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Modified Drug Delivery In Cancer Therapy

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ABSTRACT

Large number of advance drug delivery in cancer therapy. The use of current drug delivery technologies in cancer therapy requires drug delivery to cancer tissue only .Nanocarriers for drug delivery in cancer therapy plays important role nowadays. Targeted therapies are generally better than traditional chemotherapy, but they are associated with several adverse effects. Natural products have long been fertile source of cure for cancer .Gene changes in cells that cause cancer, they have been able to develop drugs that targeted these changes treatment with these drugs is called targeted therapy. Targeted therapy is used to keep cancer from growing and spreading. Nanocarrier is nanomaterial being used as transport module for another substance such as drug commonly used nanocarriers includes, micelles, polymers, carbon based material, liposome and other substances**.**

Keywords: CMC-Critical Micelle Concentration, RES-Reticular endothelial system, HIV-Human immunodeficiency virus, and HIFU-High intensity focused ultrasound, MABs-monoclonal antibodies, HBV-Hepatitis B.

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INTRODUCTION

Cancer is a disease which occurs when changes in a group of normal cells within the body lead to uncontrolled growth causing a lump called a tumor; this is true of all cancers except leukaemia (cancer of the blood). If left untreated, tumors can grow and spread into the surrounding normal tissue, or to other parts of the body via the bloodstream and lymphatic systems, and can affect the digestive, nervous and circulatory. A multicellular organism can thrive only when all its cells function in accordance with the rules that govern cell growth and reproduction.

Although cancer comprises at least 100 different diseases, all cancer cells share one important characteristic: they are abnormal cells in which the processes regulating normal cell division are disrupted. That is, cancer develops from changes that cause normal cells to acquire abnormal functions. These changes are often the result of inherited mutations or are induced by environmental factors such as The UV light, X-rays, chemicals, tobacco products, and viruses. Abnormalities in cancer cells usually result from mutations in protein-encoding genes that regulate cell division. Over time more genes become mutated. This is often because the genes that make the proteins that normally repair DNA damage are themselves not functioning normally because they are also mutated. Consequently, mutations begin to increase in the cell, causing further abnormalities in that cell and the daughter cells. Some of these mutated cells die, but other alterations may give the abnormal cell a selective advantage that allows it to multiply much more rapidly than the normal cells. This enhanced growth describes most cancer cells, which have gained functions repressed in the normal, healthy cells. As long as these cells remain in their original location, they are considered benign; if they become invasive, they are considered malignant. Cancer cells in malignant tumors can often metastasize, sending cancer cells to distant sites in the body where new tumors may form.[1]

Types of Tumours:

Tumours (lumps) can be benign or malignant.

1. Benign tumours are not cancerous and rarely threaten life. They tend to grow quite slowly, do not spread to other parts of the body and are usually made up of cells quite similar to normal / healthy cells. They will only cause a problem if they grow very large, becoming uncomfortable or press on other organs - for example a brain tumour inside the skull
2. Malignant tumours are faster growing than benign tumours and have the ability to spread and destroy neighbouring tissue. Cells of malignant tumours can break off from the main (primary) tumour and spread to other parts of the body through a process known as

metastasis. Upon invading healthy tissue at the new site they continue to divide and grow. These secondary sites are known as metastases and the condition is referred to as metastatic cancer.[1]

Environmental Factors:

Several environmental factors affect one's probability of acquiring cancer. These factors are considered carcinogenic agents when there is a consistent correlation between exposure to an agent and the occurrence of a specific type of cancer. Some of these carcinogenic agents include X-rays, UV light, viruses, tobacco products, pollutants, and many other chemicals. X-rays and other sources of radiation, such as radon, are carcinogens because they are potent mutagens.

Causes of cancer:

The prevailing model for cancer development is that mutations in genes for tumor suppressors and oncogenes lead to cancer. However, some scientists challenge this view as too simple, arguing that it fails to explain the genetic diversity among cells within a single tumor and does not adequately explain many chromosomal aberrations typical of cancer cells. An alternate model suggests that there are "mastergenes" controlling cell divisions. A mutation in a master gene leads to abnormal replication of chromosomes, causing whole sections of chromosomes to be missing or duplicated.[2]

Types of tumors:

The type of tumors that forms depends on the type of cell that was initially altered. There are five types of tumors.

