

Nano World in Cancer Therapy

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Abstract

Despite of several pandemic eruptions, cancer still remains the leading cause of death at constant rate. The risk of every alternative disease or disorder increases with the initial incidence of cancer. Cancer treatment has radically changed a lot from conventional therapies like surgery and radiotherapy to targeted therapies like thermal ablation and gene therapy. Deeper knowledge and understanding of key regulators of cancer growth and progression aided in the advancement of cancer therapy. The use of nanoparticles in cancer diagnosis and treatment has gained its importance in the next generation of cancer treatments. Nano oncology enhances the efficacy of chemotherapy for a wide gamut of invasive cancers. Here we provide an overview on the different approaches to treat cancer and discuss the pivotal role of some archetypal cancer therapies and current state and future prospects of diverse biomedical nanomaterials for cancer therapy and imaging.

Keywords: Nanoparticles- cancer therapy- dendrimers- carbon nanotubes- Nanooncology

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Introduction

Cancer is an increasing threat in the present days and a serious issue which involves uncontrolled division of abnormal growth of tissue or cells. Cancer cells have the capability to invade and destroy healthy tissue and can even migrate to other parts of body. The most prominent cancers include pancreatic, lung, liver, breast, ovarian, brain, Skin and prostate cancers. The type of cancer treatment depends on the stage of cancer and the location of cancer occurrence. Drinking alcohol, smoking, obesity and prolonged exposure to sun rays are the major risk factors for cancer growth [1], while the genetic and environmental factors also contribute for cancer development. Cancer progression is a complex condition with different stages of growth. Cancer therapy has become a great challenge in the present days with major hurdles being the lack of detection in the earlier stages, non-specific systemic distribution, and insufficient drug amount reaching the site of tumor, inability to monitor therapeutic responses, meager drug delivery and multi-drug resistance. Surgical removal of tumor, chemotherapy, radiation therapy, targeted therapies, hormonal therapy, immunotherapy, angiogenesis inhibitors and synthetic lethality are the available treatment strategies of cancer.

Chemotherapy is widely used treatment for most of the cancers. However, the chemotherapy has its own drawbacks low specificity of drugs to target, dose limiting toxicity, side effects like skin allergic reactions, pain and nerve damage and resistance mechanism to drug are the major drawbacks of chemotherapy [2]. Combinational therapy also may be used to treat cancers. Anticancer drugs in spite of having high potency to kill cancer cells are ineffective due to their inability to reach the target site in required concentrations. Hence, the new strategies for cancer therapy are in demand which is partly contributed by nanotechnology.

Nanooncology

The use of nanoparticles (NP) in the field of biomedicine and disease diagnosis is being widely explored [3]. Wide range of Nanoparticles with varied shape, size, compositions and functionalities are in use in the recent days. Nanoparticles being toxic to the cancer cells specifically and nontoxic to the normal cells are ideal for cancer therapy [4]. The cost-effective nature of nanoparticles makes them more suitable for targeted cancer therapy.

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Nanoparticles facilitates interaction with various biological macromolecules and aids in drug delivery at both cellular and systemic levels. Nanoparticles having unique properties like stability, self-assembly, biocompatibility, specificity and drug encapsulation are advantageous over free drugs. Nanoparticles enhance the penetration of drug into intracellular compartment, minimizes the side-effects caused by free drug, prevents the drugs from degradation and increases the stability of drug, enhances specificity of drug to target, decrease the systemic toxicity, increase absorption of drug by a selected tissue, prevents prior interaction of drug with nonspecific biological system and controls the distribution of drug within tissues and pharmacokinetics of drug. Nanoparticles aid in drug and gene delivery, used as fluorescent biological labels, virulent pathogens detection, detection of proteins, tumor destruction by hyperthermia (heat therapy) and aids in the enhancement of imaging [5].

