Challenges and Recent Progress of Nano Sized Drug Delivery Systems for Lung Cancer Therapy: A Review

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REVIEW ARTICLE

Kinjal Patel[*, a], Kartik Patel[b]

[a]M. B. Patel Science College, Anand Gujarat India

[b]The M. S. University of Baroda Vadodara Gujarat India.

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ABSTRACT

Lung cancer is the most malignant cancer today. The treatment of lung cancer continues to be a challenge for oncologists. The direct delivery of chemotherapeutic agents to the lungs could represent a novel therapeutic approach for patients with pulmonary metastases. Currently, many formulations of nanocarriers are utilized including lipid-based, polymeric and branched polymeric, metal-based, magnetic, and mesoporous silica. Innovative strategies have been employed to exploit the multicomponent, three-dimensional constructs imparting multifunctional capabilities. In lung cancer, nanoparticle-based therapeutics is paving the way in the diagnosis, imaging, screening, and treatment of primary and metastatic tumors. This review summarizes current progress and challenges in nanoparticle-based drug delivery systems, citing recent examples targeted at lung cancer treatment.

Keywords: Lung Cancer, Nano Drug Delivery, Target Drug delivery

1. Introduction

The chronic diseases of the airways and lungs, such as lung cancer, chronic obstructive pulmonary disease, tuberculosis, asthma, idiopathic pulmonary fibrosis, and pulmonary hypertension, impose enormous human suffering globally but their impact is far greater on developing countries and deprived population. These diseases will become one of the leading causes of death worldwide in the near future. (1) The rapid changes in life style, urbanization, and environmental degradation, smoking habit, increasing elderly population in developed countries etc., are all contributing toward the increase in patients with airway diseases. Current treatment strategies are strongly dependent on the type of malignancy and stage at the time of diagnosis but often involve a combination of surgery, chemotherapy, and/or radiation therapy. Biologically active phytochemicals present in plants and natural products, improve treatment efficiency in cancer patients and decrease adverse reactions. These phytochemicals having significant antitumor potential.

In this review, we critically discuss the challenges and reasons behind limited clinical success of targeted delivery approaches in cancer treatment, in-spite of the huge number of published reports demonstrating their therapeutic potential in pre-clinical models. We also propose the focus areas for future research that will enable successful clinical translation of promising strategies for targeted delivery of cancer therapeutics.

2. Nanoparticles and Cancer

Nanoparticles constitute nano-sized carriers (5–200 nm) (2) whose variability and versatility can be seen in the wide range of applications that are being developed for them. The ability to control aspects such as shape, size, surface charge and composition at the atomic level, together with characteristics such as their biocompatibility or their ability to transport insoluble substances, makes them an excellent tool for the treatment of numerous diseases, including cancer. (3,4) Active targeting is one of the most promising applications for NPs, since they make it

possible to take advantage of the specific characteristics and specific profile of each tumor niche to direct treatments to it by functionalizing the NPs with antibodies, (5) tumor-specific antigens (TSA), microRNAs or siRNA, which, together with the properties of certain nanomaterials used in their synthesis, such as pH and/or temperature dependent degradation, response to light, magnetic or ultrasound stimuli, make it possible to release its load specifically at the tumor site, decreasing systemic toxicity enormously with respect to traditional treatment. (6,7)

Currently, NPs have acquired a dual profile, being able to help in the diagnosis of disease in addition to granting targeted and specific therapy of disease (teragnosis). In addition, NPs could make it possible in the future to deliver personalized treatment for each patient, thus improving their response to treatment and their survival rate, striving towards achieving a complete cure. (8)

3. Lipid-Based Nanocarriers

Liposomes are the most studied delivery systems due to the biocompatibility and biodegradability that they present. The main components of these nanoparticles are phospholipids, which are organized in a bilayer structure due to their amphipathic properties. In presence of water, they form vesicles, improving the solubility and stability of anticancer drugs once they are loaded into their structure. (9) They are capable of encapsulating either hydrophobic or hydrophilic drugs. (10,11) In lung cancer treatment, liposomes may be a promising delivery system for drugs and genes. (12) The drug of choice for the treatment of NSCLC for the last two decades, cisplatin, is implicated in the development of nephrotoxicity in 20% of patients receiving high doses. (13) Table 1 lists current examples of liposomal formulations undergoing clinical trials intended for the treatment of cancer. In a recent report, researchers successfully loaded SLNs with Bcl-2 siRNA and paclitaxel for synergistic combination therapy as well as coencapsulated CdSe /ZnS quantum dots to bestow optical traceability. (14) Collectively, the properties of SLNs are ideally suited for combined chemo-and/ or gene-therapy and molecular imaging of cancer.