1. Carcinomas result from altered epithelial cells, which cover the surface of our skin and internal organs. Most cancers are carcinomas.
2. Sarcomas result from changes in muscle, bone, fat, or connective tissue.
3. Leukemia results from malignant white blood cells.
4. Lymphoma is a cancer of the lymphatic system cells that derive from bone marrow.
5. Myelomas are cancers of specialized white blood cells that make antibodies.[3]

Signs and symptoms:

There are so many a different type of cancer the symptoms are varied and depend on the disease is located. However, there including symptoms as:

1. Lumps – some cancers can be felt through the skin. Cancerous lumps are often painless and may increase in size as the cancer progresses
2. Coughing, breathlessness – persistent coughing episodes and breathlessness can be associated with lung cancer

3. Changes in bowel habit – symptoms of bowel cancer may include blood in the stools and a change in bowel habits such as constipation and diarrhoea.[4]

Prevention and early detection of cancer:

More than a third of all cancers are preventable by reducing exposure to risk factors including tobacco, obesity, physical, inactivity and sexually transmitted infections. Preventative measures such as vaccination programmes against HBV and HPV and public education campaigns are vital now, and in the future, to mitigate the expected increase of people affected by cancer in the coming decades. Early detection can also play its part in reducing the global cancer epidemic.[4]

Implementation of screening programmes to identify pre-cancer or early stage cancer is crucial in the fight against the disease in both developed and developing countries. In order for early detection programmes to be effective, strong healthcare systems must be in place to provide equity of access to diagnosis and treatment for all cancer patients. In addition, public education campaigns are needed across the world to tackle the cancer epidemic by helping people recognise the early signs of disease and encourage the seeking of prompt medical attention.

Oldest descriptions of cancer:

Human beings and other animals have had cancer throughout recorded history. So it's no surprise that from the dawn of history people have written about cancer. Some of the earliest evidence of cancer is found among fossilized bone tumors, human mummies in ancient Egypt, and ancient manuscripts. Growths suggestive of the bone cancer called osteosarcoma have been seen in mummies. Bony skull destruction as seen in cancer of the head and neck has been found too .Our oldest description of cancer (although the word cancer was not used) was discovered in Egypt and dates back to about 3000 BC. It's called the Edwin Smith Papyrus and is a copy of part of an ancient Egyptian textbook on trauma surgery. It describes 8 cases of tumors or ulcers of the breast that were removed by cauterization with a tool called the fire drill. The writing says about the disease, "There is no treatment."[4]

Evolution of cancer treatments: hormone therapy:

Another 19th century discovery laid the groundwork for an important modern method to treat and prevent breast cancer. Thomas Beatson graduated from the University of Edinburgh in 1874 and developed an interest in the relation of the ovaries to milk formation in the breasts. In 1878 he discovered that the breasts of rabbits stopped producing milk after he removed the ovaries. He described his results to the Edinburgh Medico-Chirurgical Society in 1896: "This fact seemed tome of great interest, for it pointed to one organ holding control over the secretion of another and separate organ." Because the breast was "held in control" by the ovaries, Beatson decided to test.

Removal of the ovaries (called oophorectomy) in advanced breast cancer. He found that oophorectomy often resulted in improvement for breast cancer patients. He also suspected that “the ovaries may be the exciting cause of carcinoma” of the breast. He had discovered the stimulating effect of the female ovarian hormone (estrogen) on breast cancer, even before the hormone itself was discovered. His work provided a foundation for the modern use of hormone therapy, such as tamoxifen and the aromatase inhibitors, to treat or prevent breast cancer. New classes of drugs (such as aromatase inhibitors, LHRH luteinizing hormone-releasing hormone analogs and inhibitors, and others) have greatly changed the way prostate and breast cancers are treated.[5]

Evolution of cancer treatments: radiation:

In 1896 a German physics professor, Wilhelm Conrad Roentgen, presented a remarkable lecture entitled “Concerning a New Kind of Ray.” Roentgen called it the “X-ray”, with “x” being the algebraic symbol for an unknown quantity. There was immediate worldwide excitement. Within months, systems were being devised to use x-rays for diagnosis, and within 3 years radiation was used in to treat cancer. In 1901 Roentgen received the first Nobel Prize awarded in physics. Radiation therapy began with radium and with relatively low-voltage diagnostic machines. In France, a major breakthrough took place when it was discovered that daily doses of radiation over several weeks greatly improved the patient’s chance for a cure.

The methods and the machines that deliver radiation therapy have steadily improved since then, at the beginning of the 20th century, shortly after radiation began to be used for diagnosis and therapy, it was discovered that radiation could cause cancer as well as cure it. Many early radiologists used the skin of their arms to test the strength of radiation from their radiotherapy machines, looking for a dose that would produce a pink reaction (erythema) which looked like sunburn. They called this the “erythema dose,” and this was considered an estimate of the proper daily fraction of radiation. It’s no surprise that many of them developed leukemia from regularly exposing themselves to radiation.

Intraoperative radiation therapy (IORT) is a form of treatment that delivers radiation at the time of surgery. The radiation can be given directly to the cancer or to the nearby tissues after the cancer has been removed. It’s more commonly used in abdominal or pelvic cancers and in cancers that tend to recur (come back after treatment). IORT minimizes the amount of tissue that’s exposed to radiation because normal tissues can be moved out of the way during surgery and shielded, allowing a higher dose of radiation to the cancer.

