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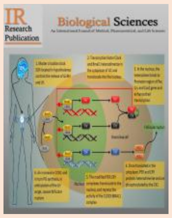

New nanotechnology approaches for treatment and palliative care of cancer

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ABSTRACT

Cancer is one of the major reasons which leads to worldwide mortality and this proportion is increasing day by day, hence advanced better treatments are required to develop. Nanotechnology, or the science of the very small, has immense potential in healthcare, from more effective drug delivery to more rapid and sensitive illness diagnosis. Traditional cancer treatments run the risk of harming healthy tissues while attempting to destroy malignant cells. By controlling medications to selectively target tumor cells, nanotechnology ameliorate chemotherapy and decreases its side effects. The US Food and Drug Administration has already approved the first generation of cancer treatments delivered by nanoparticles (FDA). The application of nanotechnology to cancer detection and medicine delivery has received a lot of attention. It can detect the chemical which relates to cancer quickly and sensitively, allowing scientists to detect molecular changes in a small fraction of cells. Nanotechnology has the potential, or we can say it has an innovative approach to develop effective medicinal treatments. Cancer detection, treatment, drug administration, imaging and diagnostic techniques, and immunotherapy will all be discussed in this review paper.

Introduction

It has been evaluated that by 2030, nearly 7.6 million people die every year extensively because cancer is responsible for 13% of all deaths, and by 2030, cancer-related deaths can reach 13.1 million.

Cancer, itself is one of the complicated diseases, in which every organ system is affected and shows a set of symptoms. Approximately, 30 % of cancer mortalities take place due to lifestyle factors like smoking and diets and can be prevented by changing lifestyle management. However, the majority of malignancies cannot be prevented through simple lifestyle changes, necessitating technological innovation to improve results. In this aspect, nanotechnology is a promising field in which using target drug delivery like liposomes, dendrimers, etc., which we will be hereby discussing provides a tremendous growth in early detection and diagnosis technology [1]. Cancer nanotechnology combines the convergence of major fields, including engineering, materials

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Abbreviations: *PGA: Polyglycolic acid, PLA: Polylactic acid, HA: Hyalauronic acid, FDA: Food and Drug Administration, MPS: Macrophage Phagocytic System, EGFR: Epidermal Growth Factor Receptor, NP: Nanoparticles, PET: Positron Emission Tomography, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, EPR: Enhanced Permeation and Retention Factor*

science, chemistry, and physics with cancer biology. In the development of devices and/or materials that are themselves or have critical components in the 1–1000-nm range for at least one dimension, with the potential to rapidly advance the status in the diagnosis and treatment of cancer, including drug delivery, gene therapy, detection and diagnosis, drug carriage, biomarker mapping, targeted therapy, and molecular imaging [2].

Nanomaterials can easily detour cell barriers due to their biological nature. It has been employed in the treatment of tumors for many years due to its active and passive targeting principles. Despite the increased efficacy, the toxicity of the synthetic drugs is much high which leads to damaging of healthy cells in the body with many side effects. In this context, nanomaterials provide improved efficacy with very less toxic effects, however, there is potential toxicity (regarding toxicity, we will discuss later in this paper) of nanomaterials hence still there is an advancement to be made for clinical management in the nanomaterials drug design or as nanovectors [3].

Nanovectors and target drug delivery system

As we have discussed, nanomedicines have the potential to remove the negative impacts that happen due to the use of single or multistep chemotherapy treatment with improved efficacy. For this, nanovectors term has been introduced as a type of targeted delivery vehicle that transports nanoscale material. By formulating the medication a drug with nanovectors, it protects the drug from a breakdown before reaching its target site, hence enhancing the efficacy of the drugs; controlling the timing and biodistribution of drugs, and preventing the drugs from interacting with normal cells and hence decreasing the adverse effect. Hence various nanovectors have been under study and are employed for various purposes in the treatment of cancer [4].

