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A REVIEW: ALTERATIONS IN CANCER THERAPY AND REGULAR OUTLOOKS

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ABSTRACT

Cancer is when abnormal cells divide in an uncontrolled way. Some cancers may eventually spread into other tissues. There are over 200 types of cancers. Major kinds of cancers are Carcinoma, sarcoma, Leukemia, Lymphoma, myeloma and CNS cancers. Cancer therapies is the use of surgery, radiation, bone marrow transplantation, gene therapy, hormone therapy, medications and other therapies to cure a cancer, shrink a cancer or stop the development of a cancer. Depending on your particular circumstances, you may receive one treatment or you may receive a combined of treatments. Nano Particles are designed as active and passive targeting of anticancer drugs to deliver and increase the intracellular anticancer concentration. There are several types of Nano particles which include lipid and Nano capsules, metal, polymeric, dendrites, and liposomes.

KEYWORDS: Cancer therapy, Gene therapy, Immunotherapy, Nano medicine, Bone marrow transplantation, RNA Interference therapy.

INTRODUCTION

Cancer origins when a cell is somehow changes so that it multiplies out of control. A tumor is a mass collected of a mass of such abnormal cells. Mostly cancers form tumors, but not all tumors are cancerous.Benign, or non-cancerous, tumors do not grow to other parts of the body, and do not create new tumors. Malignant, or cancerous, tumors throng out healthy cells, interfere with body functions, and draw nutrients from body tissues.Cancers continue to grow and spread by direct extension or through a process called metastasis, whereby the malignant cells travel through the lymphatic or blood vessels,in the end of forming new tumors in other parts of the body. The term "cancer" surrounds more than 110 diseases affecting nearly every part of the body, and all arepossibly life-threatening.[1]

The major types of cancer are lymphoma, sarcoma, carcinoma, melanoma, and leukemia. Carcinomas -- the most commonly discover cancers - originate in the skin, breasts, lungs, pancreas, and other organs and glands. Lymphomas are cancers of lymphocytes. Leukemia is cancer of the blood. It does not usually form solid tumors. Sarcomas emerge in bone, muscle, fat, blood vessels, cartilage, or other soft or connective tissues of the body. They are relatively unusual. Melanomas are cancers that arise in the cells that make the pigment in skin.

Cancer has been recognized for thousands of years as a human illness, yet only in the past century has medical science appreciate what cancer really is and how it progression. Cancer specialists, called oncologists, have made remarkable advances in cancer diagnosis, prevention, and treatment. Today, more people diagnosed with cancer are living longer. However, some forms of the disease remain irritatingly difficult to treat. Modern treatment can significantly growing quality of life and may extend survival.[1]

DIFFERENT TYPES OF CANCERS

There are over 200 types of cancer; far too numerous to include in this article. Major kinds of cancers are listed below they are

- **Carcinoma:** Cancer that begins in the skin or in tissues that line or cover internal organs - "skin, colon, lung,pancreatic, ovarian cancers," epithelial, squamous and basal cell carcinomas, melanomas, papilloma's, and adenomas.

- **Leukemia:** Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of unusual blood cells to be produced and enter the blood -- "leukemia,"lymphoblastic leukemia's (ALL and CLL), myelogenousleukemias (AML and CML), T-cell leukemia, and hairy-cell leukemia.

- **Sarcoma:** Cancer that begins in bone, fat, muscle, cartilage, blood vessels, or other connective or

supportive tissue - "bone, soft tissue cancers," osteosarcoma, liposarcoma, angiosarcoma, synovial sarcoma, rhabdosarcoma, and fibrosarcoma.

- **Lymphoma and myeloma:** Cancers that begin in the cells of the immune system -- "lymphoma," T-cell lymphomas, B-cell lymphomas, Hodgkin lymphomas, non-Hodgkin lymphoma, and lymph proliferative lymphomas.

- **Central nervous system cancers:** Cancers that start in the tissues of the brain and spinal cord -- "brain and spinal cord tumors," gliomas, meningioma's, pituitary adenomas, vestibular schwannomas, primary CNS lymphomas, and primitive neuroectodermal tumors.[2]

CANCER THERAPIES

Cancer therapies is the use of surgery, radiation, medications and other therapies to cure a cancer, shrink a cancer or stop the development of a cancer. Many cancer treatments exist.

Depending on your particular circumstances, you may receive one treatment or you may receive a combined of treatments. There are several therapeutic methods that have been used to treat tumors and their surrounding environments. Nowadays, there are many examples of chemotherapeutic agents that have been used to control different cancers in clinic such as doxorubicin, gemcitabine, paclitaxel, and cisplatin.[3] However, chemotherapy resulted in multi-drug resistance in most of the patients. So to overcome these problems new innovations were came into existence. Other than chemotherapy there are several cancer treatments had been discovered with less toxicity,high bioavailability, and with better outcomes.