Type of drug delivery in cancer therapy:

Advances in drug delivery systems:

The use of current drug delivery technologies in cancer therapy requires drug delivery to cancer tissues only, meaning that a drug delivery system should hold the anticancer drug in the blood and then allow a continuous drug release at the cancer site. The basic requirements of any drug delivery systems to deliver chemotherapeutic agent to the cancer are, first it should belong circulating in nature, second it must provide controlled and sustained release of drug. Finally it must show sufficient tumour accumulation.

All these requirements can be fulfilled by proper selection of drug delivery system. For cancer therapeutics the systems can be categorized into two major classes i.e. lipid based systems and polymer based systems. All these systems have their own advantages and disadvantages. Lipid based systems are easy to prepare having increases bioavailability as compared to free drug and it can solubilize hydrophobic drugs.[6]

Polymeric micelles are thermodynamic aggregates of amphiphilic block copolymer molecules in selective solvents above the critical micelle concentration (CMC). Due to their small size micelles can avoid uptake by the RES Reticular endothelial system resulting in prolonged circulation of the system which ultimately enhance targeting potential. The advance version includes immune micelles, thermo responsive micelles, ultra-sound sensitive formulation and pH responsive assemblies for targeting. Once the micellar vehicles are introduced into the body, they are virtually infinitely diluted below CMC and become thermodynamically unstable. The leads to disruption of micellar structures so gives burst release of entrapped drugs. On the other hand dendrimers with amphiphilic moieties are known to exhibit micelle-like behavior and have “container” properties in solution. Dendritic micelles are unimolecular micelles in which the hydrophilic and hydrophobic segments are connected covalently therefore shows greater stability as compared to micelles[.6]

Nanocarriers for Drug Delivery in Cancer Therapy:

Cancer treatment involving chemotherapy is typically accompanied by toxic side effects, thereby limiting the amount of the drug that can be given to a patient. As a result, all of the tumor tissue may not be exposed to a lethal dose of the drug. The use of nanocarriers such as liposomes and micelles can improve the pharmacological properties of traditional chemotherapeutics. Their small size (~100nm or less) allows them to readily extravasate from circulation through vascular defects typically present at tumor sites due to ongoing angiogenesis where they can then deliver encapsulate cytotoxic agents to tumor tissue. The fact that these unmodified drug delivery systems are susceptible to opsonisation while in circulation results in low tumor site accumulation. However, surface coating these nano-carriers with polyethylene glycol (PEG) allow for improved circulation times in vivo, and thereby the preferential accumulation of the drug within tumor. As a result, various clinically approved nanocarrier-based formulations such as Doxilare PEGylated .In addition, PEG-lipids used as hydrophilic corona-forming blocks in many micellar-based drugs also allow for longer circulation times However, while the presence of the PEG moiety improves tumor site accumulation of the drug, it also presents a steric barrier between the nanocarrier and tumor cells, which results in a dramatic reduction in tumor cellular uptake Therefore, delivery of the encapsulated chemotherapeutics based on leakage in the tumor microenvironment, followed by the subsequent cellular uptake of the free drug. Further limiting the overall effectiveness of the drug is the fact that some cytotoxic agents commonly used in these formulations, such as doxorubicin, have limited tumor tissue penetrability following escape from its nanocarrier due to a high affinity between this drug and various components of the extracellular environment Therefore, uniform distribution of the drug within the tumor microenvironment is not achieved, and all of the tumor tissue is not necessarily exposed to a lethal dose of the drug.

