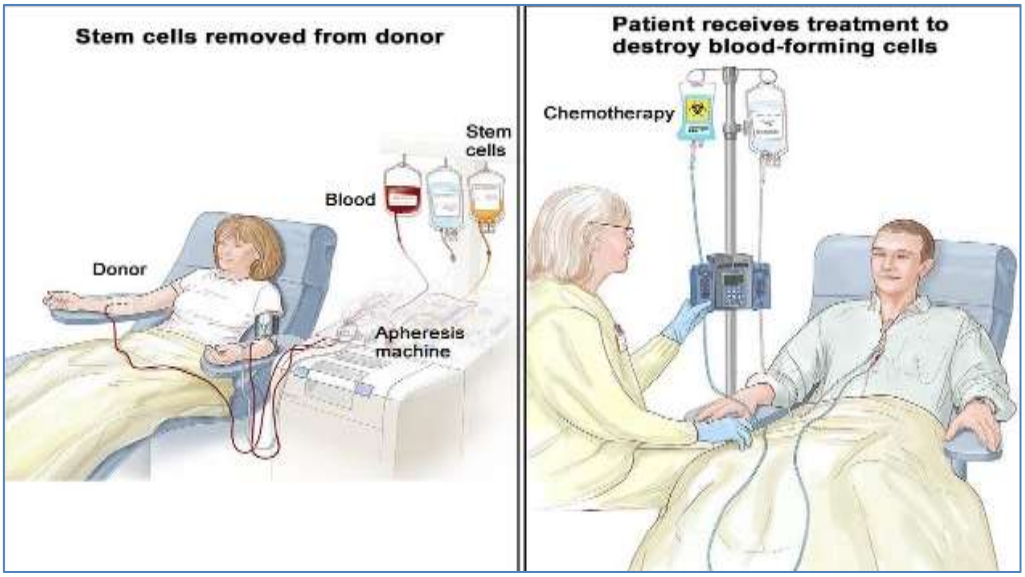

Fig-4: Transplantation of stem cells from donor to the recipient

CONCLUSION

Cancer is a complex disease involving complicated alterations in the physiological conditions of the body. There is a crucial need to search active treatment modalities for cancer, considering its severe complications. Traditional treatment methods like radiotherapy, chemotherapy, and surgery are still considered effective, but because of certain side effects to the normal body cells, we owe to work for some advancement in cancer treatment modalities. In recent times targeted therapy, personalized vaccine, gene therapy, microbiome treatment and stem cell therapy are introduced which, if used along with traditional therapies, can minimize the chances of relapse in cancer patients.

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