Some of them are

- **Immunotherapy:** Immunotherapy, also known as biological treatments, uses your body's immune system to fight cancer. Cancer can survive uncontrolled in your body because your immune system doesn't allow it as an interloper. Immunotherapy can help your immune system "see" the cancer and attack it.

- **Radiation therapy:** Radiation therapy uses high-powered energy beams, such as X-rays or protons, to dispatch cancer cells. Radiation treatment can come from a machine outside your body (external beam radiation), or it can be placed inside your body (brachytherapy).

- **Stem cell transplantation:** The main difference between a stem cell and bone marrow transplant is whether stem cells are collected from the bloodstream or bone marrow. A stem cell transplant uses stem cells from your bloodstream, or a donor's bloodstream. This is also called a peripheral blood stem cell transplant.A bone marrow transplant uses stem cells from your bone marrow, or a donor's bone marrow.

- **Bone marrow transplantation:** Your bone marrow is a spongy substance found in the center of the bonesthat makes blood cells from blood stem cells. A bone marrow transplant, also knowns as a stem cell transplant, can use your own bone marrow stem cells or those from a donor.

A bone marrow transplant allows your doctor to use higher doses of chemotherapy to treat your cancer. It may also be used to replace diseased bone marrow.

- **Targeted drug therapy:** Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to survive.

- **Gene therapy:** Gene therapy is one of the newesttherapies, which involves insertion of desired genetic material into Cancerous cell. This process is done to restore the missing gene, or to replace the mutated gene.

- **Nanomedicine:** It offers a versatile platform of biodegradable and biocompatible systems that are able to deliver regular chemotherapeutic drugs in vivo, increasing their bioavailability and concentration around tumour tissues, and improving their release profile [4]nanoparticle's can be exploited for different applications, ranging from diagnosis to therapy.

- **Hormone therapy:** Some types of cancer are fueled by your body's hormones. Examples include breast cancer and prostate cancer. Removing those hormones from the body or blocking their effects may cause the cancer cells to stop increasing.

- **Cryoablation:** This treatment kills cancer cells with cold. During cryoablation, a thin, wand like needle (cryoprobe) is inserted through your skin and directly into the cancerous tumor. A gas is pumped into the cryoprobe in order to freeze the tissue. Then the tissue is allowed to thaw. The freezing and defrost process is repeated several times during the same treatment session in order to kill the cancer cells.

- **Radiofrequency ablation:** This treatment uses electrical energy to heat cancer cells, causing them to kill. During radiofrequency ablation, a doctor guides a thin needle through the skin or through an incision and into the cancer tissue. High-frequency energy passes through the needle and causes the surrounding tissue to heat up, killing the nearby cells.

- **Clinical trials.** Clinical trials are studies to investigate new ways of treating cancer. Thousands of cancer clinical trials are ongoing.[5,6]

1. IMMUNOTHERAPY

Immunotherapy is a type of cancer therapy that helps your immune system kill cancer cells. The immune system helps your body fight infections and other

diseases. It is made up of white blood cells (WBCs), organs and tissues of the lymph system.

Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer.

The immune system finds and destroys abnormal cells (tumor) and most likely prevents or curbs the growth of many cancers. In case, immune cells are sometimes found in and around tumors. These cells, called tumor-infiltrating lymphocytes (TILs), are a sign that the immune system is responding to the tumor. People whose tumors contain TILs often do better than people whose tumors don't contain them.

Even though the immune system can stop or slow cancer growth, cancer cells have ways to avoid demolition by the immune system. For example, cancer cells may[6]

- Have proteins on their surface that turn off immune cells.
- Change the normal cells around the tumor so they interfere with how the immune system responds to the cancer cells.
- Have genetic changes that make them less visible to the immune system.
- Immunotherapy helps the immune system to better act against cancer.

TYPES

Several types of immunotherapy are used to treat cancer. These include

- **T-cell transfer therapy**, which is a treatment that boosts the natural capability of your T cells to fight cancer. In this treatment, immune cells are taken from your tumor. Those that are most active against your cancer are selected or changed in the lab to better attack your cancer cells, grown in large batches, and put back into your body through a needle in a vein.T-cell transfer therapy may also be called adoptive immunotherapy.

- **Immune checkpoint inhibitors**, which are drugs that block immune checkpoints. These checkpoints are a normal part of the immune system and keep immune responses from being too strong. By choking them, these drugs allow immune cells to respond more strongly to cancer.