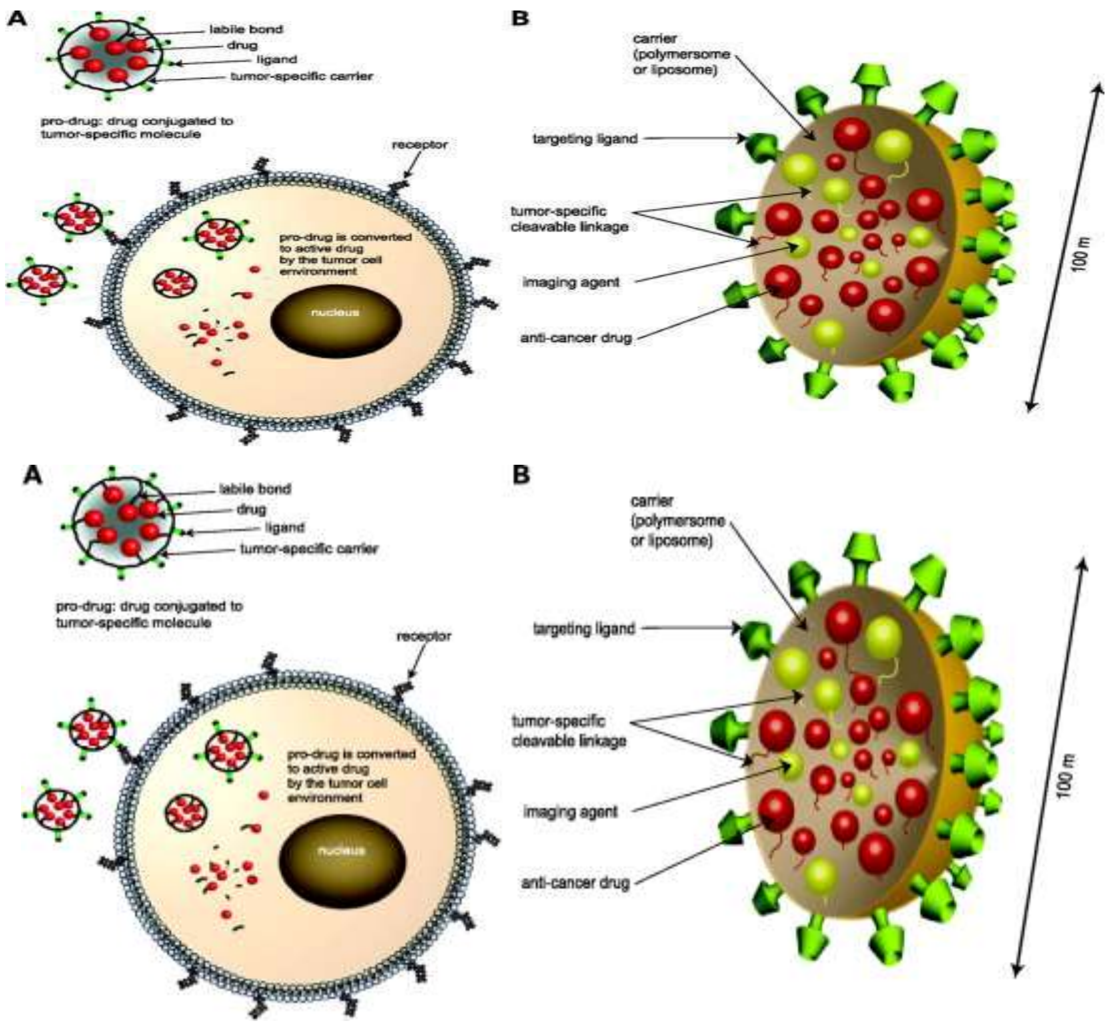

Figure 1: Surface modification to nanocarriers, Chemical conjugation of drugs directly to targeting ligand

As a result, many research groups are currently working on replacing this form of passive drug delivery with an active one in order to further improve the localization between the drug and cancer cells. This type of targeted drug delivery usually involves surface modifications made to these nanocarriers in order to accommodate surface ligands, which recognize and bind certain over expressed receptors present on the cells of interest. While there are numerous nanocarriers available for such delivery, the use of liposomes and micelles is particularly ideal as surface modifications made to them eliminates the need for direct chemical conjugation between the drug and targeting moiety which is typically required with this form of delivery. This is a particularly important aspect associated with their use as conjugation of drugs directly to the targeting ligand can negatively affect the targeting molecule in a manner that disrupts receptor/ ligand recognition.[7]

Carbon nanotubes and their importance in anticancer drug delivery:

Carbon nanotubes (CNTs) are allotropes of carbon with a cylindrical nanostructure. The discovery and subsequent widespread characterization of carbon nanotubes (CNTs) have opened up a class of materials with unexpected electrical, mechanical, and thermal properties CNTs can be used as drug-delivery vehicles or "nanocarriers‟ in cancer therapy and other areas of medicine without causing toxicity to healthy tissue while allowing prolonged release of the drug. These systems also have higher loading capacity and allow for the incorporation of targeting agents and stealth molecules may also be added to evade the immune system.[8]

Advantages of carbon nanotubes over conventional cancer therapy:

Conventional treatment such as surgery is hindered by accessibility to tumorous cells and the risk of operating near or on vital organs. Also, selective treatment in chemotherapy and radiation is limited. On the whole, present treatment methods are not very effective at stopping the spread or recurrence of cancer. Nanomedicine provides a means of targeted delivery of drugs. Since the cancerous cells are on the nanoscale, there is a potential for highly efficient drug delivery this has two major benefits. First, the total quantity of drug required is less, a concern primarily associated with the more costly drugs. Additionally, no solvent is required for delivery of the drug, which means that undesired health effects from the solvent can be prevented. Second, a lower concentration of the toxin is delivered to other parts of the body, without the risk of the protective nanocarrier degrading. Thus, fewer health side effects are suffered by the patient undergoing treatment. A further advantage of nanocarriers is that a range of drugs can be attached for a variety of purposes including; therapeutic, diagnostic, targeting and barrier avoidance.[9]

Antibodies modified drug delivery in cancer therapy:

They may work in three different ways

1. Trigger the immune system to attack cancer.
2. Stop cancer cells from taking up proteins.
3. Carry cancer drugs or radiation to cancer cells.