Nanoparticles which are nontoxic to cells and aided with improved circulation are widely used in the present days for drug delivery. Nanoparticles are used for drug release to target and kill cancer cells. Most of the conventional approaches fail due to the lack of specificity i.e., their inability to differentiate the cancer cells from normal cells which may lead to many side effects. But nanoparticles due to their nano size are highly specific to cancer cells and are widely used in targeted drug delivery. These nanoparticles interact with biomolecules both at surface and inside cells, yielding better signals [6]. For a nanoparticle to be an effective drug delivery system, it should bypass biological obstacle and deliver therapeutic agents directly to cells and tissues involved in cancer growth and metastasis [7].

Various types of nanoparticle platforms like liposomes, albumin NPs and polymeric micelles, have been approved for cancer treatment and many other nanotechnology-enabled therapeutic modalities are under clinical investigation, including chemotherapy, hyperthermia, radiation therapy, gene or RNA interference (RNAi) therapy and immunotherapy.

Lipid based, polymeric and inorganic nanocarriers are the three major nanocarriers, used in the current field of medicine and therapy. The biodegradable membrane composed of phospholipids and glycolipids with embedded hydrophobic molecules of liposomes makes them as fine therapeutic carrier. These liposomes are coated with polymers like PEG to increase its stability and half-life in circulation. Nano emulsion, phospholipid micelles, solid lipid nanoparticles and liposomes are few lipid-based nanocarriers.

Polymeric nanocarriers are composed of biocompatible polymers made up of monomeric units of D/L-lactic acid, D/L-lactic-co-glycolic acid and ethylene glycol and encapsulated with pectin, chitosan and alginate polysaccharides. Dendrimers, polymer-drug conjugates and micelles are few forms of polymeric nanoparticles. They have capability to entrap both hydrophilic and hydrophobic drugs. Polymeric nanocarriers have an aided advantage in pH- dependent controlled drug release and also facilitate surface modifications.

Iron oxide, calcium phosphate and gold nanoparticles are widely used inorganic nanoparticles. Superparamagnetic iron oxide (SSPIOs) and superparamagnetic iron oxide (USPIO) are two forms of iron oxide nanoparticles whereas noble metals are widely used in optical, imaging, sensors, cosmetics cancer therapy and drug delivery. Gold nanoparticles have gained importance due to its inert nature with high binding affinity and selectivity and are resistant to oxidation under extreme conditions. Imaging, drug delivery, detection of pathogen in food and clinical specimen and photothermal therapy are few biomedical applications. Quantum dots, silica nanoparticles, magnetic nanoparticles and carbon nanotubes are various forms of inorganic nanoparticles. The adaptable surface chemistry and small size of quantum dots permits real-time monitoring of nanoparticle-based drug delivery. However, its toxic nature on long term usage prompted the transition to gold and magnetic nanoparticles. Cylindrical Carbon nanotubes are widely used in the field of science and technology, have promising role in cancer therapy as they adsorb pathogenic microorganisms and conduct heat.

Reaching the site of target with minimal loss is the major challenge for drug delivery [10]. When tumor grows and attains certain mass and size, the existing vasculature is insufficient to sustain the tumor volume and cannot provide sufficient oxygen for survival hence few cells undergo death and release growth factors that trigger the growth of new capillaries and blood vessels. Angiogenesis in tumors involves the growth of irregular blood vessels but lacks lymphatic system. The (EPR) enhanced permeation and retention effect aids in passive targeting of nanoparticles to the site of tumor. As tumor cells require high energy levels and undergo glycolysis at high rate, which creates acidic environment, the nanoparticles which are stable at physiological pH 7.4, but are easily degraded at lower pH releasing the drug at the site of tumor should be the major criteria for efficient targeting. However, passive targeting has its own drawback, that the drug carrying nanocarriers may not necessarily be internalized by tumor cells. So, the nanocarriers are modified in such a way that drug is selectively released to the target site which facilitates active targeting (86). Peptides, carbohydrates, proteins, nucleic acids, vitamins and aptamers are either conjugated to the carriers and acts as targeting agents. Most of the cancer cells over express surface markers comparative to normal cells. These nanoparticles coated with specific antibody or ligand have capability to recognize and bind to target cells through ligand-receptor interactions. These nanocarriers release the drug When taken inside the cancer cells. vitamin folic acid (folate) and transferrin (Tf) are commonly used ligands for drug delivery as the folate receptors (FRs) and Transferrin receptors (TfRs) are overexpressed in ovarian, bladder, colon, kidney, lung and endometrial cancer. These carriers increase the chances of interaction and internalization of drug into the cancer cells. The effectiveness of active targeting depends on the size and surface properties of nanoparticles, type of ligand and its density. The use of nanoparticles in different cancers is illustrated in the (Figure 1).