- **Immune system modulators**, which enhance the body's immune response against cancer. Some of these agents affect specific parts of the immune system, whereas others affect the immune system in a more general way.

- **Monoclonal antibodies**, which are immune system proteins generated in the lab that are designed to block to specific targets on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and demolished by the immune system. Such monoclonal antibodies are a type of immunotherapy. Monoclonal antibodies may also be called therapeutic antibodies.

- **Treatment vaccines**, which work against cancer by boosting your immune system's response to cancer cells. Treatment vaccines are different from the ones that help prevent disease.[2]

2. RADIOTHERAPY

Radiotherapy (Radiation therapy) is a cancer treatment that uses high doses of radiation to destroy cancer cells and shrink tumors. At low doses, radiation is used in x-rays to see inside your body, as with x-rays of your teeth or broken bones.

At high doses, radiation therapy kills cancer cells or slows their growth by breaking their DNA. Cancer cells whose DNA is damaged beyond repair stop die. When the damaged cells die, they are broken down and removed by the body. Radiation therapy does not kill cancer cells right away. It takes days or weeks of treatment before DNA is breaking enough for cancer cells to die. Then, cancer cells keep dying for weeks or months after radiation therapy ends.[7]

Types of Radiation Therapy

There are two main types of radiation therapy internal and external beam. The type of radiation therapy that you may have depends on many factors, including[7,8]

- The type of Tumor or cancer
- The size of the tumor
- The tumor's location in the body
- How close the tumor is to normal tissues that are sensitive to radiation
- Your general health, genetic history and medical history
- Whether you will have other types of cancer treatment
- Other factors, such as your age and other medical conditions.

Internal Radiation Therapy

Internal radiation therapy is a treatment in which a source of radiation is put inside your body. The radiation source can be solid or liquid.

Internal radiation therapy with a solid source is also known as brachytherapy. In this type of treatment, seeds, ribbons, or capsules that contain a radiation source are placed in your body, in or near the tumor location. Like external beam radiation therapy, brachytherapy is a local treatment and treats only a specific part of your body.It is an internal delivery of radiation as cancer therapy. Radioactive implants are placed very near or within a tumor and deliver high doses of radiation with less harm to other organs than external radiation (Figure 1).With brachytherapy, the radiation source in your body will give off radiation for a while.[9]

Internal radiation therapy with a liquid source is called systemic therapy. Systemic means that the treatment travels in the blood to tissues all round your body, seeking out and killing cancer cells. You receive systemic radiation therapy by swallowing, through a vein via an IV line, or through an injection. With systemic radiation, body fluids, such as sweat, urine, and saliva, will give off radiation for a while.[10]

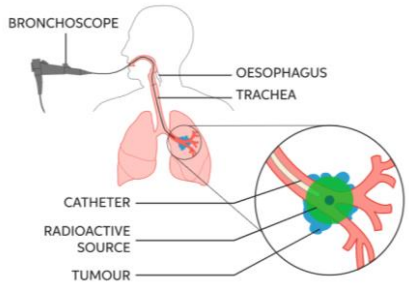

Figure 1: Internal Beam Radiation Therapy (Brachytherapy).[10]

External Beam Radiation Therapy

External beam radiation therapy comes from a machine that aims radiation at your cancer. The machine is large and may be noisy. It does not touch you, but can move around you, sending radiation to a part of your body from many directions. External beam radiation therapy is a local treatment, which means it treats a specific part of your body. (Figure 2) For example, if you have cancer in your lung, you will have radiation only to your chest, not to your whole body.[11]

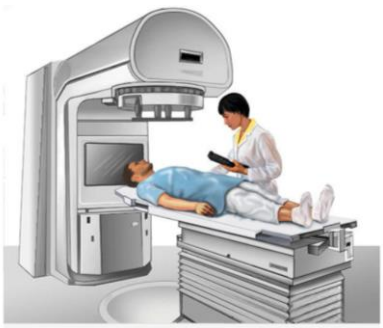

Figure 2: External Beam Radiation Therapy.[11]

Cancers treated by radiation therapy

A systemic radiation therapy is called as radioactive iodine(I-131), is most often used to treat certain types of thyroid cancer.