Types of nanoparticles

Liposomes

A form of nanovectors comprised of lipids surrounding water was the first nanotechnology-based technique to be employed as a means of administering cancer chemotherapy sites and related nanovectors to accomplish effective treatment. Liposomes, dendrimers, micelles, carbon nanotubes, nanocapsules, nanospheres, and other nanocarriers are only a few examples. Nanoparticles can be entrapped, covalently bonded, encapsulated, or adsorbed with therapeutic substances. Liposomes are made up of lipid bilayers with a hydrophilic or hydrophobic center depending on the number of lipid bilayers. Liposomes with a single lipid bilayer have an aqueous core that encapsulates water-soluble pharmaceuticals, whereas liposomes with multiple bilayers entrap lipid-soluble medications. Because they are easily removed by macrophages, they are coated with inert polymers to keep them stable in physiological circumstances. Polyethylene glycol is often used to coat liposomes (PEG). Advanced drug delivery systems based on poly (ethylene glycol) (PEG) are a significant advancement in cancer treatment. PEGylation increases the retention period of treatments such as proteins, enzymes, tiny molecular medicines, liposomes, and nanoparticles by shielding them from numerous degrading mechanisms that occur inside a tissue or cell, hence increasing their therapeutic potential [6]. Liposomes coated with hyaluronic (HA) improve circulation time and enhance the targeting of HA receptor-expressing tumors, according to an in vivo study. Liposomal drug delivery allows for both active and passive targeting. For selective drug delivery, liposomal nanoparticles can be conjugated with antibodies or ligands. They offer the advantages of being biodegradable, non-antigenic, and having a fast transport rate. They can also be made to administer pH-sensitive drugs or provide thermotherapy. When compared to the delivered medicine in its free form, long-circulating liposomes can deliver 3 to 10 times more drugs to solid tumors. If the encapsulated medications are released from extravagated liposomes, it's quite likely that these vesicles will be able to overcome the tumor cells' multidrug resistance. As a result, tumors with a low resistance factor should be predicted to regress [6].

Dendrimers

Dendrimers are three-dimensional tree-like structures with multifunctional cores that are branched in three dimensions. Amino acids, carbohydrates, and nucleotides, for example, are produced from synthetic or natural materials. Dendrimers can be made by carefully controlling the polymerization of monomers to get the desired form and size. Due to its unique branching point, dendrimers can be conjugated into a variety of molecules, including both hydrophobic and hydrophilic molecules. They can also be loaded with pharmaceuticals through hydrophobic contacts, hydrogen bonds, or chemical linkages exploiting the voids in their cores. Dendrimers can transport genes, medicines, anticancer agents, and other materials [6].

Micelles

Micelles are spherical formations in which molecules with hydrophobic ends combine to form a central core and other molecules' hydrophilic ends come into touch with the liquid environment around the core. Micelles are a good vehicle for delivering water-insoluble medications that are carried in the hydrophobic core [6].

Nanospheres

Nanospheres have a spherical shape and are made up of a matrix system that evenly distributes the medication through entrapment, adhesion, or encapsulation. For targeting purposes, the surface of these nanoparticles can be changed by adding ligands or antibodies [6].

Nanocapsules

Nanocapsules, on the other hand, are vesicles with a central core that contains medicine and is surrounded by a polymeric membrane. Surfaces can be coated with targeting ligands or antibodies [6].

Fullerenes

Fullerenes (also known as Buckyballs) and nanotubes are a type of carbon molecule that takes the shape of a hollow sphere or an ellipsoid tube. Atoms may be confined inside fullerenes, while antibodies or ligands are linked to the surface to allow them to be targeted. Carbon nanotubes are changed to make them water-soluble and functionalized so that they can be coupled to peptides, proteins, nucleic acids, and medicinal substances. Nanotubes can have a single or several walls. Polymers such as poly (alkyl cyanoacrylates), poly (methylidene malonate), and polyesters such as poly (lactic acid), poly (glycolic acid), poly (e-caprolactone), and their copolymers are suitable for nanoparticle formation. Because of their biocompatibility and biodegradability, poly (e-caprolactone), poly (lactic acid (PLA), poly (glycolic acid) (PGA), and their copolymers have received the greatest attention [6].

Quantum dots

Quantum dots are colloidal fluorescent semiconductor nanocrystals size range (2-10 mm) and are composed of the central core made up of elements from group II-VI or group III-V overcoated with a shell comprised of second semiconductor material. These are photostable and have unique optical and electronic properties and show size and composition tunable emission spectra and high quantum yield. They are resistant to photobleaching. They are used in cancer imaging and diagnosis [7].

Gold Nanoparticles

Gold Nanoparticles have the advantages of their properties like ease of functionalization, good stability, low toxicity, and high biocompatibility [8].

Iron oxide

Iron is one of the most crucial micro-elements in the human body which participates in various biological activities- in the construction of hemoglobin. FDA has approved iron-based nanoparticles for use in inorganic nanomedicines. Iron red oxide nanoparticles are a well-established nanotherapeutic platform for clinical studies for various cancer [8].

Silica nanoparticles

Due to their high porosity and surface area as well as excellent biodegradability Silica nanoparticles are highly selected. Silica nanoparticles are used in specific drug delivery, gene therapy, and targeted imaging [8].

Doxil

Doxil, a liposomal version of doxorubicin, was the first nanomedicine to get clinical approval. The US Food and Drug Administration (FDA) authorized Doxil in 1995 for AIDS-related Kaposi's sarcoma [9].

