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The potential of nano technology based drugs in lung cancer management

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Abstract
Nanotechnology is defined as research and technology development at the atomic, molecular, or macromolecular level, in the length scale of approximately 1-100 nanometer (nm) range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size. Active and passive delivery is among the two type of nanoparticle based drug delivery system. Although, nanoparticle based drug delivery show some limitation, their advantage increase their need worldwide. This special property assigned to them attracts many scholars to apply it for controlling many chronic diseases like asthma, HIV, lung cancer and etc.
Lung cancer is the leading cause of mortality and morbidity among cancer related death worldwide. Among this 85%-90% of lung cancer death is contributed by non-small cell lung cancer. This extreme mortality rate is arises due to lack of suitable pharmaceutical care and ineffective convectional therapeutic strategies. In course with desperate attempts to address these issues independently nanomedicine based therapeutics is being sought as favorable solution. Despite the fact that physiochemical property of nanoparticles increases the need for nanomedicine, the aspect of being at nano scale by itself confers the system with an advantage of passive accumulation at the site of tumor. However there is work left behind the scientists to widely apply these smart new technologies to increase patient out come and minimize healthy cost. Generally, a broad perspective of three major subclasses of such nanoscale based lung cancer drug delivery approach namely; polymeric nanoparticles approach, metal based nanoparticles and bio-nano particle approach are widely applicable.

Keywords: Nanoparticles, Polymeric nanoparticles; Metal nanoparticles; Bio-nanoparticles; Small cell lung cancer, Non small cell lung cancer.

Introduction
The conceptual underpinnings of nanotechnologies were first laid out in 1959 by the physicist Richard Feynman in his lecture, "There's plenty of room at the bottom". The term "nanotechnology" was created by Norio Taniguchi of Tokyo University in 1974 to describe the precision manufacture of materials with nanometer tolerances [1]. Nanotechnology definitely promises to serve as drug delivery carrier of choice for the more challenging conventional drugs used for the treatment and management of chronic diseases such as cancer, asthma, hypertension, human immunodeficiency viruses (HIV) and diabetes [2]. Depending on the method of preparation nanoparticles, nanospheres, or nanocapsules can be constructed to possess different properties and release characteristics for the best delivery or encapsulation of the therapeutic agent [3].
Patients with lung cancer may undergo surgery, chemotherapy, radiation, or multimodality therapy, depending on the histologic type of the tumor, its size and location, and the presence of metastases at diagnosis [4]. At present lung cancer accounts for 23% of total cancer related mortality, outnumbering breast cancer, colon cancer, and prostate cancer combined together [5]. The extreme lethality of lung cancer is ascribed to the lack of early diagnostic strategies as in almost 50% of the cases the disease is confirmed in stage IV, leaving low chance of survival [6]. The inaccessibility to the deeper portions of the lung for conventional therapy further adds up to the complication in the treatment process [7].
The incidence of lung cancer can be broadly classified into two major types on the basis of histologic appearance, one being small cell lung cancer (SCLC) and the other being non-small cell lung cancer (NSCLC) [8]. The only subclass of lung cancer that is not associated with smoking is adeno-carcinoma which arises due to occupational and environmental exposure to carcinogenic agents such as radon, asbestos, and other types of radiation [9].

Small cell lung cancer

The initial pretreatment evaluation of a SCLC patient should include a medical history, a clinical examination including neurologic examination, laboratory tests (i.e., complete blood cell count with differential, serum electrolytes, liver function tests, calcium, lactate dehydrogenase, blood urea nitrogen, and serum creatinine), and chest radiography. Additional testing is guided by suspicious signs or symptoms detected during the physical examination along with common sites of SCLC metastases. Small cell lung cancer cells are detected in an extensive number of sites (e.g., liver 69%; adrenals 65%; bone and bone marrow 54%; pancreas 51%; brain 28% to 50%) during autopsy of patients diagnosed with SCLC [10]. In those with presumed limited-stage SCLC, a CT scan of the chest and abdomen, bone scan, and CT scan or magnetic resonance imaging (MRI) of the brain are needed [11].

A bone marrow biopsy may be obtained if no extra-thoracic disease is detected. SCLC is less prominent and more aggressive with mean survival of 4 months if left untreated [12]. Its extreme lethality roots from rapid growth rate, early metastasis, and fast metabolism. SCLC originates from neuroendocrine tumors and is thus studded with neurosecretory vesicles and neurofilaments [13]. It accounts for almost 80% to 85% of the lung cancers and is not susceptible to conventional chemotherapy and radiation therapy.