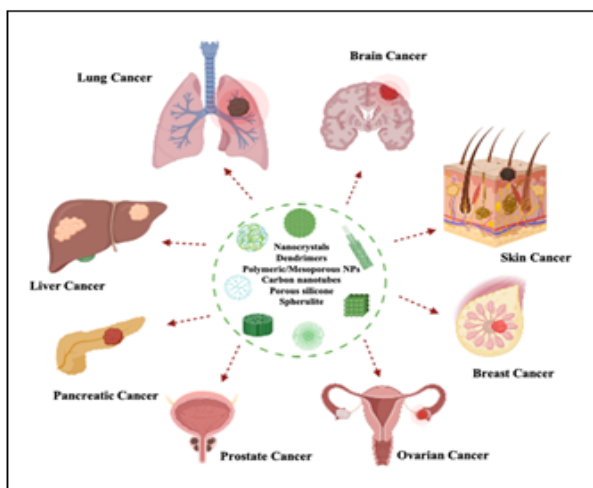


Figure 1. Applications of Nanotechnology in Cancer Therapy

Pancreatic Ductal Adenocarcinoma (PDA)

The fourth most common cause of cancer death is Pancreatic ductal adenocarcinoma. Pancreatic cancer is the most threatening malignancies. Tobacco usage inherited genetic syndromes, overweight, obesity, diabetes, exposure to chemicals, chronic pancreatitis and liver cirrhosis are most causes of pancreatic cancer. Symptoms of pancreatic cancer include jaundice, weight loss, poor appetite, vomiting and back pain. Most of the PDA cases become obvious in the later stages when the tumor as grown extensively and is highly inoperable. Traditional chemotherapy involves administration of 5-fluorouracil and gemcitabine, but the tumors have become resistant to these drugs partly due to the presence of thick stroma that reduces delivery of drug to cancer cells [12]. Combination therapies with the use of Gemcitabine and other drugs have come into existence. Surgical resection also showed a ray of hope for cure [13-14]. Ultrasound-mediated PDA therapy by either micellar or Nano emulsion encapsulated paclitaxel resulted in suppression of metastasis [15]. Nanoparticle albumin bound paclitaxel are designed to deliver insoluble drug to the site of tumor. Liposomal-based nanoparticles are used to encapsulate Irinotecan which increases the efficacy of drug delivery [16]. Ultrasound-responsive nanoparticles are used in ultrasound mediated drug delivery were the nanoparticles are accumulated at the site of tumor via enhanced permeability and retention (EPR) effect and release the encapsulated drug in response to ultrasound. In circulation nanocarriers are often removed by reticuloendothelial system or get absorbed to the blood proteins. To extend the particle residence time in circulation, these nanoparticles are coated with poly (ethylene oxide). Magnetic hyperthermia or photoactive hyperthermia have proved to be effective against cancer but lack specificity. Cytotherapy specifically delivers nanoparticles to the site of tumor [17].

Liver Cancer

Hepatocellular carcinoma (HCC) is the most

common type of primary liver malignancy that arise from hepatocytes. Apart from this there are two types of liver cancer that arise from bile ducts and blood vessels of liver. It's the third leading cause of mortality and ranks sixth in occurrence among all malignancies [17]. Swollen or bloated stomach, Nausea, weight loss, fever, Jaundice and loss of appetite are few symptoms of liver cancer. These cancer cells grow at very higher rate and often spread to other parts of body. They are detected at very later stages making the treatment difficult [18]. Patients with advanced cirrhosis, fibrosis and predisposed to hepatitis B are at high risk of developing HCC. People with later age groups, male humans, alcohol abuse, obesity, diabetic and family history are various factors that influence the HCC occurrence [19]. Liver cancer is diagnosed as nodules in ultrasound investigation, quadruple phase computed tomography (CT) scan and Magnetic resonance imaging (MRI). Various therapeutic approaches like liver resection, transplantation, systemic and local therapy aids in cure. Trans Arterial Chemo Embolization (TACE) and Radiofrequency Ablation (RFA) have become prominent clinical tools of therapy [20-21].