Passive and active targeting

Passive and active targeting are two essential processes involved in the differentiation of malignant and non-malignant cells. The enhanced permeability and retention (EPR) effect is used in passive targeting to increase the concentration of nanoparticles in the tumor. To localize nanoparticles to cancerous cells, active targeting may involve selective molecular recognition of antigens, which are frequently proteins expressed on the surfaces of cancer cells, or utilizing biochemical properties associated with cancer tissues such as matrix metalloproteinase secretion. Both passive and active targeting techniques can be used separately or in combination. Surface changes of nanoparticles assist both tactics by reducing the uptake by the

Table 1. Types of nanoparticles [5].

Inorganic nanoparticles	**Organic nanoparticles**
Nanoshells	Micelles
Silica nanoparticles	Liposomes
Gold nanoparticles	Dendrimers
Quantum Dots	Lipid nanoparticles
Nanoceria	Fullerenes
Iron oxide nanoparicles	Nanospheres

macrophage phagocytic system (MPS) and thus increasing the duration of the circulation. Nanoparticle targeting methodologies employing tumor features that are peculiar and unique have been described. When dealing with tissue targeting for drug administration, two aspects of anomalous vasculature and the specific metabolic environment caused by inadequate blood flow resulting from the anomalous vasculature must be taken into account [10].

Passive targeting via the EPR

In passive targeting, as we discussed above, the Enhanced Permeability and Retention (EPR) effect is used. The EPR is based on the nanometre size range of nanoparticles and the two important features of tumor cells, i.e. leaky vasculature and impaired lymphatic drainage [8]. The impaired lymphatic drainage in the tumor contributes to the nanoparticle's retention. The encapsulation of small molecule drugs in nano-sized drug carriers enhances their pharmacokinetics and provides tumor selectivity with fewer side effects. The discovery of the EPR effect is done by Maeda et al. In the 1980s [11].

Active targeting

Active targeting via direct interactions in ligands and receptors targets specifically malignant cells. Active targeting acts through overexpression of certain receptors such as folate on the tumor cells. The ligands on the surface of nanoparticles are chosen to target molecules that are over-expressed on the surface of cancer cells allowing them to differentiate between cancer cells and healthy cells [9]. Receptor-mediated endocytosis occurs when ligands on nanoparticles bind with receptors on the surface of cancer cells, allowing internalized nanoparticles to successfully release therapeutic medicines. As a result, active targeting is particularly well suited to the delivery of macromolecular drugs, such as proteins and siRNAs. Monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates are examples of targeting moieties. These ligands attach to receptors on targeted cells, with the transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR) being among the most studied [12].

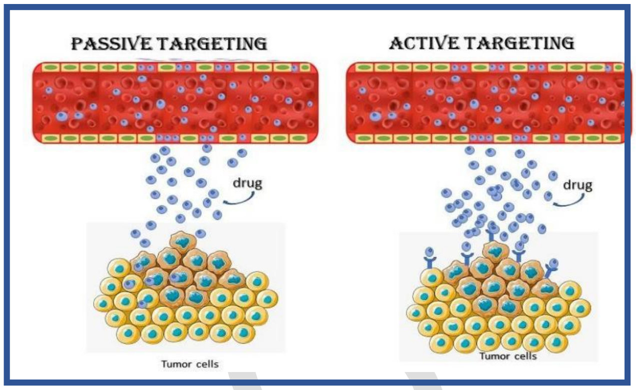

Figure 1. Schematic Diagram of Passive and Active Targeting [5].

Selected drug delivery system

In our body, iron is transported via transferrin protein into the cells which is a kind of serum glycoprotein. In many solid tumor cells, transferrin protein receptors as compared to normal cells, hence as a result, transferrin-conjugated nanoparticles act as an active targeting technique for cancer medication delivery. These modified nanoparticles have been found to have a greater cellular absorption efficiency and improved intracellular drug delivery as compared to unmodified nanoparticles [13].

Imaging with nanoparticles

Increased contrast sensitivity, binding avidity, and targeting specificity are all advantages of targeted nanoparticles. The use of nanoparticles in cancer treatment for direct imaging is based on their increased permeability and retention impact (ETR). Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), Ultrasound, and Optical Imaging are only a few of the applications (modalities) that have been created so far. Nanoparticles are made of various types of materials and occur in various compositions, sizes, forms, and architectures. These various materials and shapes vary from spheres, rods, and cubes to snowflakes, flowers, thorns, hemispheres, worms, discoid, and chains—a wide range that allows many imaging modalities (Ex-Optical Imaging, MRI, Nuclear Imaging) to combine disease diagnosis and therapy into so-called "therapeutic" (therapy+diagnostic) applications.

Table 2. Table representing imaging devices with salient features [15].