Non-small cell lung cancer

The American Joint Committee on Cancer 34 has established a TNM staging classification for lung cancer based on the primary tumor size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M). For comparison of various therapeutic modalities, a simpler stage grouping system is also used in which stage I refers to tumors confined to the lung without lymphatic spread; stage II refers to large tumors with ipsilateral peribronchial or hilar lymph node involvement; stage III includes other lymph node and regional involvement; and stage IV includes any tumor with distant metastases.

The primary tumor is assessed with chest x-rays and fiber optic bronchoscopy, whereas lymphatic spread is usually assessed by mediastinoscopy, gallium-67 citrate scanning, and CT. If the history and physical examination or other routine clinical studies (e.g., complete blood cell count and liver function tests) suggest the possibility of metastatic disease, then special scans (e.g., bone, brain, or liver) or biopsies (e.g., bone marrow or liver) may be necessary for staging [14]. NSCLC can be further sub-classified into epidermoid, large cell, broncho-alveolar, adenocarcinoma, and squamous cell carcinoma. Each of these NSCLC histological subtypes is distinct and responds in diverse means to specific therapies [15].

Lung Cancer Management

Patients with lung cancer frequently have numerous concurrent medical problems. Such problems may be related to invasion of the primary tumor and its metastases, paraneoplastic syndromes, chemotherapy and radiotherapy toxicity, or concomitant disease states (e.g., cardiac disease, renal dysfunction, chronic obstructive pulmonary disease, asthma, or diabetes). Depression is also common and sometimes persistent in patients with SCLC and NSCLC hence, should be treated [16]. Current therapeutic strategies such as chemotherapy and radiation therapy is only effective in the initial stages of treatment of SCLC, whereas NSCLC are less sensitive to such treatment modalities, which leaves surgery (only in stages I, II, and some of IIIA) and gene therapy as other possible alternative to tackle NSCLC and lung cancer stem cells [17].

Thus, the complete eradication of lung cancer requires a new approach such as utility of nanoscale materials. It is by the virtue of nanoscale dimension of lung cancer therapeutic that they are capable of effectively transcending bronchial epithelium barrier and accumulating in deep lung regions. Different works establish the possibility of using such nanogel-based pulmonary delivery system for delivery of anticancer drugs specifically to lung cancer cells [18]. The extensive research in the field of nanotechnology has opened up a whole new range of nanomaterials for cancer therapy and diagnosis [19]. The applications of these nanoparticles in cancer therapies has been effective to a great extent owing to their inherent small dimensions which enables them to specifically accumulate in tumor cells as they permeate through the leaky vasculature in the vicinity of tumor cell mass (enhanced permeability and retention effect) [20]. Another advantage of nanoscale system is that they are capable of effectively overcoming clearance by the kidney and thereby provide good blood circulation time for the drugs they carry.

[21]. Besides, majority of chemotherapy regimens used in the management of lung cancer are intensive and are associated with a wide variety of toxic effects. These limitations exaggerate the demand for new and advanced drug delivery, which is nano particle based, to enhance optimum use of those medication [22].

Nano technology approach lung cancer drug delivery

Extensive research in the field of nanotechnology has opened up a whole new range of nanomaterials for cancer therapy and diagnosis [23]. The most favorable property of such a system is its ability to support high loading capacity of therapeutic and imaging agents owing to high surface-area-to-volume ratios of nanoparticles [24]. The area of nanomedicine is too broad to cover all the aspects in a single review article. Thus, here emphasize is on nanomaterials that have shown great promise for applications in lung cancer diagnosis and therapy.

Basically they are three important nanoparticle based lung cancer drug delivery system that are widely applicable. These include:

I. Polymeric nanoparticles-based approaches
II. metal nanoparticles-based approaches, and
III. bionanoparticles- based approaches

I. Polymeric nanoparticles-based approaches

Polymeric nanoparticles provide a common platform for inclusion of a drug of therapeutic potential, an imaging agent, and an appropriate targeting moiety to end up with a perfect nanotheranostic drug delivery system. The versatility in physiochemical modification of polymer properties enables it to be tuned to the requirements for drug encapsulation. The most commonly used polymer systems for lung cancer therapeutics includes poly ε-caprolactone (PCL), polylactic acid (PLA), polylactide-co-glycolide (PLGA), alginic acid, gelatin, and chitosan. PLGA is among the most successful Food and Drug Administration (FDA)-approved biodegradable polymers used for formulation of a nanoscale drug delivery system. Apart from drugs, PLGA can be used for delivery of proteins and various other bio-macromolecules such as ribonucleic acid (RNA), deoxy ribonucleic acid (DNA), and peptides [25].

