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Advances in drug delivery for cancer treatment

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ABSTRACT

The division of cells in an organism, in an uncontrolled way leads to the production of tumors. The presence of these tumours causes a number of different forms of disease called cancer. Cancer is one of the most complicated diseases which can neither be cured completely nor prevented. Various methods of treatments are implicated to cure cancer and until nineteenth century and 20 century the major advances were made in general surgery and cancer surgery. The late 19 century led to the evolution of cancer treatments initiating Hormone therapy, Radiation, Chemotherapy and Immunotherapy. Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. Chemotherapy was considered as one of the drug delivery method but its side effects have greater impact on the body. The advanced Chemotherapy is considered as the targeted drug delivery system which exactly acts on cancer cells leaving behind the normal cells. The growth in our knowledge of cancer biology has led to remarkable progress in cancer prevention, early detection and treatment which has led to the innovation in advancement of cancer treatment such as Targeted therapy, Nanotechnology, Robotic surgery, Liposomal drug delivery , Activity of bio surfactants on targeted cells and Gene therapy. This review is an enumeration of recent advancement in Cancer therapy.

INTRODUCTION

Cancer is a condition in which the body cells of affected area keep multiplying at an abnormal rate. Cancer is not a single disease and cancers are different. When we refer to HIV, Polio or the mumps, there will always be some variations between the individual's cell and the invaded cells and that relative uniformity has all manner of useful implications for treatment. But in case of cancer the tumour grows infinitely without restriction and these cells resembles the normal cells at basic level. Hence, diagnosis of cancer is at early stage is difficult. Therefore, various advancements in the methodology for curing cancer is adopted which has the efficacy to differentiate between the targeted and non-targeted cells and destroy them.

Earlier cancer treatment:

Surgery: Surgery is one of the method used earlier to remove the cancer cells. This method is very effective in the earlier stage of cancer. But in later stages of the cancer the surgery cannot be done because it would have spread across many other neighbouring tissues. Before nineteenth century the Surgery was very primitive with many complications, including blood loss. During the end of 20th century, surgeons become expert in removing the cancerous tissue by avoiding the removal of excess normal tissues. From the trends of lumpectomy and mastectomy the removal of tumour in bones and soft tissues become possible. These progresses are due to use of better surgical instrument. Later the surgery combined with Chemotherapy or radiation for effective treatment. [Published by American cancer society in an review titled "THE HISTORY OF CANCER"]

Radiation: Radium was the first radioactive material used for therapy which has relatively low-voltage diagnostic machines. Shortly after introduction of radiation treatment it was discovered that radiation could cause cancer as well as cure it. Advances in radiation physics and computer technology helped in using radiation more precisely. This precise methods includes the following

1) Conformal radiation therapy (CRT)
2) Intensity-modulated radiation therapy (IMRT)
3) Conformal
4) Proton beam radiation therapy
5) Stereotactic radiosurgery
6) Stereotactic radiation therapy
7) Intraoperative radiation therapy (IORT)
8) Chemical modifiers or radiosensitizers

The aim of this research into different types of substances is to develop agents that will make the tumor more sensitive without affecting normal tissues. [Published by American cancer society in an review titled "THE HISTORY OF CANCER"]

Chemotherapy: A compound called nitrogen mustard used in war fields was studied and found to work against lymphoma. This compound more effective agents since it is an alkylating agent and it kills the rapidly growing cancer cells by damaging their DNA. Soon after aminopterin was introduced, a compound related to the vitamin folic acid, produced remissions in children with acute leukemia. Aminopterin blocked the chemical reactions needed for DNA replication. This drug was the predecessor of methotrexate, a cancer treatment drug used commonly today.

Researchers discovered drugs that block different functions in cell growth and replication. Thus, the era of chemotherapy had begun. Over the years, chemotherapy drugs (chemo) have successfully treated many people with cancer. Long-term chemotherapy treatment have even cured many patients with Hodgkin disease. Even if the cancer is not cured chemotherapy helps in controlling the cell growth and increases the survival period of the individual. Today, several approaches are available to improve the activity and reduce the side effects of chemo. These include: Formulating new drugs with different drug delivery techniques. Researchers are in action to discover a novel drug which can exactly target the cancer cells. To reduce the side effects of the drugs.