Another type of systemic radiation therapy, called targeted radionuclide therapy, is used to treat some patients who have advanced prostate cancer or gastro-enteropancreatic neuroendocrine tumor (GEP-NET). This type of treatment may also be mentioned to as molecular radiotherapy. Brachytherapy is most often used to treat cancers of the head and neck, breast, cervix, prostate, and eye.[12]

3. STEM CELL TRANSPLANTATION

Stem cell transplants are methods that replace blood-forming stem cells in people who have had theirs destroyed by the very high doses of chemotherapy or radiation therapy that are used to treat certain cancers. (Figure 3)

Blood-forming stem cells are important because they grow into different types of blood cells. The main types of blood cells are:

- White blood cells, which are part of your immune system and help your body fight infection
- Red blood cells, which carry oxygen throughout your body
- Platelets, which help the blood clot

You need all three types of blood cells to be healthy.[13,14]

Types of Stem Cell Transplants

In a stem cell transplant, you receive normal blood-forming stem cells through a needle in your vein. Once they enter your bloodstream, the stem cells travel to the bone marrow, where they take the location of the cells that were destroyed by treatment. The blood-forming stem cells that are used in transplants can come from the bone marrow, bloodstream, or umbilical cord. Transplants can be

- Allogeneic, which means the stem cells come from someone else. The donor may be a blood relative but can also be someone who is not related.
- Autologous, which means the stem cells come from you, the patient
- Syngeneic, which means the stem cells come from your identical twin, if you have one.

To reduce possible side effects and upgrade the chances that an allogeneic transplant will work, the donor's blood-forming stem cells must match yours in certain ways.[14]

4. TARGETED THERAPY

Targeted therapy is a cancer treatment that uses drugs to target particular genes and proteins that are involved in the growth and survival of cancer cells. Targeted therapy can affect the tissue environment that helps a cancer grow and survive or it can target cells related to cancer growth, like blood vessel cells.[15]

TYPES OF TARGETED THERAPY

There are several different types of targeted therapy. The most common types are monoclonal antibodies or small-molecule drugs.

Monoclonal antibodies

Monoclonal antibodies block a specific target on the outside of cancer cells. The target might also be in the area around this cancer. Monoclonal antibodies can also send toxic substances right to cancer cells. For example, they can help chemotherapy and radiation therapy reach cancer cells better. Monoclonal antibodies are also a type of immunotherapy.[16]

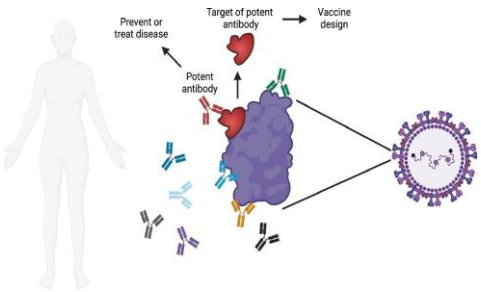

Figure 3: The monoclonal antibodies against infectious pathogens.[16]

How does targeted therapy work against cancer?
Most types of targeted therapy help treat cancer by interfering with specific proteins that help tumors grow and spread throughout the body. They treat cancer in many ways. They can

- **Help the immune system destroy cancer cells.** One reason that cancer cells bloom is because they can hide from your immune system. Certain targeted therapies can mark cancer cells so it is easier for the immune system to find and kill them. Other targeted therapies help boost your immune system to work better against cancer.

- **Stop cancer cells from growing.** Healthy cells in your body usually divide to make new cells only when they receive strong signals to do so. These signals bind to proteins on the cell surface, revealing the cells to divide. This process helps new cells form only as your body needs them. But, some cancer cells have changes in the proteins on their surface that tell them to divide whether or not signals are present. Some targeted therapies interfere with these proteins, preventing them from telling the cells to divide. This process helps slow cancer's uncontrolled growth.

- **Stop signals that help form blood vessels.** Tumors need to form new blood vessels to grow beyond a certain size. In a process called angiogenesis, these new blood vessels form in response to signals from the tumor. Some targeted therapies called angiogenesis inhibitors are designed to interfere with these signals to prevent a blood supply from forming. Without a blood supply, tumors stay small. Or, if a tumor already has a blood supply, these treatments can cause blood vessels to die, which causes the tumor to shrink.

- **Deliver cell-killing substances to cancer cells**. Some monoclonal antibodies are combined with toxins, chemotherapy drugs, and radiation. Once these monoclonal antibodies attach to targets on the surface of cancer cells, the cells take up the cell-killing substances, causing them to die. Cells that don't have the target will not be harmed.

- **Cause cancer cell death**. Healthy cells die in an orderly manner when they become damaged or are no longer needed. But, cancer cells have ways of avoiding this dying process. Some targeted therapies can cause cancer cells to go through this process of cell death.

