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Review Article

SUPRAMOLECULAR DRUG CARRIERS IN CANCER THERAPEUTICS

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ABSTRACT

Cancer has a significant effect on society worldwide. Statistics on cancer explain what happens in a large set of people and give a real picture of the burden on society. A number of cancer treatments are accessible nowadays and enormous numbers are in the pipeline, but society still faces several lacks in full therapy cure. The objective is to determine, parallel to the kinds and uses of supramolecular drug carriers, and the incidence and incidences of cancer with various medical systems concentrated primarily on targeted structures. Rational drug delivery designs have shown important interest in enhancing therapeutics in latest years with regard to leveraging supramolecular chemistry that is ‘‘chemistry beyond molecules." Particular tunable and dynamic non-covalent interaction of engineering can be used for drug delivery. Advantages of this include molecular composition control, improved drug integration and targeting pathways, and new delivery devices which respond to a various physiological indicators. One of the largely recognizable motivations for supramolecular drug delivery is macrocyclic hosts-guest complexes. The scope of this review is to give a clear picture that how supramolecular drugs carrier plays an effective role in cancer treatment.

Keywords: Cancer, sarcoma, targeted therapy, supramolecular carrier

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INTRODUCTION

Uncontrollable growth of abnormal cells anywhere within a body is known as cancer. It consists of more than 100 types of different diseases. More than 200 malignant growth types are present which, nearly every part of our body can develop. This malignancy refers to the cell tissue's abnormal growth. Anything that may lead to an abnormally normal body cell can cause cancer. The development of cancer is linked with several factors related to cell abnormalities.[1-3]

There are more than approx. 200 types of cancer, so far as per the literature available. The cancers listed in quotes are the general names of some cancers.[4]

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

Leukemia: Cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood -- "leukemia," lymphoblastic leukemia (ALL and CLL), myelogenous leukemia (AML and CML), T-cell leukemia, and hairy-cell leukemia

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 lymphoproliferative lymphomas

Sarcoma: Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue "bone, soft tissue cancers," osteosarcoma, synovial sarcoma, liposarcoma, angiosarcoma, rhabdosarcoma, and fibrosarcoma

Central nervous system cancers: Cancers that begin in the tissues of the brain and spinal cord "brain and spinal cord tumors," gliomas, meningiomas, pituitary adenomas, vestibular schwannomas, primary CNS lymphomas, and primitive neuroectodermal tumors

There are several different staging methods for cancer as regards the cancer diagnosis, and the criteria for stages can vary between distinct types of cancer.

According to the NCI, the common elements considered in most staging systems are as follows:

- Cell type and tumor grade (how closely the cancer cells resemble normal tissue cells)

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- The presence or absence of metastasis
- Tumor size and number of tumors
- Site of the primary tumor
- Lymph node involvement (spread of cancer into lymph nodes)

Table- 1 TNM classification of cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Based on growth, tumors are of two types malignant and benign. A benign tumor develops slowly and usually doesn't lead to death for the patient. Tumors with malignancies or cancer develop faster. The patients are not located and often fatal. A compact tumor does not always form cancer cells. Leukemia is a blood-forming tissue cancer, for example, where carcinogenic cells circulate in the body and act in a certain sense like healthy cells. They eventually move healthy cells, preventing them from working normally. Carious genetic material damage transforms the cell from normal to malignant, a multi-stage process of carcinogenesis. In the cell's growth regulatory system the damage gradually accumulates. A genetic defect begins cancer. Human genetic factors, genes that are called chromosomes found in the cell. Genes, such as their distribution, control the functions of cells. Mutation and changes in genes undergo because of failure of cell's regulatory system. Cancer does not develop because of a single genetic defect. It develops because of gene mutation during the process of cell growth and cell differentiation regulation.[5]