S.No.	Devices	Sensitivity (mol)	Limitations	NP Solutions	NP Types
1.	CT	10^{-6}	Low soft tissue contrast Low sensitivity	Increase contrast, Molecular targeting	Gold/Silver nanoparticles
2.	Optical	10^{-12} - 10^{-15}	Poor depth penetration, poor contrast stability	Multimodal contrast, stability and photo bleaching resistance	Quantum Dots, Gold/Silver nanoparticles
3.	MRI	10^{-9} - 10^{-6}	Low sensitivity	Enhance contrast, Multimodal imaging	Iron oxide nanoparticles
4.	PET	10^{-14} - 10^{-15}	Poor spatial resolution	Multimodal contrast	Radionuclide loaded nanoparticles
5.	US	10^{-8}	Low sensitivity, poor imagecontrast	Enhance contrast	Silica nanoparticles

Increased contrast sensitivity, binding avidity, and targeting specificity are all advantages of targeted nanoparticles [14]. Nanoparticle platforms can passively collect in tumor tissues due to abnormally leaky vasculature and the lack of a functional lymphatic, drainage system in tumor tissues, as we know. The EPR effects are a collective term for these unusual events. Imaging cancer is crucial for guiding treatment decisions and analyzing the effectiveness of previously administered treatments. Cancer imaging has improved thanks to the use of nanoparticles for image contrast and enhancement [15]. A good clinical nanoparticle imaging probe should be biodegradable or quickly eliminated, have low toxicity, and produce a robust imaging signal.

Fate of nanoparticles

To successfully target nanoparticles to malignancies or tumors, many biological, physiological, and physical hurdles must be overcome. The analysis of starting location of administration can be crucial. Nanoparticles injected into the stomach or lungs, for example, would first encounter epithelial barriers. Another early hurdle to targeted nanoparticle delivery is metabolic events or cellular reactions at the injection site. After entering the body, nanoparticles' shape, size, and surface properties may generate episodes that act as a secondary barrier to the target site: material diversion away from the intended site due to unwanted interactions. Nanoparticle targeting can be said to be successful only when there will be a uniform and effective distribution of the medication to the target site of tumor tissue. After reaching the site of action, there is a chance of affecting the action of nanoparticles because of the metabolic and physical aspects of tumor cells. So, overall, these barriers can control the overall success of any nanoparticle-based drug design for targeting [16].

Safety concerns for nanomaterials in nanomedicine applications

The use of nanomaterials is extensively applied in radiation diagnostics and therapy because of their unique properties like optical, magnetic, and thermal capabilities. But now nanomaterials are used also as nanomedicines, especially in cancer treatments but their safety and toxicity must be addressed before fully utilizing nanomedicines in therapeutic management [17]. Nanoparticles' toxicity should be specifically assayed to check their toxicity before clinal trials. Also, non-loaded drug nanovectors should be assayed since the toxicity of drugs and nanoparticles can be distinguished when the whole formulation will be investigated. Route of administration like in the case of inhalation can lead to inflammation in the pulmonary. Nanoparticles may also produce new effects which may not be seen before with larger particles (eg, mitochondrial damage, uptake through olfactory epithelium, platelet aggregation, and cardiovascular effects) [18]. As a result, progress in evaluating techniques to correctly test the negative side effects of nanoparticles could lead to future development in altering the physiochemical properties, lowering human dangers, and boosting the healthy evolution of nanotechnology's therapeutic purposes. Specific drug delivery formulation must be applied with an enhanced therapeutic ratio. Several commercially licensed nanotherapeutics such as Doxil and Abraxane, have fewer adverse effects, however, other nanomaterials like metallic and carbon-based particles are poisonous [18]. For any medicine to reach its target site, it has to overcome many barriers. Immunological clearance, renal clearance, enzymatic and mechanical breakdown, vascular endothelium, extracellular matrix, cell membrane, lysosome, and membrane pumps are all examples of these barriers. Nanoparticles have the potential to reduce drug clearance and improve drug accumulation in sick tissue, resulting in increased therapeutic efficacy and fewer toxic effects [19].

Conclusion

Where current methods like chemotherapy, immunotherapy, radiation therapy, and surgery are used in cancer treatment also lead to the risk of destruction or damage to normal tissues and hence show adverse effects but as the science is growing, new technologies are being developed and getting advanced like nanotechnology which can reduce the problem of adverse effects caused due to current treatment methodologies while providing improved efficacy to the target site. The physical properties of the nanoparticles are also used like energy absorption and re-radiation to destroy the tumor cells. The application of nanotechnology is used in the target drug delivery, imaging is now widely getting developed and used while the focus is also made to reduce the toxicity of the nanoparticles. Nanotechnology has the potential to eradicate the problems of the current treatments. Innovations in the field of drug designs using nanotechnology should be the focus on selectivity, efficacy, and safety.

Contribution of authors

All authors contributed equally to this work. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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