To demonstrate this, a research group headed by Sengupta *et*

al. in 2005 fabricated bi-phospholipid-coated PLGA core nanoparticles wherein doxorubicin (doxo) is conjugated to PLGA while comberstatin is mixed with phospholipid and encapsulated in the outer lipid bilayer. Considering the specific case of lung cancer, the polymer PLGA has proved to be a prospective carrier molecule [26]. In one such attempt by Wu *et al.* in 2001, endostatin-loaded PLGA microspheres were fabricated by emulsification-evaporation technique. This system could attain the desired therapeutic effect at lower concentration of drug thus avoiding predisposition of normal healthy cells to cytotoxic drugs [27].

The most common anticancer drug administered for NSCLC is paclitaxel (PTX). A chitosan derivative, i.e., N-(2-hydroxy-3-trimethylammonium propyl) chitosan chloride (HTCC) was investigated as carrier for PTX by Lv *et al.* in 2011 [28]. In recent past, Liu *et al.* in 2010 have successfully conjugated lung cancer-targeting peptide (LCTP) and fluorescent-labeled molecule (FITC) on the surface of acetylated derivative of poly amadoamine (PAMAM) dendrimer. This system demonstrated time- and concentration dependent cellular uptake under in vitro conditions and in athymic mice, it was thus established as a promising drug carrier for targeted cancer nanotheranostics [29].

The lung cancer cell line, A549 was successfully transfected with green fluorescent protein by poly ethyleimene (PEI), which is PEICho l/DNA complex. This gene delivery system could overcome interaction with plasma proteins which further contributes to the improvement of its efficacy. An increment of 50% in mean length of survival of the in vivo model was observed [30]. Such targeted delivery of microRNAs (miR145) to CD133 marker screened lung adenocarcinoma stem cells was reported by Chiou *et al.* in 2012. They adapted polyurethane-short branch-polyethylenimine (PU-PEI) as favorable carrier for microRNAs. The delivered miR145 specifically suppressed the stem cell-like properties and render them susceptible to chemotherapy or radiotherapy [31].

In a recent study by Guthi *et al.* in 2010, a multifunctional PEG-b-PDLLA (poly D,L-lactide) micelle system grafted with LCTP was loaded with SPIONs and doxo. The formulation exhibited αvβ6-dependent cell targeting towards H2009 lung cancer cells with very good specificity [32]. Another such standard nanoparticle formulation specific for lung cancer cells, called expansile, was developed by Griset *et al.* in 2009. It was validated against Lewis lung carcinoma cells in murine models. It was enabled with a unique potential to release drug payload in response to highly acidic pH present in the vicinity of cancer cells [33]. In another similar work by Zubris *et al.* in 2012, a pH-responsive hydrogel loaded with PTX expansile was synthesized and was concluded to be a promising system for targeted delivery to pulmonary lung adenocarcinoma cell lines (A549) [34].

II. Metal nano particles based approaches

Currently, we regularly come in contact with metal nanoparticles through various means, such as water, food, cosmetics, and medicine, as they are widely used in a variety of everyday appliances. Some of the nanoparticles have showed cytotoxic effects on lung cells. However, their cytotoxicity depends on various factors, including size, concentration, and time of exposure. A precise control over these parameters can enable their application in lung cancer therapy and diagnosis. Recently, Barash *et al.* in 2012 proposed a nanodevice based on gold NPs sensors that classify the lung cancer histology by detecting the lung cancer-specific patterns of volatile organic compound profiles. It is capable to differentiate between healthy and lung cancer cell, small and non-small cell lung cancer and subtypes of NSCLC [35]. Although, metal-based nano therapeutic system has been the major subject, when it comes to their in vivo application for lung cancer treatment, its toxicity and biocompatibility remain a concern to be addressed. In order to overcome these two issues, current researchers have shifted their focus towards utilizing the bio-nanotechnology-based therapeutic system, wherein a pre-existing biological system/component is integrated to the therapeutic nanoparticles [36].