Key facts about cancer

- Cancer caused 80 million deaths worldwide, which makes it the second-largest leading cause of death, which means out of six deaths one is caused by cancer worldwide.
- In lower-middle-income nations, 70% of deaths occur due to cancer.
- Around a third of cancer deaths result from the five most important risks of behavior and diet; high body weight, low intake of fruit and vegetables, poor physical activity, consumption of alcohol and tobacco.[6]
- Tobacco consumption is one of the main causes of cancer out of all important risks and it causes 22% of overall cancer mortality.
- In lower-middle-income nations, infections like hepatitis as well as human papillomavirus account for 25 percent of cases of cancer.[7]
- Late-stage presentation and inaccessible diagnosis and treatment are common. In 2017, only 26 percent of countries with low incomes reported general public pathology services. In comparison with less than 30% of low-income countries, over Ninety percent of the high-income countries are available for treatment.
- Cancers have an important economic impact and are growing. In 2010, the total annual estimated economic burden of cancer was around the US $1160 billion.[8]
- Only one in 5 countries with a low and middle income have data to guide cancer policy.

Prevalence [9, 10, 11]:

- In the year 2012, approximately 14.1 million new cases of cancer occurred worldwide.
- Out of 10, more than four cases of cancer occur in those nations that have low or medium Human Development index (HDI) level.
- Lung, bowel, prostate, and female breast cancer are the most common types of cancer that occur worldwide, and these four accounts overall 40% of the total cancer cases diagnosed globally.
- Particularly in men, lung cancer is the main type of cancer and it accounts for one in ten of all cancer diagnosed worldwide in men.
- A worldwide based study in 2012 publishes that in last five years almost 3.25 crore people who were diagnosed with cancer were living a good life.
- In 2008, cancer has taken away approximately 169.3 million years of healthful life, globally.
- Globally, by the end of 2030 (estimated), there will be 23.6 million new cancer cases each year.
- Based on four-year data (2011-2015), in both males and females there will be 439.9/100,000 new cases per year and the cancer mortality rate is 163.5/100,000 per year.
- Death due to cancer is more in men than women; it is 196.8 for men and 139.6 for women out of 100,000. Based on ethnicity/race and sex, cancer deaths are highest among African American males and lowest in Pacific Islander/Asian women which are 239.9 and 88.3 per 100,000 respectively.
- Even after such high mortality, in 2016 cancer survivors were estimated 15.5 million in the United States and it is expected to reach around 20.3 million by the end of 2026.

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- In 2017 in the United States, approximately 15,270 children in the age group of 0 to 9 were found affected by cancer, and out of those 1,790 were died of cancer disease.

Future Estimates [12]

In America, from 2010 to 2020, the estimated number of newly discovered cases of cancer would rise by about 24 percent in men and 21 percent in women which increase the total number of cases from 900,000 per year to one million per year.

We expect the types of cancer whose cases will increase the most would be-

- Melanoma, the deadliest type of skin cancer, in white males and females.
- Bladder, prostate, liver, and kidney cancer in males
- Thyroid, lung, uterine, and breast cancer in females

Cigarette smoking, overweight, lifestyle is the main reasons why these cancer incidences are increasing. Smoking cigarette is the main cause of many cancers, especially lung cancer. Since 1964, when the first Smoking and Health reports of the Surgeon General were published, the smoking rate of the United States has declined. As a result of it, from the mid-1980s, in males and in the late 1990s newly discovered cases of lung cancer have been decline more quickly in males than females. But during 2010 and 2020 the new number of cases of lung cancer will remain the same in males; however, it is expected that the new cases of lung cancer among females by 2020 each year.[13]

The risk of female colorectal, breast, esophagus, kidney, pancreas, and uterine cancer is higher because of overweight and obesity. Overweight and obese is increasing by more than 2/3rd in adults and 1/3rd in children from the past few decades. Except for colorectal and breast cancer, the weight of cancer is expected to rise from 30% to 40% by 2020.[14]

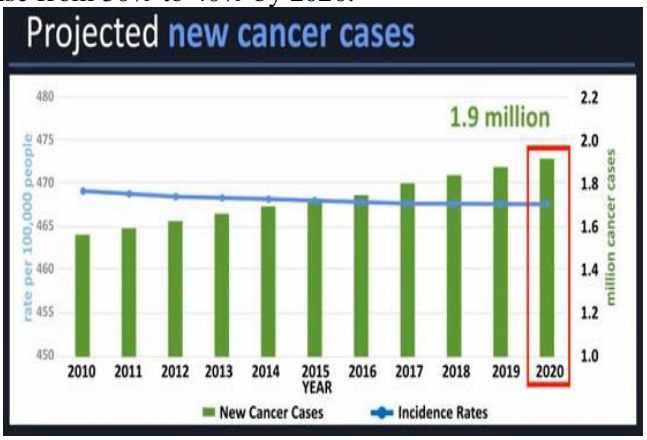

Figure-1: Estimated New Number of Cancer Cases with incidence rate from 2010 to 2020

(Source:https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm)

This graph demonstrates that from 2010 to 2020 the new number of cancer cases is projected to reach around 1.9 million every year from 1.5 million, even though the incidence rate of cancer is estimated to remain almost the same.