- **Starve cancer of the hormones it needs to grow**. Some breast and prostate cancers require certain hormones to grow. Hormone therapies are a type of targeted therapy that can work in two ways. Some hormone therapies prevent your body from making specific hormones. Others prevent the hormones from acting on your cells, including cancer cells.[17,18,19,20,21]

5. GENE THERAPY

Gene therapy implicit any procedure intended to treat or reduce a disease by genetically modifying the cell of a patient.[4] The material to be shifted into patient cells may be genes, gene fragments, or oligonucleotides. Gene transfer therapy can be conducted either as in vivo or ex vivo approaches. In the in vivo approach, targeted cells are approached directly, such as the intradermal injection of a metastatic nodule, or intravesical treatments for superficial bladder cancer. In the ex vivo approach, targeted cells from a tumor are selected, then collected, grown in culture media at a controlled microenvironment, manipulated genetically by the introducing of a new gene or protein (transgene) in the cell genome, then introduced back into the host. The ex vivo approach is much simpler to achieve as it is easier to manipulate target cells externally.[22]

Gene transfer is a new 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. This treatment method is very flexible, and a wide range of genes and vectors are being used in clinical trials with successful outcomes.

Gene therapy is deliberate as the introduction of a normal copy of a defective gene in the genome in order to cure specific diseases.[23] The first application dates back to 1990 when a retroviral vector was exploited to deliver the adenosine deaminase (ADA) gene to T-cells inpatients with severe combined immunodeficiency (SCID).[24] Further research demonstrated that gene therapy could be applied in many human rare and chronic disorders and, most significantly, in cancer treatment. Approximately 2,900 gene therapy clinical trials are currently ongoing, 66.6% of which are related to cancer.[25] Different strategies are under evaluation for cancer gene therapy:

- expression of pro-apoptotic[26,27] and chemo-sensitizing genes[28]
- expression of wild type tumour suppressor genes[29]
- expression of genes able to solicit specific antitumour immune responses and
- Targeted silencing of oncogenes.

METHODS OF GENE THERAPY

Gene therapy implicit an approach that aims to delete, modify, or replace abnormal gene (s) at a target cell.

Such target cells may be malignant primary or metastatic nodules, circulating tumor cells or dormant stem cells, and specific cells such as T-cell lymphocytes or dendritic cells. With the presence of over 20,000 active genes in human cells, exposed to numerous factors whether hereditary, environmental, infectious or spontaneous, inexhaustible possibilities for gene mutation, aberration, dysfunction or deletion have been expected, leading to clinical presentation of various medical disorders, including cancer.

GENE TRANSFER DELIVERY SYSTEMS

Several methods have been developed to facilitate the entry of genetic materials (transgenes) into target cells, using various vectors. They are broadly divided into two major categories: viral (or bacterial) and non-viral vectors [Table 1]. Viruses usually bind to target cells and introduce their genetic materials into the host cell as part of their replication process. As they enter target cells, they can carry a load of other genetic material called transgenes. For non-viral vectors, different approaches have been used, using physical, chemical, as well as other modes of genetic transfer. Transferring genetic material directly into cells is referred to as ―transfection, while moving them into cells carried by a viral or bacterial vector is termed ―transduction. Non-viral approaches have the advantage of safety and easy modifiability, but have a lower transfection efficiency compared to viral vectors.[30]

Table 1: Viral and Non-viral Vectors.

Viral Vectors	Non-Viral Vectors
Adeno-associated virus	Lipid nanoparticles
Lentivirus	Polymer nanoparticles
Sendai Virus	Exosomes
Adenovirus	Peptide based complex
Bocavirus	iTOP
	Feldan shuttle

Physical mediated gene transfer: DNA genetic material that is coated with nanoparticles from gold or other minerals, and with their kinetic energy supplemented by squeezed air or fluid (gene gun), or using ultrasound, can force the genetic material into the target cell, followed by the release of DNA into its nucleus. They are best matched for gene delivery into tissue or in case of gene vaccination.[31]

The electroporation gene therapy approach aims to achieve cellular membrane disruption with high-voltage electrical pulses, resulting in the formation of Nano pores through which naked DNA, foreign genetic materials, and even chemotherapeutic agents can enter cells.[31,32] This approach is best suited for plasmid DNA-based gene transfer therapy with the advantage of effectiveness in a vast array of cell types, ease of its administration, lack of genome integration with the risk of malignancy, as well as the low potential for undesirable immunogenicity.[33] Electroporation is presently being tested in several clinical trials, especially on patients with malignant melanoma, prostate cancer, colorectal cancer, and leukemia.[34]