Multiple chemotherapy drugs are used over single agents. This combination of drugs helped in curing fast growing cancers such as luekemia. Multiple chemotherapy drugs are evolved from constant clinical trials which helped in designing the combination of drugs more appropriately [Published by American cancer society in a review titled "THE HISTORY OF CANCER"].

Disadvantages in the earlier methods of cancer treatment: These are some of the disadvantages in the earlier method of cancer treatment

Radiotherapy can damage or destroy normal cells as well as destroying cancer cells and cause treatment side effects. Most side effects are temporary. Surgery can be followed only during the earlier stage of cancer. The worst disadvantages of chemotherapy are the short term negative side effects such as: nausea, diarrhoea, constipation, dizziness and extreme discomfort. Although these side effects may only occur for a certain period after the initial treatment, they can certainly be severe and painful for the patient. Hair loss is also evident after the chemotherapy treatment. Chemotherapy may also lead to infertility which can affect a person's ability to conceive a child. Sometimes, one course of chemotherapy does not work and that is when another one is needed. The treatment process will therefore be longer than intended to be and plus, there is always a risk that the cancer may emerge after treatment has ended.

Advanced cancer treatment:

Targeted drug delivery: The predominant drug accumulation within a target zone that is independent of the method and route of drug administration is known as Targeted Drug delivery (You Han Bae, 2011).

Targeted therapy involves in implementing a specific interaction between the drug and the receptor of the target cell at molecular level (You Han Bae, 2011). Effective targeted drug delivery systems require four key requirements:

1) The drug carrying vehicle should able to retain the concentration and composition of the drug more effectively.

2) The drug should have the intensity to evade the cancerous cell.

3) The drug should able to target the affected cell leaving the non-affected cells.

4) The drug should able to release the therapeutic components to the system properly.

Targeted works in several ways they are as follows (You Han Bae, 2011)

1) Growth signal inhibitors.

2) Angiogenesis inhibitors.

3) Apoptosis-inducing drugs.

Classification of the current targeted drug delivery processes:

1) Systemic targeting based on blood circulation and extravasation: This includes the following: A)Ligand–receptor interaction mediated, B)Locally-activated delivery

2) Self-triggered release of the drug at the target cells.

3) Externally-activated release of the drug at the target cells.

4) Intracellular targeting involves**:** Low-pH activation technologies that use default pathway delivery

5) Lysosomes**:** Mechanisms that avoid (default) lysosomal delivery

Targeted drug deliveries are of two types.1) Passive Targeting.

2) Active Targeting (You Han Bae, 2011)

Passive targeting: The leaky vasculature is formed around the targeted cancer cells in passive targeting; it is also called as the enhanced permeation and retention (EPR) effect. (You Han Bae, 2011)

The EPR effect: The main tumour targeting principle of many drug delivery systems is based on the EPR effect of nanoparticles (You Han Bae, 2011). The key observation of the role played by EPR started with the enhanced antitumor effect of arterially infused highmolecular- weight antitumor agent SMANCS dissolved in lipid lymphographic agent in man. SMANCS is the styrene–maleic acid copolymer (SMA)-conjugated protein antitumor agent neocarzinostatin (NCS). NCS is a seven-stranded β-sandwich protein secreted by Streptomyces neocarzinostaticus with antitumoral activity, but with significant general cytotoxicity. The molecular weight of SMANCS is around 16,000 g/mol (two SMA chains with molecular weight of 2000 each were grafted to one NCS of 12,000). Ethiodol is an injectable radio-opaque diagnostic agent containing 37% iodine combined with ethyl esters of fatty acids of poppy seed oil. (You Han Bae, 2011)