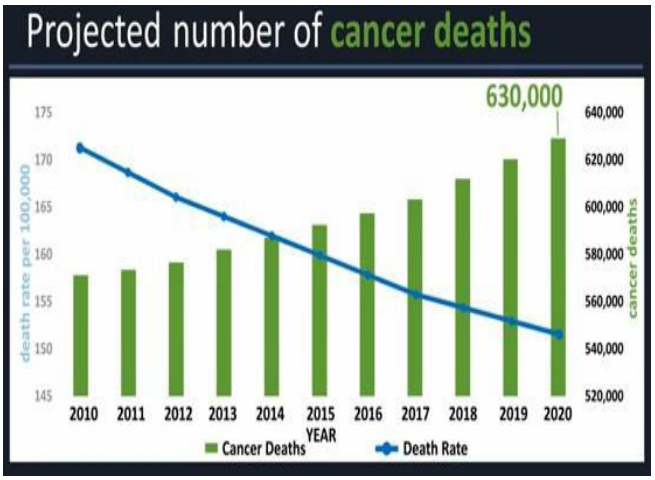

Figure-2: Estimated Number of Deaths due to Cancer, from 2010 to 2020

(Source: https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm)

This graph demonstrates that from 2010 to 2020, the total number of deaths due to cancer is estimated to reach 630,000 every year from 575,000. But, during the same period, the date rate due to cancer is estimated to decrease from 171 to 151/100,000.

DRUG DELIVERY SYSTEMS

"Drug delivery systems (DDS) are called as systems which deliver optimal amounts of pharmaceuticals to the target location, increase the effectiveness of drugs and reduce adverse impacts".[15]

DDS refers to techniques and formulations intended for transportation of a drug preferentially to its target objective. The majority of anti-cancer medicines largely depend on differential cancer cell killing. The development of cancer treatment was largely motivated by the assumption that we will find medicines with an action mechanism that allows greater discrimination between cells and cells of the normal system if we screen enough drugs.[16] The pharmacokinetics of the drug transported are generally changed drastically by DDS. The drug delivery system plays an important role in the treatment of cancer by improving the therapeutic index of an anticancer molecule. This can be done by active or passive focusing. Other benefits of oncology delivery systems may be reduced toxic effects on normal tissues, simplified medication management, and patient compliance improvements.[17]

Several DDS (for example nanoparticles) and drug targeting systems have been approved and are being

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developed (e.g. monoclonal antibodies). These systems have been developed to overcome conventional chemotherapeutic agents ' lack of specificity. They can be designed to improve traditional chemotherapy agents ' pharmacological and therapeutic properties. Nanoparticles, whose size varies between several nm and several centuries nm, depending on their intended use, have a strong potential to supply drugs and tumor control.[18] There are some criteria's for an ideal DDS, those are following [19]

- Bio-compatible
- Inertness
- Patient Comfort ability
- Mechanically should be strong
- Readily to process
- Proficient to achieve high drug loading
- Easy to administer and to remove
- Secure from accidental release
- Leachable impurities free
- Fabricate and sterilize should be easy

So, this DDS was categorized into two types which, are enlisted below.

1. Matrix delivery systems: This includes a solid matrix of polymer containing a dispersed drug. For this, there are two systems currently available for local or systemic cancer treatment.