The use of nanoparticles to target HCC has come into existence. Reticuloendothelial system (RES) includes Kupffer cells, specific macrophages widespread throughout the liver sinusoids engulf these nanoparticles and thus interfere with imaging and drug delivery. Hence to evade the RES macrophages uptake of NPs and also to increase the specificity of NPs to tumor target these NPs are coated with polymers such as polyethylene glycol and various tissue-specific ligands. The ligands conjugated to NPs increase the specificity of NPs to target cells and thus hold as promising approach to cure liver cancer [22-23].

Lung Cancer

Small cell and non-small cell lung cancers are two types of lung cancers most commonly observed in men in the present days [24]. The most common symptoms of lung cancer are cough, dyspnea, hemoptysis, and systemic symptoms such as weight loss and anorexia. Various risk factors of lung cancer include tobacco usage, exposure to asbestos, radon, arsenic, chromium, nickel and soot. Surgery, chemotherapy and radiation are standard treatment options for lung cancer depending on the stage of malignancy, respectability and overall performance [25]. The first-line treatment for advanced stage of lung cancer is Chemotherapy in which chemotherapeutic drugs are usually administered intravenously for systemic circulation [26]. The synergistic effect of doxorubicin and paclitaxel incorporated into porous PLGA microparticles was evaluated for treatment of metastatic lung cancer [27]. Gene therapy involves the use of oligonucleotides to specifically target and regulate the abnormal genetic expressions which are related to cancer development in cancer cells. Compared to the con-ventional therapeutic approaches, gene therapy via Nano approach is generally expected to provide higher efficiency on cancer treatments and minimize the systematic cytotoxicity in cancer patients [28].

Breast Cancer

Breast cancer is one of the most common cancers worldwide. Triple-negative breast cancer (TNBC), with absent or minimal expression of estrogen and progesterone receptors, and human epidermal growth factor receptor 2 are most common in younger women [29]. The choice of available treatments depends on tumor characteristics such as biomarkers, tumor size, metastatic disease, ligands, and antigens or endocrine receptors expression. Chemotherapy has improved, but many drugs still do not reach the tumor site at effective doses and are often associated with high systemic toxicity and poor pharmacokinetics [30]. Multidrug resistance, the principal mechanism by which many cancers develop resistance to drugs, is also a key factor in the failure of many forms of chemotherapy. Combined with surgical resection, chemotherapy and radiation, it affects patients with a variety of blood cancers and solid tumors, including breast cancers. Mastectomy was carried out based upon tumor size (relative to breast size) Radical mastectomy was used earlier for the treatment of breast cancer detected at earlier stages where mastectomy is usually followed by radiotherapy and/or chemotherapy. Breast conservation therapy (BCT) has come into existence. The risk of local recurrence is decreased on application of Whole-breast radiotherapy (WBRT) after breast-conserving surgery (BCS). Sentinel lymph node biopsy (SLNB) is now the standard of care. Among nanoparticles, various lipid nanoparticles, namely liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and lipid polymer hybrid nanoparticles, have been developed over the past few years for breast cancer therapy [31-32].