Active targeting: Active targeting is defined as a specific interactions between drug carrier and the target cells, usually through specific ligand–receptor interactions Ligand–receptor interactions are possible only when the two components are in close proximity (b0.5 nm). The term "active targeting" has a flavour of guiding a drug/drug carrier to a target site like a cruise missile does. The term "active targeting" simply means a specific "ligand–receptor type interaction" for intracellular localization which occurs only after blood circulation and extravasation. This is why increasing blood circulation time by PEGylation (i.e., modifying the surface of nanoparticles with polyethyleneglycol). (You Han Bae, 2011)

Ligand–receptor interactions: Nanoparticles arrive at the target site via the systemic circulation and requires efficient interaction between the ligand and receptor after nanoparticles meet their target cell. Efficient ligand–receptor interaction for "active targeting" is dependent upon a variety of factors that include: the extent of target cell selective expression of the receptor relative to non-target cells, receptor availability on the target cell surface, the rate of internalization vs shedding of that surface receptor following ligand binding, etc. Further, the expression of a promising tumour targeting receptor may not be homogenously distributed within a tumour or may change in its surface expression over time thus, one can envisage conditions where the mere presence of a particle ligand on nanoparticles does not ensure "active targeting". (You Han Bae, 2011)

Nanoparticles in cancer treatment: Nanoparticle platforms are characterized by their physicochemical structures (Frank Alexis, 2010), including1) Liposomal nanoparticles; 2) polymer–drug conjugates; 3)lipid-based nanoparticles; 4)polymeric nanoparticles; 5)protein-based nanoparticles; 6)biological nanoparticles and 7)hybrid nanoparticles.

Posomal drug delivery system: Liposomes are considered an effective nanoparticle drug delivery vehicles. Liposomes are natural Phospholipids which are highly biocompatible and biodegradable. They have low intrinsic toxicity and low immunogenesity (Lise Norkjaer Bjerg, 2013). Other liposome-based agents such as liposomal anthracyclines, have had the greatest impact in cancer treatment to date. Liposomal drugs are formulated and designed by keeping the previously modelled liposomes as reference (Park, 2004). Physiologic targeting of drugs to tumors is achieved using long-circulating liposomes (Park, 2004). Lipids are nano sized vesicles formed by self-assembly of both hydrophobic and hydrophillic lipids and excipients. The lipids form a bilayer continuous parallel packing, with the hydrophilic head groups positioned towards the aqueous environment. Hydrophilic molecules can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the lipid bilayer. (Frank Alexis, 2010)

Liposomes must be used to carry very potent drugs due to their low encapsulated load (Frank Alexis, 2010) Liposomes with anthracyclines are very effective against breast cancer (Lorusso, 2007). The liposomal delivery of the anthracycline anti-neoplastic drug doxorubicine (DXR) are very effective against many types of cancer. To increase the encapsulated load DXR can be used as drug and this encapsulation helps in maintaining the stability (Erik Hagtvet, 2011). Ultrasound mediated liposomes are produced for cancer treatment (Erik Hagtvet, 2011). Pegylated liposomal doxorubicin or stealth liposomes has the following characteristics

1) They possess long circulation period in the blood stream.

2) The pharmokonetics is very reliable and

3) The drugs are accumulated exactly on the cancer tissues (Cattel, 2003). Future liposome therapeutics are building on these validated designs as well as on pharmacologic insights into their mechanisms of delivery (Park, 2004)

Polymer–drug conjugates nanoparticles: The nanoparticle which is under investigation for advanced treatment for cancer. They are currently in clinical trials as advanced as phase III (Frank Alexis, 2010). Polymer-drug conjugates avoid the interaction of the drugs with macromolecules such as protein in their path (Gemma Vilar, 2012). Polymer–drug conjugates are formed by attaching drugs to the side chains of the polymer residue. This process allows great doses of drugs. The size of polymer–drug conjugates is generally below 20 nm. HPMA-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer (PK1) was the first synthetic polymer–anticancer drug conjugate to enter clinical trials. The pharmokinetics of the polymer – drug conjugates varies with small changes in their character, hence forming a new chemical entity (Frank Alexis, 2010).

