Cancer Chemotherapy and the role of Nanochemistry

Aarushi Gupta[1], Aarti[1], Shubhdeep Kaur[2], Raveena Kumari[1] and Sheetal Kaur[2]

[1]Chemistry (H) Miranda House; [2]B.Sc. Life Sc. SGTB Khalsa College

Abstract

Cancer is a group of diseases in which there is uncontrolled division of cells in the body. An estimated 7.6 million lives are lost each year to cancer. Currently, major cancer therapies are surgery, radiation, and chemotherapy. All three methods risk damage to normal tissues or incomplete eradication of the cancer. The need for advanced technology for cancer treatment is, therefore, clearly evident. Nanotechnology-based cancer therapy is one such option that extends beyond drug delivery into the field of diagnostics and the creation of new therapeutic agents which exploit the unique properties of materials at the nanoscale. Although small compared to cells, nanoparticles are large enough to encapsulate many molecules of multiple types and there is targeted delivery of these drugs. Targeted delivery helps in the prevention of normal tissues or cells being affected because of which a high amount of drug can be delivered with lesser side effects in comparison with other therapies or surgeries.

Keywords: Tumour, nanoparticles, nanomedicine, liposomes, dendrimers.

Introduction

As is well-known, 'Cancer' is an umbrella term for a large group of diseases caused when abnormal cells grow out of control and spread to other tissues and organs. It is one of the leading causes of death worldwide with an estimated 7.6 million lives lost each year. Cancer cells divide uncontrollably and destroy body tissue. Unlike normal cells, cancer cells ignore signals to stop dividing and give rise to tumours, (or neoplasms, from Greek *neo*, "new," and *plasma*, "formation"), which are masses of abnormal cells. Cancerous or malignant tumours spread aggressively while *benign* tumours remain localised. A tumour remaining localized to its area of origin and posing little risk is *benign*. The process of spreading of cancerous tumour cells in distant areas of the body is known as *metastasis*. Possibly genetic and environmental factors or a combination of both can cause cancer. However, causes are not known for most types of cancer. Though certain general lifestyle guidelines are given by the medical fraternity to minimise the risk of developing cancer, these do not seem to

work universally. In the absence of definite methods of predicting or preventing cancer, the only hope is early detection and treatment to remove or shrink the tumour and prevent its recurrence.

CONVENTIONAL CANCER THERAPY

Surgery, radiation, medication and combination therapies are used to cure cancer or slow its progress.

Surgery: It is a procedure in which a surgeon removes the cancerous tumour from the body. Surgery may be used in combination with other types of treatment. The common side effects of surgery are pain, fatigue, appetite loss, swelling around the site of surgery, drainage from the site, numbness, bruising around the site, infection, lymphedema and organ dysfunction.

Radiation Therapy: This treatment uses high doses of radiation to kill cancer cells and shrink tumours. There are two main types of radiation therapy: *external* beam radiation, in which radiation is directed from outside the body at the patient's cancer site; and *internal* radiation therapy in which the radiation source is as close as possible to the tumour site. The major side effect of radiation therapy is that in addition to killing cancer cells, radiation can affect nearby healthy cells.

Hyperthermia (Thermal therapy or Thermotherapy): In this treatment, body tissue is exposed to high temperatures to damage and kill cancer cells with minimal injury to normal tissue. Most normal tissues are not damaged during hyperthermia if the temperature remains under ~44°C but regional differences in tissue temperature may cause burns, blisters, discomfort or pain.

Bone marrow transplant (stem cell or hematopoietic stem cell transplant): This is a treatment that replaces the patient's bone marrow with healthy cells either from his/her own body (autologous) or from a donor (Allogeneic). It is used to treat cancers such as leukaemia, myeloma and lymphoma. Various problems such as pain and nausea can happen shortly after the transplant from having the bone marrow wiped out by medicines or radiation just before the transplant.

Immunotherapy: Immunotherapy is a treatment used to cure cancer by boosting the immune system. The immune system tries to detect and kill cancer cells but it has a hard time doing this because the onset of cancer in the body occurs by converting normal cells to cancer cells which fool the immune system. Immunotherapy may be used to cure cancer fully or gradually decrease the growth of cancer in two ways: either by boosting the fortification of the immune system so that it can detect and kill cancer cells or by producing substances artificially which are superior to the immune system's defence elements, which jointly with the immune system, detect and kill cancer cells.

Hormone Therapy: Some cancers use hormones to evolve or grow. Hormone therapy is used to suppress the growth of such cancers by blocking or removing

hormones that stimulate the growth of the cancer. Side effects could be hot flashes, loss of bone density, mood swings, fatigue, nausea, vomiting, etc.