The basic structure of immunoglobulin molecule consists of two identical heavy chains (long) with a molecular weight of 50000 each and two light chains (short) with a molecular weight of 23000 which are held together by non-covalent forces as well as by disulfide linkages. Each chain contains inter-chain di-sulfide linkages and in addition also has a region of a constant amino acid sequence, a region of variable amino acid sequence. Antibodies of same class share the constant region in their heavy chains and may have kappa or lambda type light chains. The carboxyl ends (ends of constant region) of the heavy chains form the FC region (responsible for binding to FC receptors present on many cells). The amino acid sequences of the variable region that are similar in the light and heavy chains are helpful in determining the specificity of a particular amino acid. Amino (NH2) terminals (ends of the variable region) serve as the binding sites for antigens.

Antibodies as carriers in cancer diagnosis:

Monoclonal antibodies (MAbs) obtained in highly purified form and in unlimited amounts with uniform antigen specificity and affinity can be used as carriers in cancer diagnosis and in targeted drug delivery to tumour cells. Monoclonal antibody technique is the most definitive for studies on oncofoetal antigens. Most melanomas have large amounts of melanoma associated antigens such as P97, a proteoglycan and a GD3 ganglioside. Clone specific antigens which are operationally highly specific for the given neoplasm have been demonstrated as idiotypic determinants in B-cell leukemias.

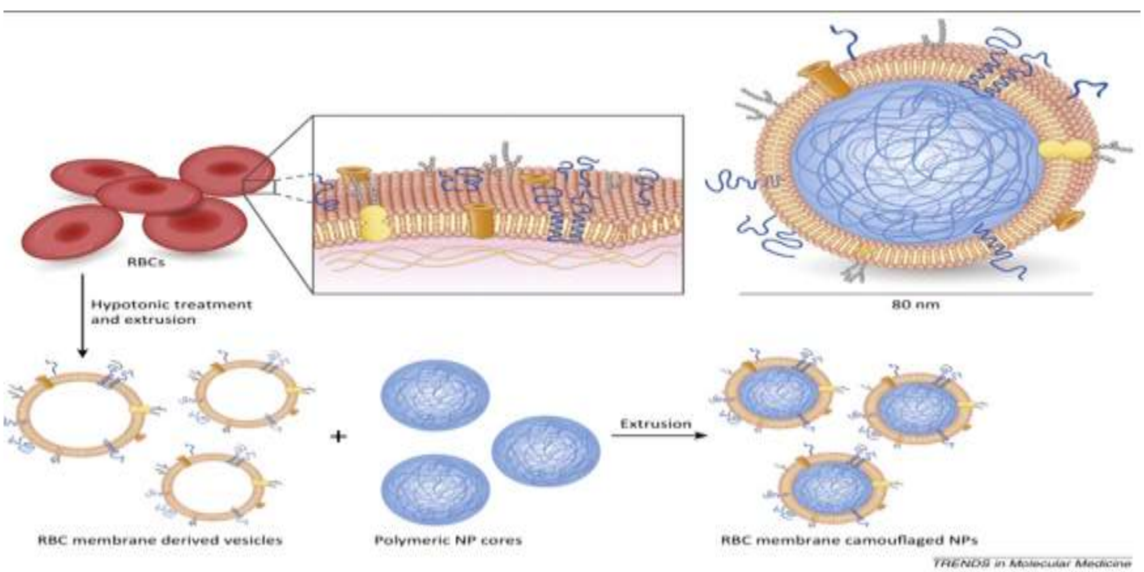

Figure 2: Antibodies as carriers in cancer

Non-invasive cancer treatment:

This preclinical treatment involves using radio waves to heat up tiny metals that are implanted in cancerous tissue. Gold nanoparticles or carbon nanotubes are the most likely candidate. Promising preclinical trials have been conducted although clinical trials may not be held for another few years.

Another method that is entirely non-invasive referred to as Tumor Treating Fields has already reached clinical trial stage in many countries. The concept applies an electric field through a tumour region using electrodes external to the body. Successful trials have shown the process effectiveness to be greater than chemotherapy and there are no side-effects and only negligible time spent away from normal daily activities. This treatment is still in very early development stages for many types of cancer.