Ovarian Cancer

Ovarian cancer ranks as the fifth leading cause of death due to cancer in women Ovarian cancer is the most common among gynecological malignancy. Most of the ovarian cancers are of epithelial origin [33-34]. Nonepithelial ovarian cancers include germ cell and stromal derived tumors. Ovarian cancers are diagnosed at stage III or IV. The risk of ovarian cancer is decreased by pregnancies, contraceptive use, and tubal ligation or hysterectomy [35]. No symptoms are detectable for ovarian cancer until it spread beyond the ovaries. Few symptoms include bloating, abdominal pain, frequent urination, and irregular menstrual bleeding. The presence and stage of the disease is confirmed by biopsy analysis and histological assays. The first-line treatment for ovarian cancer is cytoreductive surgery [36]. Cisplatin or Carboplatin are used for the treatment of ovarian cancer but unfortunately cancer cells have developed resistance to these drugs. The second line of therapies includes PEGylated liposomal doxorubicin administration. Computer tomography, magnetic resonance imaging (MRI), positron-emission tomography/single photon emission computed tomography (SPECT), ultrasound, and optical imaging are commonly used imaging techniques to detect ovarian cancer. The use of nanoparticles to specifically localize in tumor tissues has decreased the systemic toxicity following IP administration [37]. Xenograft

studies have showed improved outcome in ovarian cancer when nanoparticle-encapsulated chemotherapies (paclitaxel-loaded expansile nanoparticles) was used at the time of cytoreductive surgery [38]. Nanoceria reduced angiogenesis in an ovarian cancer model.

Oral Cancer

Oral cancer is one of the most devastating ruinous disease occurring worldwide. It refers to any cancerous growth that occurs within the oral cavity [39]. Oral cancer is the third leading cause of death (after heart disease and stroke) in developed countries and the second leading cause of death (after heart disease) in the United States. Oral cancer is diagnosed in the later stages when the tumor becomes aggressive and immune to therapeutic drugs. Saliva from suspected patients is used for quantitative assessment of biomolecules using enzyme-linked immunosorbent assay (ELISA), micro-satellite analysis and high-performance liquid chromatography (HPLC) techniques [40]. Common oral cancer treatments include chemotherapy, radiation and surgery either alone or in combination. The major problem with chemotherapy to oral cancer is rapid clearance of the drug from the site of absorption due to scavenging by saliva and mechanical stress, unpalatable taste and absorption of the drug by oral mucosa. The epidermal growth factor receptor is a cell surface receptor biomarker that is over expressed in epithelial cancer but not in normal cell [41]. The anti epidermal growth factor receptor antibody conjugated nanoparticles specifically and homogeneously bind to the surface of cancer type cells with greater affinity than to non-cancerous cell. The gold nanoparticles were conjugated to antibodies to enhance the specificity of NPs to target cells. Silica-gold Nano shells labeled with oncoprotein specific antibodies were used to target oral squamous cancer cells [42]. Doxorubicin and methotrexate loaded nanoparticles showed higher efficiency on squamous cell carcinoma of tongue when compared to free doxorubicin and methotrexate. Naringenin (NAR, which is an antioxidant)-loaded nanoparticle proved promising role as drug delivery system for targeted delivery of naringenin for oral cancer chemoprevention. Magneto hyperthermia is used to treat oral cancer where magnetic nanoparticles (MNPs) coated with polyphosphate were used [43].

Skin Cancer

The skin is the largest protecting barrier of the human body. Skin cancer occurs mostly due to sunlight and pathogenic infections. Chemotherapy and radiation are most commonly used therapies. The skin forms an effective barrier to the external environment and is impermeable to the drugs due to epidermal cell cohesion and stratum corneum lipids. However, the use of nanoparticles in diagnosis and treatment of skin cancer has become prevalent in the present days. Nanoparticles are used for drug delivery as they increase the permeation capacity, stability of drug and active substances are released in a controlled manner. The efficacy of docetaxel was increased when embedded in Solid lipid nanoparticles (SLNs) against malignant

melanoma. Dendrimers are being used for immunotherapy, and radio-immunotherapy of melanoma and squamous skin carcinoma. Carbon nanotubes are used for diagnosis and treatment of melanoma. 5-FU-loaded poly butyl cyanoacrylate nanoparticles were used for local treatment for basal cell carcinoma.

However, the use of nanoparticles has major drawbacks like biocompatibility, ease of availability and the cost of nano therapy, which can be improved in addition to improving tumor response rates for the effective cancer treatment.

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