Cryoablation: This is an alternative cancer treatment when surgical elimination of cancer may be hard or impossible. It is a method in which cancer cells are killed under extremely cold conditions. A wand-like needle known as Cryoprobe is injected into the body cooled by nitrogen/liquid nitrous oxide, which freezes the tissues.

Gene Therapy: Cancer cells are the result of mutation of genes in the cell which results in uncontrolled cell division, forming a tumour. Damaged genes may be inherited or result from environmental or lifestyle factors. The fault may be in the *oncogenes*, genes that make cells divide and grow or *Tumour suppressor genes*, genes that stop the division of cells. Gene therapy may be used to replace the abnormal or missing genes or prevent the oncogenes from functioning. Introducing genes into cancer cells that activate the immune system to attack and identify the cells as foreign particles can be another way. Gene therapy has been introduced quite recently, so all the side effects are not known.

Combination Therapy: In this, two or more treatments are used together to treat cancer. The multiple therapies simultaneously work on the cancer. Combination therapies also avoid the resistance developed by cancer cells to one kind of treatment. With an optimal dose of different drugs, the side effects, tumour growth and cancer stem cell population can also be reduced. For some cancers, the most effective method is a combination of surgery, radiation therapy and chemotherapy. Sometimes combination therapy is given for reducing the symptoms or side effects and prolonging life rather than curing cancer. Combination therapy can be most useful for people with advanced cancer or cancers that cannot be removed through surgery.

Chemotherapy

Chemotherapy is a systematic method of cancer treatment that involves using chemicals to either arrest the growth of fast mutating cancer cells or to prevent them from damaging the other healthy cells of the body. Generally, a combination of drugs is injected into a patient's body and carried by plasma to the specific areas affected by cancer. Anti-cancer drugs are 'cytotoxic' i.e. they inhibit cell division and cause cancer cells to die. Chemotherapy is often used in combination with other therapies like radiation therapy, surgery etc. Some of the major classes of chemotherapeutic agents are alkylating agents, antimetabolites, plant alkaloids and antitumor antibiotics. These classes of drugs have actions that either prevent cell replication or destroy the DNA that ultimately leads to cell death. The drugs used are classified into three generations till now based on the chronology of their discovery and their effects.

First-Generation Drugs: The earliest breakthrough in the evolution of chemotherapy was the use of alkylating agents. Nitrogen mustard was one of the agents which had alkylating activity

towards DNA preventing its replication and ultimately leading to cell death. These first- generation nitrogen mustards are generally not used now due to their toxicity towards normal cells and the resistance developed by tumour cells over the years.

Second-Generation Drugs: The second-generation drugs were mainly Cisplatin and its derivatives. The mode of action of Cisplatin or cis-diamminedichloroplatinum (II) is based on its ability to crosslink with the purine bases on the DNA, causing damage to the DNA and finally inducing apoptosis (self-destruction) of the cancer cells. Derivatives of cisplatin like carboplatin, oxaliplatin, enloplatin etc. produce fewer side effects compared to cisplatin but are less effective in their action against the cancer cells. Due to this reason, most of the drugs include cisplatin in combination with other agents, such as doxorubicin (a plant alkaloid) or cyclophosphamide.

Third-Generation Drugs: The third-generation drugs combine cisplatin and its derivatives with certain cytotoxic agents to overcome drug resistance developed by cancerous cells. The mode of action of these drugs involves cell apoptosis. Some drugs such as vinorelbine, a plant alkaloid, inhibit the microtubule structures present in the cells which ultimately leads to cell death.

Apart from the limited healing action and toxicity of cancer drugs, the cost of chemotherapy is very high for most cancer patients and can spell financial ruin for families.

Side Effects of Chemotherapy

One of the biggest limitations of chemotherapy is that it can kill healthy cells along with cancer cells. Mostly the side-effects are observed in the areas where healthy cells divide rapidly. All the side effects may or may not be observed in every patient based on the amount and type of chemotherapy and how the body reacts to it. Some of the common side effects include fatigue, vomiting and nausea, pain, hair loss – it is the most notable temporary side effect of chemotherapy, bone marrow suppression, low WBC counts, low RBC counts and central nervous system problems. To minimize the side effects, new modifications for drugs and delivery systems are constantly being researched.