Protein nanoparticles: Protein Nanoparticles are designed by using Human Serum Albumin as a drug that cures the cancer. Protiens are natural biomolecules hence they are far better than the polymer drugs. Recently albumin-bound paclitax was approved by the Food and Drug Administration (FDA) for metastatic breast cancer therapy. The researchers are going on in clinical trials for progressing the use of protein nanoparticles as a therapeutic agent. (Frank Alexis, 2010). Flexible modification of surface structures, adjustment of covalent attachment of drugs and targeting ligands are possible in protein nanoparticles (Warangkana Lohcharoenkal, 2014).

Biological nanoparticles: Bacteria are unicellular microorganisms with different shapes and sizes. It can encapsulate essential components of the cytoplasm there by acting as Biological nanoparticles carrying therapeutic effects to the cancerous tissues. Drug delivery system developed by EnGeneIC Pty Ltd called a "nanocell", which consists of anucleate globular bacteria (~400 nm) is found out to be cancer therapeutic biological agent (Adler, 1967). Doxorubicin, paclitaxel, and siRNA can be encapsulated in the biological nanocells through drug diffusion into the bacteria within a few hours. The sign of toxicity has not appeared in the higher organisms such as pig (Frank Alexis, 2010).

Hybrid nanoparticles: The lipid–polymer nanoparticles and solid liposomal nanoparticles characteristics are combined to form a high efficient Hybrid nanoparticles. They are composed of at least two different materials to form the core and the corona structure. In general, metallic and polymeric materials form the core and are coated with a single or multiple lipid layers to form a protecting membrane (corona) similar to a liposome or micelle (Frank Alexis, 2010).

Activity of biosurfacants: Biosurfactants are novel, versatile and has diverse properties which could possibly have a therapeutic property (Edurdo J.Gudina, 2013). Molecules with surface activity produced by microorganisms that can be used in many biomedical applications. The anti-tumour potential of these molecules is being studied, although results are still scarce and few data are available regarding the mechanisms underlying such activity (Cristina Duarte, 2014). Comprising a range of chemical structures, such as glycolipids, glycoproteins and lipopeptides, among others different biosurfactants are expected to exhibit diverse properties and physiological functions. The biosurfactant was shown to be more active than surfactin against the studied breast cancer cells (Cristina Duarte, 2014)

Immunotherapy: Drugs aimed at specific immune checkpoints are being developed to help the immune system better kill cancer cells. Some of these biologic agents, which occur naturally in the body, can now be made in the lab. Examples are interferons, interleukins, and other cytokines. These agents are given to patients to imitate or influence the natural immune response. They do this either by directly altering the cancer cell growth or by acting indirectly to help healthy cells control the cancer. [Published by American cancer society in an review titled "THE HISTORY OF CANCER"]

Robotic surgery: This term refers to manipulation of surgical instruments remotely by robot arms and other devices controlled by a surgeon. Robotic systems have been used for several types of cancer surgery; radical prostatectomy is among the most common uses in surgical oncology. As mechanical and computer technology improve, some researchers expect future systems will be able to remove tumors more completely and with less surgical trauma. [Published by American cancer society in an review titled "THE HISTORY OF CANCER"]

CONCLUSION

Hence, the treatment for cancer has been evaluated from the beginning in this review. The advanced methods such as Targeted drug delivery, The liposomal drug delivery ,The advanced multiple drug chemotherapy, Immunotherapy, Robotic surgery, The nanotechnology in cancer treatment, The activity of biosurfactants and protein nanoparticle treatment plays a vital role in understanding and analysing about the cancer treatment and

their strategies. Many cancer cures are possible only with the help of these advanced and advancing methods. The clinical trials are still going on with an aim to provide a most efficient treatment for the cancer. These methods will be a main base for the development of other novel method of drug delivery to the cancer.

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