- Zoladex (goserelin, a gonaderelin analogue peptide)
- Gliadel

2. Drug targeting systems: Increased drug delivery in tumor cells and decreased drug deliveries in normal tissues concentration or concentrations. There are two methods of targeting drugs [20]:

- Passive: Medicinal accumulation in the areas around leaked-vasculated tumors; commonly known as the enhanced permeation and retention EPR (more on the EPR effect below) effect. Almost all drug carriers are passively targeted, whether or not such distribution is intended.
- Active: Used to describe specific interactions between drug/drug carrier and the target cells, usually through specific between ligand and receptor.

BARRIERS IN SUCCESSFUL DRUG DELIVERY [21]

- Incorrect amount of medicinal product, required controlled rate of drug, take much time to reach action site i.e. cancer cells and avoidance of the normal cells to achieve the required therapeutic effect.
- Bio-distribution of Drug
- Multidrug Resistance (MDR): In this case, cancer cells' resistance to medicines is a factor that would influence to achieve cancer chemotherapy's objective negatively and can be gained through non-cellular and cellular mechanisms MDR.
- Clearance by Reticuloendothelial System (RES): Quickly blood clearance through the reticuloendothelial system (RES) is also a problem to achieve cancer therapy objective. It consists of monocytes and macrophages in reticular connective tissue (e.g. spleen). These cells phagocytize and remove from the bloodstream cell debris, pathogens, and other external materials. The hydrophobicity, particle size, load on the surface (Juliano, 1976), composition profile of the system affect the delivery system clearance capacity.
- Anticancer drugs hydrophobicity: Hydrophobic nature of a cancer drug is also a problem in cancer chemotherapy, due to the toxicity of most anti-cancer medications to normal and cancer cells, so an intravenous drug must be developed instead of an oral drug. Intravenous formula retains the drug into the system to provide a sustained release to minimize the exposure of the drug to normal cells.

  Nano technological targeted cancer chemotherapy has been introduced to overcome all these issues. The targeted system of nanotechnology includes nano capsules, nanoparticles, nano methane, pH-sensitive liposomes, nano crystals, nanotubes, steep nanoparticles, fibrosomes, etc. This delivery involves selecting and effective location of the drug movement on pre-recognize therapeutic receptors (like overexposed receptors), while reducing toxicity (by limiting its exposure to non-target sites), maximizing the therapeutic index, and enhancing drug biodiversity, which plays an important role in the success of process of cancer chemotherapy.

SUPRAMOLECULAR CARRIERS

A supramolecular or "super molecule" assembly is a well-defined molecule complex that consists of non-covalent bonds. Drugs are loaded to the specific cells within them. These techniques are very useful in the treatment of cancer-targeting drug delivery systems.[22] Nano scale drug delivery systems are usually considered a major difference between traditional treatments, and this difference in advanced treatment is because of better targeting of tumor site and enhanced bleeding preservation. However, most drug delivery systems have minimal loading efficiency or highly threatened by serious side effects in normal organ conditions. The ideal solution for cancer can be the supramolecular drug delivery system (SDDDS) which is composed of a pure form of drugs through supramolecular interactions. [23]

Supramolecular carriers used in general therapeutics [24]

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- **Supramolecular nanoparticles [25]:**

In creating nanoparticles for drug delivery, supramolecular principles can be used. One example was the use of dendrimers, molecular macromolecules with branches, offering numerous possibilities for super molecule design via more exotic core structures made from metal-ligand coordination or ordered hydrogen bonding units.[18,26,27] A dendrimer was created through two branching units, terminating with a viologen guest through a ternary complex formation between two viologens and a CB macro cycle in one, particularly interesting design.[29] Dendrimers have a partial benefit as pharmaceutical carriers because of their defined nanostructure and controlled surface valence. Dendrimers can also be designed to encapsulate a drug in a designed hydrophobic environment, sequestering it and improving solubility like macro cyclic hosts.[30] Camptothecin, for example, was used to improve cellular uptake and cellular death when used as a molecular encapsulation strategy for the anti-cancer drug. [31] Another route for drug carriers of the nano scale was prepared by super molecular dendrimer aggregates; it led to a versatile nanocarrier that operated in a variety of solvents to supply Polar and Non-polar aggregates.[32] Ionic dendrimer building blocks that are self-assembled have also demonstrated that their supramolecular structure provides a more potent anti-bacterial function.[33] E.g. Self-assembled supramolecular nanoparticles