Nanochemistry in cancer treatment and diagnostics

As is clear from the above discussion, none of the conventional therapies for cancer, including chemotherapy, have shown complete success and they also have serious side effects. In addition, the cost of chemotherapy, the most widely used cancer treatment, is also very high. Researchers are, therefore, constantly on the lookout for improved formulations that will show a better success rate in arresting the progress of cancer with minimum side effects and lower costs. It is widely known that Nanoscience, an evolving field in science

and technology, is the study of structures and materials on an ultra-small scale. At least one dimension of a nanomaterial encountered in nanoscience and technology is in the range of 1–100 nm. Nanochemistry is a branch of nanoscience and technology which was described by Geoffrey Ozan, a pioneer in the field, as "an emerging sub-discipline of solid-state chemistry that emphasizes the synthesis rather than the engineering aspects of preparing little pieces of matter with nanometre sizes in one, two or three dimensions". The earliest example of applying nanoparticles for medicinal purposes are possibly the *bhasmas* (ash obtained through incineration) whose preparation in nanometre dimensions is derived from *Ayurveda*, the ancient Indian health science. The Putapaka method and the Kupipakwa method of preparing bhasma that have been described in *Rasashastra*, a branch of Ayurveda, are on par with the green nanotechnology of the contemporary era. Recent research has shown that the application of nanochemistry has the potential to enhance recovery rates for several types of cancer

Nanoparticles can target cancer biomarkers and cancer cells with pinpoint accuracy. As a result, more accurate and sensitive diagnoses can be made. However, nanoparticles have no inherent properties that allow them to target tumour cells and distinguish them from normal cells, or to distinguish between multiple cell types with minimum damage to healthy organs. They have to be specially designed to identify the unique surface of tumour cells.

Nanomaterials for cancer diagnosis: Several types of materials, including DNA, RNA, targeting molecules and peptides, carbohydrates, and imaging agents, can be functionalized on various nanoparticles. Some of the materials utilised for cancer detection include nanoshells, carbon nanotubes, quantum dots, supermagnetic nanoparticles, nano-wires, nanodiamonds, dendrimers, and freshly created nanosponges. Some of them are discussed below.

Nanoshells: Nanoshells are rounded encapsulated shells, which are coated with thin metallic shells to improve biocompatibility and optical absorption. Antibodies can be attached to nanoshells to get them to specifically recognize and target cancer cells in vitro. These shells have proven their use in many novel applications as biosensors for sensitive detection of biomarkers.

Nanotubes: The most promising tool in cancer diagnosis are nanotubes. These are carbon nanotubes that are elongated, fullerenes in tubular form. These tubes have physiochemical properties which make them unique and also come with the dual advantage of both detecting and delivering drug molecules to cancer cells.

Nanowires: Nanowires are one-dimensional systems with their cross-section in the nanoscale and a length-to-width ratio of 1000 or greater. Silicon nanowires are frequently employed in biosensing applications that rely on the semiconductor

capabilities of this material. These nanowires are said to be capable of monitoring brain electrical activity without requiring the use of a brain probe or causing damage to the brain parenchyma. Polymer nanowires, another type of nanowire, have the benefit of altering shape in response to electrical fields, allowing precision guidance through the brain's circulatory system to the specific region of interest.

Nanomaterials for cancer treatment

Liposomes: Liposomes are biodegradable, biocompatible, spherical self-closed structures. They have revolutionized cancer treatment since they are the most successful nanocarriers for drugs. Bingham (1965) for the first time observed that phospholipids in aqueous medium form closed bilayer structures. Later, the name liposome was given to these structures by Sessa and Weissman (1968). There are different types of liposomes, divided on the basis of size and the number of phospholipid membrane layers. Several strategies could be adopted in the use of liposomes since liposomes are capable of both targeted drug delivery and controlled drug release. Drugs are loaded in liposomes in two ways:

- Active loading – drug is loaded after the formation of liposomes.
- Passive loading – the drug is loaded during the formation of liposomes.

Releasing drugs through liposomal structures leads to an incredible increase in the therapeutic index (comparison of the amount of a drug that causes the therapeutic effect to the amount that causes toxicity) because normal tissue uptake gets reduced and limited. These structures do not cause any serious toxic reactions. There is also an antibody-based approach, using immunoliposomes (antibodies attached to the liposome surface) which are specific to tumour cells. While there are many advantages of liposomes, there are still some limitations that persist such as high cost and less stability in an aqueous environment.

Polymeric Nanoparticles: Polymers that have a range of 1-1000 nm are known as Polymeric Nanoparticles. These particles are colloidal, easily synthesized, inexpensive, biodegradable and biocompatible. Active pharmaceutical agents are composed within these polymers. These polymers could be natural as well as synthetic. Polymer nanoparticles are used as drug delivery agents as well as in combination therapies. Researchers have found that well-designed, targeted, polymeric nanomedicines can avoid destruction in lysosomes (membrane-bound cell organelle containing digestive enzymes**)** due to the harsh environment including low pH and enzymatic degradation. These particles are nontoxic and improve the efficacy and pharmacokinetic profile

i.e. absorption, distribution, metabolism, and excretion aspects, referred to as ADME of the drug. However, polymeric nanoparticles still have certain limitations

like low drug loading capacity, inability to carry hydrophilic drugs, high cost of synthesis etc.