High-intensity focused ultrasound (HIFU) is still in investigatory phases in many places around the world In China it has CFDA approval and over 180 treatment centers have been established in China, Hong Kong, and Korea. HIFU has been successfully used to treat cancer to destroy tumours of the bone, brain, breast, liver, pancreas, rectum, kidney, testes, and prostate. Several thousand patients have been treated with various types of tumours. HIFU has CE approval for palliative care for bone metastasis. Experimentally, palliative care has been provided for cases of advanced pancreatic cancer. High-energy therapeutic ultrasound could increase higher-density anti-cancer drug load and nanomedicines to target tumor sites by 20x fold higher than traditional target cancer therapy "Increasing the density of nanomedicines improves their ultrasound-mediated delivery to tumours.[10]

Cancer therapy with plants based natural products:

Natural Products have long been a fertile source of cure for cancer, which is projected to become the major causes of death in this century. However, there is a continuing need for development of new anticancer drugs, drug combinations and chemotherapy strategies, by methodical and scientific exploration of enormous pool of synthetic, biological and natural products. There are at least 250,000 species of plants out of which more than one thousand plants have been found to possess significant anticancer properties. While many molecules obtained from nature have shown wonders, there are a huge number of molecules that still either remains to be trapped or studied in details by the medicinal chemists. The article reviews many such structures and their related chemistry along with the recent advances in understanding mechanism of action and structure-function relationships of nature derived anti-cancer agents at the molecular, cellular and physiological levels. Taxol, one of the most outstanding agents, has been found beneficial in treatment of refractory ovarian, breast and other cancers. Another prominent molecule includes Podophyllotoxin. Synthetic modification of this molecule led to the development of Etoposide, known to be effective for small cell cancers of the lungs and testes. Camptothecin isolated from Camptothecaacuminata also have been extensively studied. Other important molecules discussed include Vincristine, Vinblastine, Colchicine, Ellipticine and Lepachol along with Flavopiridol, a semi-synthetic analogue of the chromone alkaloid Rohitukine from India, a pyridoindole alkaloid from leaves of Ochrosia species and many more. The review also deals with the lesser-known plants of sub-Himalayan region.[11]

Targeted therapy:

The term "targeted drug delivery" used in drug delivery is distinct from "targeted therapy" ("targeting therapy") that is frequently used in drug discovery. Targeted drug delivery, refers to predominant drug accumulation within a target zone that is independent of the method and route of drug administration. On the other hand, targeted therapy or targeted medicine means specific interaction between a drug and its receptor at the molecular level. Effective targeted drug delivery systems require four key requirements: retain, evade, target and release.. For formulations intended for I.V. administration, this means efficient drug loading into some type of delivery vehicle, sufficient residence in the circulation to reach intended sites of the body, retention by specific characteristics within intended sites (i.e., targeting), and drug release at the intended site within a time that allows for effective function of the drug. Obviously drug targeting to specific sites in the body requires different delivery systems depending on the drug delivery route selected. Here we will focus on drug targeting of I.V. administered formulations, and in particular formulations for delivering anticancer drugs.[12]

As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop drugs that target these changes. Treatment with these drugs is often called targeted therapy. Targeted therapy drugs, like any drug used to treat cancer, are technically considered "chemotherapy." But targeted therapy drugs do not work in the same ways as standard chemotherapy drugs. They are often able to attack cancer cells while doing less damage to normal cells by going after the cancer cells‟ inner workings the programming that sets them apart from normal, healthy cells. These drugs tend to have different (and often less severe) side effects than standard chemotherapy drugs. Targeted therapies are used to treat many kinds of diseases. Here we will focus on their use to treat cancer. In the past, only a few cancers could be treated with targeted therapy, but now these drugs are used to treat many different types of cancer. Targeted therapies are a major focus of cancer research today. Many future advances in cancer treatment will probably come from this field. Here we will explain:

1. The different ways that targeted therapy can work
2. Some of the types of targeted therapy
3. What you can expect if you are being treated with targeted therapy (including some common side effects)

Targeted therapy work:

Targeted therapy is used to keep cancer from growing and spreading. To become cancer cells, normal cells go through a process called carcinogenesis. Cancer cells may then grow into tumors or reproduce throughout a body system, like blood cancers do. Scientists have learned a lot about the molecules that are part of this process and the signals a cell gets to keep this process going. Targeted therapy disrupts this process. The drugs target certain parts of the cell and the signals that are needed for a cancer to develop and keep growing. These drugs are often grouped by how they work or what part of the cell they target.[12]

Targeted therapy or treatment:

Depending on the type of cancer and its stage (if and how far it has spread), targeted therapy can be used to

1. Cure the cancer
2. Slow the cancer's growth
3. Kill cancer cells that may have spread to other parts of the body
4. Relieve symptoms caused by cancer your doctor will talk to you about the goals of your therapy before you start treatment.[12]

Immunotherapy: the big new hope for cancer treatment:

Immunotherapy is the most exciting development in cancer treatment in years, beginning to take off at a time when much cancer drug research seems to be hitting a brick wall. More and more of the orthodox chemotherapy drugs have very small effects, buying people with the advanced disease a few months or even just weeks of life.[13]

Excitement over new cancer drugs is a dangerous thing. There have been melanoma drugs before that were greeted as miracle cures. These "targeted drugs", the BRAF inhibitors, caused tumors to vanish completely. There was euphoria at cancer conferences. But within a few months, the disease came back with the enthusiasm for immunotherapy may be better placed because this vengeance and killed.[13]