- **Supramolecular micelles [34-39]:**

Supramolecular micelles have gained significant attention among scientific communities because of their drug delivery applications and controlled release feature. The free energy among the hydrophil hydrophobial interface is reduced by the spontaneous organization of amphiphiles: the hydrophobic segments are collecting into the heart and the hydrophilic segment is contacted into the water to make a shell. The hydrophobic and hydrophilic blocks are also associated with non-covalent interactions which give stimulus receptivity for supramolecular micelles and thus function as nano capsules loaded with hydrophobic molecules. In the meantime, this distinctive characteristic may serve therapeutics because, due to its low solubility, limited stability, and toxicity, the amphiphilic means dual nature makes supranational micelles appropriate carriers for several medicines that have seen problems to deliver the molecule in tissues. External or internal stimuli like enzymatic degradation, light, and pH change can be used to release the hydrophobic micelle molecules, which are supposed to be more appropriate for biological use because of the greater acidity of a few intracellular tumors and compartments as compared to normal tissues and blood. E.g. Fluorescent supramolecular micelles

- **Supramolecular vesicles [40-45]**

Vesicles due to their distinct cavities are largely investigated for efficient encapsulation and drug delivery. Vesicles have been extensively examined as a single nano-sized carrier. Dynamic membranes vesicles present a perfect model system meant for the study by vesicle aggregation behavior, including fusion, adhesion, and fission, of biological membranes' different activities, and this emerging area also attracted great attention. Many molecular units are employed for the manufacture of vesicles, and the development of smart nano-carriers, which leads to the formation of supramolecular segments with dynamic features to develop vesicles that are much encouraging in nature. In short, Supramolecular vesicles are made up synthetically with the help of supramolecular building segments or blocks and these are generally called flexible membranes which incorporate the liquid into their interior side. Tedious synthesis is avoidable based on that simplistic supramolecular strategy and the vesicles obtained are dotted with stimuli. The construction of SVs usually consists of the use as building segments or blocks of supra-amphiphiles (super-amphiphiles) that are connected by dynamic non-covalent interactions with hydrophobic and hydrophilic parts of the amphiphilic molecule. E.g. CAAP5G

- **Supramolecular hydrogels [46-51]:**

Hydrogels are a network of 3D hydrophilic polymers that have cross-linked physical features these have similar features as soft biological tissues and these can incorporate a vast amount of water due to surface capillary effect or surface tension which makes it more and more important in terms of various applications ranging from academic, research and industry. The supra-molecular hydrogels create 3D cross-link networks by interacting between host, host-guest recognition and electrostatic interaction with many non-covalent interventions like metal-ligand coordination, hydrogen bonds which reduce its structural flexibility and changes the macroscopic performance and that create 3D cross link networks. Such non-capacitive hydrogels show moderate mechanical properties and reversible gel sol transition behavior, which respond to various broad spectrums of bio-related stimuli like bioactive molecules, pH, enzymes, redox agents. E.g. DNA-Hydrogels, Bio-Inspired Hydrogels

Benefits of Supramolecular drug carriers in cancer treatment

- Advantageous for targeting drug delivery in cancer

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- Controlled release of a drug on targeted site
- Biodegradability,
- Biocompatibility
- Bio-stability

CONCLUSION

Current cancer treatment management and drugs have several limitations like new drug resistance, dose-limiting toxicity, the non-specific bio-distribution of the cancer drugs. These several limitations lead to the development of a liposomal drug delivery system very rapidly to cure cancer patients with the limited side effect. Various ways of supramolecular designs have been discussed which can be incorporated alongside drug delivery systems and drug design strategies to improve the treatment of cancer. The long history of the use of macro-cycles as drug carriers, whereby a guest drug is included within a host carrier, is one proven example. Advances in recent years for the creation of supramolecular materials offer opportunities to develop controlled release depots, which may further be designed to respond to a specific biomarker or disease indicator. These materials may themselves elicit drug-like function, either through therapeutic bio-mimicry or through bioactivity associated with their structure. Finally, there are many opportunities to use modular design to append targeting units onto drug carriers.

This way we thus see great excitement and purpose of using supramolecular design in creating new therapeutics, and look forward to the continued emergence of technologies rooted in these design principles in the coming years.

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