Chemical mediated gene transfer: Cationic liposomes are microscopic vesicles of synthetic phospholipids and cholesterol that can enter into cells by endocytosis[35], with the capability of carrying a variety of molecules such as drugs, proteins, nucleotides, plasmids and large genes.[35] Their advantage is selectivity to endothelial cells, a relatively high rate of gene transfer efficiency, a broad application as carriers for many genes, and the lack of severe side effects.[35] When combined with small interfering RNA (siRNA), cationic liposomes may lead to the inhibition of tumor proliferation, inducement of apoptosis, and enhancement of radio sensitivity to tumor cells.[36]

Synthetic viruses have been developed to exploit the efficiency of viral vectors and the advantage of liposomes.[37] Once they enter the target cell, DNA is released from the endosome. This method has shown promising results in preclinical studies.[38,39,40,41] Transposons can also transport genetic material inside the cell as well as into the nucleus.[42]

Bacterial mediated gene transfer Some bacteria have the capability of specifically targeting tumor cells, leading to RNA interference (RNAi) and gene silencing with blockage of RNA functions, including cellular metabolism and protein synthesis. Examples include Escherichia coli, Salmonella typhimurium, Clostridium, and Listeria.[43] Bacterial vectors can deliver pro-drug-converting enzymes and cytotoxic agents into tumor cells, and can mediate the host immune response. They can be engineered to carry magnetic or fluorescent material to enhance the advantages of diagnostic approaches in tumor localization, such as with magnetic resonance imaging (MRI)[44], and even in the development of cancer vaccines.[45] However, the outcome has been far less pronounced compared to other RNA interference silencing techniques. Overall, genetically engineered bacteria acting as vectors for RNA interference are relatively safe, effective, practical and cheaper to manufacture compared to viral vectors. They selectively colonize and grow within the tumor. They can also be administered orally, hence their use in the management of gastrointestinal disorders.[46]

Viral mediated gene transfer: Viruses are small particles that contain either RNA or DNA, and may be single-stranded (ss) or double-stranded (ds). The viral structure consists of a genome surrounded by a protective protein coat (viral capsid) which helps the virus attach to host cell receptors, and prevents viral destruction by cell nuclease enzymes. Some viruses may also have a lipid bilayer envelope derived from the host cell's membrane, and an outer layer of viral envelope made of glycoprotein.[45] A complete viral particle (vision) by itself is unable to replicate. For propagation, the virus needs to insert its genetic material into a host

cell, in order to acquire metabolic and biosynthetic products for viral transcription and replication.

6. NANO DELIVERY SYSTEMS

Cancer treatments are currently limited to surgery, radiation, and chemotherapy. All three methods risk harms to normal tissues or incomplete eradication of the cancer. Nanotechnology offers the means to target chemotherapies directly and selectively to cancerous cells and neoplasms, guide in surgical resection of tumors, and enhance the therapeutic efficacy of radiation-based and other current treatment modalities. All of this can add up to a decreased risk to the patient and an increased probability of survival.[46]

Nano delivery systems are mainly based on delivery of curative through use of nano material properties. Although small compared to cells, nanoparticles are large enough to encapsulate many small molecule compounds, which can be of multiple types. At the same time, the relatively large surface area of nanoparticle can be functionalized with ligands, including small molecules, DNA or RNA strands, peptides, aptamers or antibodies. These ligands can be used for therapeutic effect or to direct nanoparticle fate in vivo. These properties enable amalgamation drug delivery, multi-modality treatment and combined therapeutic and diagnostic, known as theranostic action. The physical properties of nanoparticles, such as energy absorption and re-radiation, can also be used to disrupt diseased tissue, as in laser ablation and hyperthermia applications. Innovative strategies include the design of nanoparticles as artificial antigen presenting cells and in vivo depots of immunostimulatory factors that exploit nanostructured architecture for sustained anti-tumor activity.[47]

DELIVERING CHEMOTHERAPY: The traditional use of nanotechnology in cancer therapeutics has been to improve the pharmacokinetics and reduce the systemic toxicities of chemotherapies through the selective targeting and delivery of these anticancer drugs to tumor tissues. The advantage of Nano sized carriers is that they can increase the delivered drug's overall therapeutic index through Nano formulations in with chemotherapeutics are either encapsulated or conjugated to the surfaces of nanoparticles.

This capability is largely due to their harmonious size and surface properties. Size is a major factor in the delivery of nanotechnology-based therapeutics to tumor tissues. Selective delivery of nontherapeutic platforms depends primarily on the passive targeting of tumors through the enhanced permeability and retention (EPR) effect.