A whole new way of tackling cancer, Scientists have long puzzled over the failure of the body's own defensive immune system to attack cancer cells in the same way that it will fight a cold virus. They have discovered that cancer - just like the human immunodeficiency virus (HIV) that causes Aids – can hide from the T-cells that seek out and kill invaders. Cancer Research UK, which has been funding some of the research, says the cancer cells have developed a sort of "secret handshake" which persuades the T-cells not to attack.[14]Immunotherapy is treatment that uses certain parts of a person's immune system to fight diseases such as cancer. This can be done in a couple of ways:

1. Stimulating your own immune system to work harder or smarter to attack cancer cells
2. Giving you immune system components, such as man-made immune system proteins

Types of cancer immunotherapy:

The main types of immunotherapy now being used to treat cancer include:

Monoclonal antibodies:

These are man-made versions of immune system proteins. Antibodies can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.

Immune checkpoint inhibitors:

These drugs basically take the "brakes" off the immune system, which helps it recognize and attack cancer cells.

Cancer vaccines:

Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.

Other, non-specific immunotherapies:

These treatments boost the immune system in a general way, but this can still help the immune system attack cancer cells.[14]

Targeted therapy of lung cancer:

Targeted therapy of lung cancer refers to using agents specifically designed to selectively target molecular pathways responsible for, or that substantially drive, the malignant phenotype of lung cancer cells, and as a consequence of this (relative) selectivity, cause fewer toxic effects on normal cells.

Most previous chemotherapy drugs for cancer were (relatively) non-selective in their activity. Although their exact mechanisms of action were varied and complex, they generally worked by damaging cells undergoing mitosis, which is usually more common in malignant tumors than in most normal tissues. Targeted agents are designed to be selective in their effects by modulating the activity of proteins necessary and essential for oncogenesis and maintenance of cancer, particularly enzymes driving the uncontrolled growth, angiogenesis, invasiveness and metastasis characteristic of malignant tumors. The increased differential activity usually results in fewer troubling side effects for cancer patients, particularly less nausea, vomiting, and death of cells in the bone marrow and gastrointestinal tract, and increased effectiveness against tumor cells.[15]

Radiation therapy:

Radiation therapy is a proven method of killing cancers and tumors inside of the body. Radiation therapy can be achieved through the use of x-rays, photons, protons, as well as heavy ions. Radiation therapy works by external particles (or protons) interacting with cell structure in the body, causing excitation and ionization. The released charged particles have the ability to destroy the cancer cell's DNA. If the DNA has been significantly altered, so the cell can no longer replicate, it is considered to be destroyed. Since the applied radiation will irradiate all cells, for therapy to be effective, the risk of irradiating healthy cells must be minimized while maximizing the damage done to the cancerous cells.[16]

Wilson, in 1946, first proposed using protons as an effective method of radiation therapy. The first medical case treated with protons was a pituitary tumor in 1954. There are many advantages for using protons for therapy: unlike x-rays and photons each of which will give a large dose of radiation to the healthy cells on its path to the tumor, the dose deposited by the proton while traveling through healthy tissue is smaller. The protons give off the majority of their energy at the end of their path. This is denoted by the Bragg Peak (see figure. 1). The distance the protons travel is determined by their initial energy. By using a modified Bragg Peak, one can select a range of proton energy and a range of distance by which to deposit dosage. Another reason for using proton therapy is protons are deflected less than electrons. Because the protons are more massive in size, the momentum transfer from hitting cells is less likely to cause a change in direction. This means when the protons are traveling through tissue the protons will stay collimated and will not diverge and deposit their energy into healthy cells. Using protons for radiation therapy gives great control so energy can be deposited into exact locations within the tumor.[17]

In theory, use of protons should reduce the exposure of normal tissue to radiation, possibly allowing the delivery of higher doses of radiation to a tumor. Proton therapy has not yet been compared with standard external-beam radiation therapy in clinical trials.[17]

Internal radiation therapy:

Internal radiation therapy (brachytherapy) is radiation delivered from radiation sources (radioactive materials) placed inside or on the body .Several brachytherapy techniques are used in cancer treatment. Interstitial brachytherapy uses a radiation source placed within tumor tissue, such as within a prostate tumor. Intra-cavitary brachytherapy uses a source placed within a surgical cavity or a body cavity, such as the chest cavity, near a tumor. Episcleral brachytherapy, which is used to treat melanoma inside the eye, uses a source that is attached to the eye.

In brachytherapy, radioactive isotopes are sealed in tiny pellets or “seeds.” These seeds are placed in patients using delivery devices, such as needles, catheters, or some other type of carrier. As the isotopes decay naturally, they give off radiation that damage nearby cancer cells .If left in place, after a few weeks or months, the isotopes decay completely and no longer give off radiation. The seeds will not cause harm if they are left in the body (see permanent brachytherapy, described below). Brachy therapy may be able to deliver higher doses of radiation to some cancers than external-beam radiation therapy while causing less damage to normal tissue.[18]

Photodynamic therapy:

Photodynamic therapy (PDT) is a treatment that uses special drugs, called photosensitizing agents, along with light to kill cancer cells. The drugs only work after they have been activated or “turned on” by certain kinds of light. PDT may also be called photo radiation therapy, phototherapy, or photo chemotherapy.