III. Bio-nanoparticles-based approaches

Inclusion of such biological system/component renders the system with improved stability and biocompatibility. Similar results were obtained by using apoferritin-encapsulated Pt nanoparticles that can act as artificial antioxidant as they mimic the biological enzymes such as catalase, peroxidase, and SOD that can be exploited in fighting against the ROS-mediated disease by scavenging hydrogen peroxide and superoxide [37] Viral nanoparticles (VNPs) emerged as an interesting topic of research in the field of biomedical applications specifically for drug delivery owing to their biocompatible nature, wide range of shapes and sizes, and ease in supporting surface modification by a variety of functional moieties [38]. VNPs obtained from different sources such as plant viruses, animal viruses, and bacteriophages have been used in variety of biomedical applications ranging from biosensing, bioimaging, to drugs/gene delivery system and also in vaccine development [39].

Study conducted by Veljanski *et al.* in 2012, wherein they used conventional chemotherapeutic drug along with genetically modified oncolytic viruses (OVs) for lung cancer therapy. The inability of chemotherapeutic agents to kill cancer stem cells is well complemented by OVs-mediated gene therapy [40]. In course with similar approach, a research group headed by Robertson in 2011 has demonstrated the use of engineered T4 viral nanoparticles as a molecular probe and has used the same to study uptake mechanism in lung cancer cell (A549) [31].

Challenges to widely apply nanomedicine for lung cancer therapy

Some major health risk associated with nanomedicine includes cytotoxicity, translocation to undesired cells, acute and chronic toxicity; some unknown, unpredictable and undefined safety issues, environmental impacts of nanomaterials and non-biocompatibility limit their use [32]. The change in the physicochemical and structural properties of synthesized Nps with a decrease in size can be responsible for a number of material interactions that can lead to toxic effects [33]. Besides this nanoparticles have intrinsic toxicity profiles. Formation of free radicals such as super oxide anion or hydroxyl radical may also be increased with high surface area. Accordingly oxidative stress may play an important role in nanoparticle (NP) toxicity especially for metal-based NPs [41].

Nanoparticles are more toxic when incorporated into the human body than larger particles of the same materials. Nanomaterials can enter the human body through several ports. Accidental or involuntary contact during production or use is most likely to occur via the lungs, from which a rapid translocation is possible to other vital organs through the bloodstream [42].

Nanoparticles have pronounced environmental effects even at

very low aqueous concentrations [43, 44]. Engineered NPs lacks bio compatibility with the human cells. As NPs introduced into the body, the immune system recognizes them as foreign and elicits a multilevel immune response. When this occurs, the activity of one or more components of the immunoregulatory complexes is directly enhanced, and immunostimulatory effects such as flu-like symptoms and hypersensitivity to unrelated allergens are observed [45].

There is poor drug Loading Efficiency in nanovehicles. The volume of a drug reservoir in a nano-sized drug carrier is extremely limited in comparison to macro drug delivery systems. The loss of a drug during the loading process is also not negligible [46]. Eventually, multiplex nanoparticles may be capable of detecting malignant cells (active targeting moiety), visualizing their location in the body (real-time *in vivo* imaging), killing the cancer cells with minimal side effects by sparing normal cells (active targeting and controlled drug release or photothermal ablation), and monitoring treatment effects in real time [47-49].

Conclusions

Nanotechnology is a research and technology development at the atomic, molecular, or macromolecular level. Nanotechnology based drugs, owning this special property, they tend to overcome short come of conventional chemotherapy in drug delivering and targeting. Now a days, invention of this smart technologies led promising ambition to take over control of chronic disease like asthma, HIV, cancer and etc. Besides their application, due to some limitation associated with them they are not widely applied yet.

Lung cancer is among major complication from which people of the world suffered. In spite of developing varied therapeutic and pulmonary drug delivery strategies for lung cancer, it still remains a leading cause of cancer-related deaths. The major drawbacks of current lung cancer treatment procedures which are in practice as of today are lack of tools for drug targeting and delivery. Thus improvement in these aspects can help in realizing improved lung cancer management. As evident from the discussion in this article, material of nanoscale regime holds promising results for devising better lung cancer theranostic systems. In search of such nanoscale theranostic systems for lung cancer, materials such as polymers, metal composites, and other bio-nano approaches have been sought after. Considering the issue of toxicity, bio-nano approaches have gained the attention of researches in recent past. As obvious from examples cited in this review work, it could be easily stated that polymers still hold better scope as a carrier for therapeutic agents. Now days, even though many interesting and improved way of practicing are on clinical trial concerning wide use of nanomedicine based lung cancer drug delivery, there is work left behind scientist to fully apply this technology to increase patient outcome and decrease healthy cost. Generally, nanomedicine shows promising effect concerning lung cancer management and diagnosis beyond certain challenge associated with it.

Conflict of Interest

The authors declare no conflict of interest

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