This phenomenon relies on defects specific to tumor microenvironment such as defects in lymphatic drainage, along with increased tumor vasculature permeability, to allow nanoparticles (<200 nm) to accumulate in the tumor microenvironment. Furthermore, the timing or site of drug release can be controlled by triggered events, such as ultrasound, pH, heat, or by material composition.[48]

NANO ENABLED IMMUNOTHERAPY: Immunotherapy is a promising new front in cancer treatment encompassing a number of approaches, including checkpoint inhibition and cellular therapies. Expanding the benefits of immunotherapy requires a greater understanding of tumor-host immune system interactions.[49]

Nanotechnologies are also being investigated to deliver immunotherapy. This includes use of nanoparticles for delivery of immunostimulatory or immunomodulatory molecules in combination with chemo- or radiotherapy or as adjuvants to other immunotherapies.[50,51,52,53] Standalone nanoparticle vaccines are also being designed to raise sufficient T cell response to eradicate tumors, through co-delivery of antigen and adjuvant, the inclusion of multiple antigens to stimulate multiple dendritic cell targets, and continuous release of antigens for prolonged immune stimulation.[50] Molecular blockers of immune-suppressive factors produced can also be co-encapsulated in nanoparticle vaccines to alter the immune context of tumors and improve response.Additional uses of nanotechnology for immunotherapy include immune depots placed in or near tumors for in situ vaccination and artificial antigen presenting cells.[51,52]

CANCER TARGETTING WITH CONJUGATED NANO PARTICLES

Nano Particles have been used to produce one or more of the followings actions. They prevent the degradation of the combined drug. They also increase its absorption through the epithelial diffusion that ultimately results in reaching the optimum concentration in a short time.Nano Particles also alter the pharmacokinetic and distribution of the drug in the tissue and increase the intracellular efflux in cancer cells.[53] Nano Particles are designed as active and passive targeting of anticancer drugs to deliver and elevate the intracellular anticancer concentration. Enhancing the permeability and retention effects of anticancer drugs is considered as passive targeting of Nano Particles to the tumors. However, actively targeted Nano particles can be designed based on tumor microenvironment- and ligand-directed targeting to the tumor cells.[54] Therefore, as aindividual inherent property of Nano particles to the solid tumors, the nanoparticle is considered as an excellent tumor-targeting vehicle. This effect makes the accumulation of Nano particles preferable at the tumor site. In addition, the multifunction of Nano particles allows targeting the tumor site that is directly connected to the main blood circulation.[55] This action considered as a major advantage of Nano particles against MDR mechanisms.

COMMON NANO PARTICLES USED IN CANCER THEARPY: There are several types of Nano particles

which include lipid and Nano capsules, metal, polymeric, dendrites, and liposomes.[56]

Liposomes: Liposomes are mixed drug delivery systems normally collected of phospholipids. It is consisting of the concentric bilayer vesicles with layers of aqueous media separating the lipid layers. The small unilamellar vesicles have particle size range of 20–80 nm and consist of a lipid outer layer with an aqueous core. The type of phospholipids determined the charge of the surface of the liposomes (charged or uncharged).[57] Both hydrophobic and hydrophilic drugs are included in liposomes. The hydrophobic drug is dissolved in the lipid layers, while hydrophilic drugs inhabit remain in the aqueous core. Several liposomal drugs are now marketed including AmBisome® (amphotericin B), Doxil® (doxorubicin hydrochloride), and Visudyne® (verteporfin). These preparations inhibit direct P-gp efflux or bypassing P-gp through an endocytosis pathway.[57] A liposome is a vesicle which consists of phospholipid membrane and can be filled with chemotherapy. Phospholipids have hydrophilic head and hydrophobic tail. Liposome is one of the most common Nano particles that is approved for treatment of cancer.[58,59,60] Liposomes are usually administrated as a potential targeting and delivery tool of the chemotherapy because liposomes able to minimize elimination, increase the targeting, and reduce the toxic side effect of the chemotherapeutical agents.[61] Doxorubicin is one of the commercial available chemotherapies in a liposome dosage form (e.g., Doxil and Myocet).[62] Pharmaceutically, the liposome improves the pharmacokinetic and pharmacodynamics properties of the drug used; hence, the survival of cancer patients increases compared with parenteral drug treatment.