Depending on the part of the body being treated, the photosensitizing agent is either put into the bloodstream through a vein or put on the skin. Over a certain amount of time the drug is absorbed by the cancer cells. Then light is applied to the area to be treated. The light causes the drug to react with oxygen, which forms a chemical that kills the cells. PDT might also help by destroying the blood vessels that feed the cancer cells and by alerting the immune system to attack the cancer. The period of time between when the drug is given and when the light is applied is called the drug-to-light interval. It can be anywhere from a couple of hours to a couple of days, depending on the drug used. [19]

Hyperthermia to treat cancer:

Hyperthermia usually is taken to mean a body temperature that is higher than normal. High body temperatures are often caused by illnesses, such as fever or heat stroke. But hyperthermia can also refer to heat treatment – the carefully controlled use of heat for medical purposes. Here, we will focus on how heat is used to treat cancer.

When cells in the body are exposed to higher than normal temperatures, changes take place inside the cells. These changes can make the cells more likely to be affected by other treatments such as radiation therapy or chemotherapy. Very high temperatures can kill cancer cells outright (thermal ablation), but they also can injure or kill normal cells and tissues. This is why hyperthermia must be carefully controlled and should be done by doctors who are experienced in using it. Current instruments can deliver heat precisely, and hyperthermia is being used (or studied for use) against many types of cancer.[20]

Hyperthermia used to treat cancer:

Treatment can be local, regional or whole-body hyperthermia, depending on the extent of the area being treated.

Local hyperthermia:

Local hyperthermia is used to heat a small area like a tumor. Very high temperatures are used to kill the cancer cells and destroy nearby blood vessels. In effect, this cooks the area that is exposed to the heat & as with cooking, the higher the temperature and duration of exposure, the greater the effect seen within tissues. Thermal ablation comprises the treatments where very high temperatures cause irreversible damage to cells whereas smaller rises in temperature constitute mild hyperthermia. Radio waves, microwaves, ultrasound waves, and other forms of energy can be used to heat the area. When ultrasound is used, the technique is called high intensity focused ultrasound, or HIFU, sometimes also referred to as just focused ultrasound.

The heat may be applied in different ways:

1. External: High energy waves are aimed at a tumor near the body surface from a machine outside the body.
2. Internal: A thin needle or probe is put right into the tumor. The tip of the probe releases energy, which heats the tissue around it.[20]

Lasers in cancer treatment:

The word Laser stands for Light Amplification by Stimulated Emission of Radiation. Laser light is different from regular light. The light from the sun or from a light bulb has many wavelengths and spreads out in all directions. Laser light, on the other hand, has a single wavelength and can be focused in a very narrow beam. This makes it both powerful and precise. Lasers can be used instead of blades (scalpels) for very careful surgical work, such as repairing a damaged retina in the eye or cutting through body tissue.[20]

Types of lasers:

Lasers are named for the liquid, gas, solid, or electronic substance that’s used to create the light. Many types of lasers are used to treat medical problems, and new ones are being tested all the time. Today, 3 kinds of lasers are commonly used in cancer treatment: carbon dioxide (CO_2), argon, and neodymium: yttrium aluminum garnet (Nd: YAG).[20]

Carbon dioxide (CO^2) lasers:

The CO_2 laser is mainly a surgical tool. It can cut or vaporize (dissolve) tissue with fairly little bleeding as the light energy changes to heat. This type of laser is used to remove thin layers from the surface of the skin without going into the deeper layers.[20]

Argon lasers:

The argon laser only goes a short distance into tissue. It's useful in treating skin problems and in eye surgery. It's sometimes used during colonoscopies (tests to look for colon cancer) to remove growths called polyps before they become cancer. It can be used with light-sensitive drugs to kill cancer cells in a treatment known as photodynamic therapy (PDT). (You can learn more about this in our document titled Photodynamic Therapy.[20]

CONCLUSION

The introduction of active agents derived from nature into the cancer armamentarium has changed the natural history of many types of human cancer. The issues relating to safety, efficacy, accumulation and disposal, toxicity are important aspects of drug delivery. Potential of dendrimers as vehicle for site-specific delivery of anti-cancer drugs seems to be promising approach but their high costs, complex synthesis procedure and cytotoxicity issues are a matter of concern when compared to other delivery systems. Significant information has accumulate degrading the most convenient carrier systems (e.g. liposomes) and possible ways of using them for the targeted delivery of drugs, imaging agent, and genes into tumor, thus the above article shows that above method of cancer treatment is beneficial with less side effect.

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