Polymer-drug nano-conjugates: There are two strategies for the delivery of drugs with nanoparticles which are:

- Encapsulate drugs via noncovalent bonds.
- Prepare nanoparticles using polymer-drug conjugates.

In Polymer-drug nano-conjugates, a low molecular weight drug is conjugated with a polymer via covalent bonds. Generally, anticancer drugs are insoluble in water, so these nano-conjugates are designed to increase the aqueous solubility of these drugs. These are 'prodrugs' that get activated after reaching their destination. Some disadvantages for these structures are complexities of synthesis and characterisation, low drug loading capacity etc.

Dendrimers: Dendrimers are 1-100 nm in size, highly branched, and commonly used 3-Dglobular macromolecules. They have three different parts:

- Central core
- Hyperbranched mantle
- Corona with peripheral reactive functional groups (star-like)

There are different kinds of dendrimers such as polyamidoamine, melamine, triazine etc. They are used both as carrier/delivery devices and as drugs. The drug can be non-covalently encapsulated or covalently attached to its surface. Experiments have shown positive responses for dendrimers modified with folic acid which resulted in a large reduction in tumour mass. They fulfil all the requirements like solubility, specificity, stability, biodistribution, therapeutic efficiency, immune clearance, cell penetration, and off-target interactions. Hence they are the best category of nanoparticles for the treatment of cancer.

The main drawbacks are lower yield and difficulties in obtaining higher generations due to sterichindrances when the branches are connected to the core.

Inorganic nanoparticles: Inorganic nanoparticles have unique size and shape-dependent optoelectronic properties. There is a wide range of these particles. Mesoporous, silica-based nanoparticles, elemental metals – gold, silver, platinum, metal oxides, and metal salts are some examples of inorganic nanoparticles. These are applied in phototherapy in cancer treatment. Superparamagnetic iron oxide nanoparticles (SPIONs) are used in inducing magnetic-field- responsive functionality of drug delivery systems because it is a good sorbent. Gold and silver nanoparticles are used because of their unique optical properties, facile surface chemistry, and appropriate size scale. Tumour detention can be done by attaching ligands to these nanoparticles. For targeted delivery of drugs, mesoporous silicates are under intensive study. One of the major limitations of the use of these particles is

poor solubility. They remain in circulation for a very short time and cannot interact sufficiently with the cancerous cells.

Theranostics

As the name suggests, Theranostics is a combination of therapy and diagnostics. Nanoparticles like dendrimers, liposomes etc., provide various advantages in the field of theranostics due to their ability to perform dual roles. With nanoscience targeting, diagnosis and therapeutics can be applied in one nanomedicine. The main aim of using nanoparticles in theranostics is to get a higher level of improvement in treatment outcomes of several diseases. Also, nanoparticles possess a high capability to target specific tissues or organs, which provides a big opportunity to use them in cancer treatment in the form of nanotheranostics. Theranostics also provide a good option to reduce the high cost of treatment by doing a two-in-one job e.g. targeted siderophore loaded with the drug Doxorubicin has been used as a theranostic agent for imaging and treatment of colon carcinoma (Nosrati, Abnous and Ramezani June 2021).

Conclusion

Cancer is one of the leading causes of death worldwide. Treatment methods for cancer are constantly improving. Methods used for treatment include surgery, chemotherapy, radiation therapy, gene therapy, hyperthermia, combination therapy, bone marrow transplant, immunotherapy, etc. Among these, chemotherapy is widely used because it is convenient for doctors and has a high success rate. Over many decades chemotherapy has been one of the most successful therapies for cancer but it has many toxic side effects that are harmful to the patients. Molecules isolated from natural products have been introduced in chemotherapy in an attempt to reduce side effects. Combinational therapy based on chemotherapy mediated by nanotechnology has been the recent trend in clinical research. Nano-carriers, which are products with multiple applications, have been a prime research focus to enhance the efficiency of combination therapy because of their numerous advantages. The latest advances in the treatment of cancer with the help of nanochemistry have proven to be successful in many cases. Nanomedicine application areas include therapy including drug delivery, diagnostics and theranostics. Liposomes, dendrimers, polymeric nanoparticles etc. are different nanoparticles used as drug carriers as well as drugs themselves. They are effective, have negligible toxic effects on healthy tissues and increase the therapeutic index of drugs. However, there are some limitations of nanoparticles related to their preparation and cost which make it difficult to apply nanomedicines to every patient. Research is continuing to overcome these limitations.

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