Polymer, Lipid Nano capsules, and Nanoparticles

Nano capsules have polymeric membrane (polymers or a combination of hydrophilic/lipophilic surfactants) that covers the liquid core (essential oils and triglycerides). The hydrophobic drugs are loaded in the lipid core and considered as a reservoir allowing a high drug loading with sustained release. Therefore, Nano capsules are ideal for lipid-soluble drug preparation.[63] Lipid Nano particles (or Nano capsules) are commonly used to overcome P-gp-mediated drug resistance.[64] an example of that is the use of Nano sponge.[65] *In vivo*, polyalkylcyanoacrylate Nano particles can reverse P-gp activity by an endocytosis process.[66] Polyisohexylcyanoacrylate (PIHCA) chemotherapy Nano particles showed more cellular uptake and cytotoxicity than free drugs in resistant cells. The mechanism of delivery of these Nano particles is by the changing the positive charge of drugs to ion pair with cyanoacrylic acid (a nanoparticle degradation product) increasing its diffusion across cell membranes.[67] A new polymer-lipid hybrid nanoparticle (PLN) system was used to bypass P-glycoprotein, leading to improved uptake and cytotoxicity of chemotherapy in resistant cells.[68] Drug-loaded sodium bis(2-ethylhexyl) sulfosuccinate (AOT)-alginate Nano particles significantly increased the chemotherapy cytotoxicity in resistant cells and overcome P-gp-mediated drug resistance.[69]

Polymer-Drug Conjugates

Poly(N-[2-hydroxypropyl]methacrylamide) (polyHPMA) and HPMA copolymers are water-soluble, nonimmunogenic synthetic polymers. HPMA copolymer-chemotherapeutic drug conjugates exhibit potent effect to overcome MDR.[69,70,71] The endocytosis pathway is the mechanism of action whereas the conjunction of polymer-drug was hydrolyzed by enzymatic reaction in the lysosome of the cells, resulting in the release of the drug from the conjugate. The MDR1 expression was downregulated by HPMA conjugates and decreases the resistance against Taxol of resistant cells.[72,73] Additional mechanisms are inhibition of detoxification genes encoding glutathione and UDP, induction of apoptosis signaling pathways, and downregulation of DNA repair.[74] The most commercially available albumin-based NP is paclitaxel (nab-paclitaxel; Abraxane).[75] Albumin-based nanomedicine is able to formulate the hydrophobic chemotherapy in injection with broad-spectrum doses (high dose) and quickly reaches to the maximum concentration of drugs in plasma with higher bioavailability.[76] Thus, nab-paclitaxel (IV) is degraded into paclitaxel and albumin without any significant change in pharmacokinetic or tissue distribution of the chemotherapeutical agent.[77] In addition, by increasing the time of treatment with nab-paclitaxel (for several weeks), the rate of response and progression of the breast cancer patients were significantly increased more than the standard paclitaxel treatment.[78]

Pluronic Micelles

The micelles are naturally present in the body that utilizes the endogenous surfactant bile salts to complete lipid digestion.[79] Micelles functionally facilitate the absorption of water-insoluble fat and fat-soluble vitamins.[80] Their size is normally within in a range between 5 and 100 nm; amphiphilic molecules consist of a core: hydrophobic fragments and shell and hydrophilic moieties.[81] Water-insoluble drugs are usually intravenously administrated with an adjuvant solubilizing agent such as ethanol, which mainly has common toxic side effects.[82] The micelle nanoparticle formulation of these hydrophobic drugs is usually used to avoid the addition of the harmful adjuvant.[83]

Folate-conjugated poly(ethylene glycol)-b-copolycarbonates and methoxy poly(ethylene glycol)-b-copolycarbonates loaded with doxorubicin improve the cytotoxicity of doxorubicin via FA receptor-mediated endocytosis.[84] Clinical trials were used to treat metastatic GIT adenocarcinoma using SP1049C-doxorubicin micelles of plutonic L61 and F127. The accumulation of doxorubicin in tumors was more than free doxorubicin with normal distribution of polymer in normal tissues.[85,86] The mechanism of action of micelles

is changing the structure of the membrane, decreasing membrane fluidization, and inhibiting function and expression of efflux transporters, such as P-gp and MRPs.[87,88] These subsequently sensitize resistant cancer cell to the chemotherapeutic agents[89], increasing the proapoptotic[90], decreasing the levels of glutathione (GSH) and glutathione-S-transferase (GST) activity, inhibiting the mitochondrial respiratory chain[91], decreasing oxygen consumption[92], and decreasing both mitochondrial membrane potentials[93], and the production of reactive oxygen species and release of cytochrome C in MDR cells are additional mechanisms.[94,95]

CONCLUSION

Cancer is a multidimensional disease and is one of the leading causes of death globally. The contributing factors involvingparticular genetic background, chronic submissions to various environmental stresses and improper diet. All these risk factors lead to the aggregation of molecular changes or mutations in some essential proteins in cells which contributes to the beginning of carcinogenesis. As synthetic drug causes many side effects, and the cancerous cells become resistance to the synthetic drug. Innovative cancer treatment must be considered. The usage of innovative cancer treatment not only decreases mortality, butalso effective treatment of cancer could be done.

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