Table 1. Lists current examples of liposomal formulations undergoing clinical trials

Sr.No.	Composition	Indication	Phase/Stage
1	Liposomal Cytarabine	Central nervous system malignancies, Stage IV breast cancer	II/ Active
2	Liposomal Cytarabine-Daunorubicin	Acute myeloid leukemia	I/ Active
3	Liposome Encapsulated Mitoxantrone (LEM)	Advanced cancer	I/Completed
4	Liposomal LE-SN38	Advanced cancer	I/Completed
5	Doxil Liposomal Doxorubicin	Resistant solid malignancies	I/Completed
6	BLP25 Liposome Vaccine	Lung neoplasms Non-small-cell lung carcinoma	II/Completed
7	Liposomal Entrapped Paclitaxel Easy to Use (LEP-ETU)	Advanced cancer	I/ Active

4. Targeted Drug Delivery

The whole idea targeted drugs go back to the year 1906 when Ehrlich (15) first suggested the ‘magic bullet’. The permanence of this idea is a strong sign of its appeal, but the ‘magic bullet’ is still a challenge to implement in the clinic. The problem is with three things; first thing is finding the target for a specific disease state; to find a drug that efficiently treats this disease; and discovering

an idea of taking the stable form of the drug while avoiding the immunogenic and nonspecific interactions that efficiently clear foreign material present in the body. (16) Targeted drug delivery includes giving medication to a patient in such a way that it enhances the amount of the medication in a few parts of the body in comparison to others. Targeted drug delivery includes concentrating the medication in the tissues of interest while decreasing the relative concentration of the medication in the other tissues. (17) The drug is administered in such a manner that the drug is only active in the targeted area of the body and then the drug is released over in a controlled manner e.g., colon targeted drug. This enhances efficacy and decreases side effects. It is very hard for a drug molecule to reach its endpoint in the complicated cellular network of an individual. Targeted delivery of drugs helps the drug molecule to reach preferably to the required region. The benefit of using this method includes a decrease in dose & side effect of the drug. (18) Research associated with the development of targeted drug delivery system is nowadays highly favored in the pharmaceutical field. (19,20)

Active and passive targeting

Passively targeted NCs, which rely solely on the EPR effect, may be insufficient to achieve efficient tumor targeting. We need more systematic studies to understand the interaction of NCs with physiological barriers, and the cues identified from those should be used to develop more sophisticated strategies. Active targeting strategies are much more complex than passive approaches. (21) In addition to the challenges associated with physiological barriers and tumor heterogeneity, a major challenge is posed by the complex design and engineering of these systems, which can complicate their pharmaceutical development and scale-up under good manufacturing practice (GMP) production and add significantly to the cost of the therapy. Additionally, for both passive and active targeting strategies, the development of companion diagnostic imaging technologies to evaluate the targeting efficiency of NCs is crucial. Pre-selection of suitable patients and tailoring treatments to specific patients will improve tumor accumulation, treatment efficacy, and therapeutic outcomes. (22)

5. Challenges for Nanoparticle-Based Drug Delivery in Lung Cancer Therapy

The past decade has witnessed tremendous growth and development of drug delivery technology utilizing nanoparticle systems. It is expected that the ongoing research efforts in nanomedicine will continue to lead towards safe, efficient, and feasible drug delivery and highly sensitive and improved imaging agents for diagnostic and disease monitoring applications. However, nanomedicine research is facing numerous challenges in bridging rapidly developing novel ideas and translating them into clinical practice. A number of obstacles including immune reaction, rate of clearance from circulation, efficiency in targeting, and ability to cross biological barriers will follow when these nanoparticle systems enter the preclinical and clinical testing arenas. (23) Having a solid understanding of the biological behavior of nanoparticles is imperative to achieve the highest drug delivery efficiency. Resident alveolar macrophages detect the presence of foreign particles, followed by engulfment via phagocytosis and finally digestion in lysosomal of macrophages. The bioavailability of anti-cancer drugs to cancer cells provides an indirect reflection of success rate of therapy. To achieve this, we should determine the key factors that affect the bioavailability of drug in lungs such as aqueous solubility, dissolution rate, efflux of drugs and drug clearance by alveolar macrophages. Table 2 outlines the factors involved in determining the bioavailability of drugs into tumor cells.

Table 2. Outlines the factors involved in determining the bioavailability of drugs into tumor cells.

Sr.No.	Type of drugs	The partition coefficient (log *P*)	Water solubility
1.	Paclitaxel	3.50	Practically insoluble (24)

2.	Docetaxel	4.10	Practically insoluble (25)
3.	Doxorubicin (HCl)	0.65	Soluble
4.	5-Fluorouracil	−0.89	Sparingly soluble (26)
5.	Celecoxib	3.68	Practically insoluble (27)
6.	Cisplatin	−2.19	Soluble (28)

Additionally, further consideration must be given to the complexity of nanoparticles and how this may have a negative impact on drug delivery. Multifunctional nanoparticles are hot topics in the field of nanomedicine. (29,30) A nanoparticle with a large number of surface functional groups provides an avenue for the attachment of multiple kinds of biomolecules for targeted drug delivery and diagnostic applications for lung cancer. A careful analysis of these nanoparticle systems, however, is necessary prior to testing in an *in vivo* system.

6. Conclusion

Nanoparticle-based medicine has infinite potential with novel applications continuously being developed for use in cancer diagnosis, detection, imaging, and treatment. These systems are already helping to address key issues with traditional anticancer agents such as nonspecific targeting, low therapeutic efficiencies, untoward side effects, and drug resistance as well as surpassing their predecessors with the ability to detect early metastasis. Many technical, pharmacological and service developments have been made in the staging and treatment of lung cancer over the past 10 years but questions still remain about how to best implement these and their cost effectiveness. Further research is needed to ascertain whether newer radiotherapy techniques, such as SABR, are equivalent to surgery for early stage lung cancers. Much discussion still surrounds the newer targeted agents' cost effectiveness and whether improving early supportive care might be a good use of resources.

Although new treatments are available there are inequalities in access to them and further consideration in commissioning of resources is needed to tackle the hub and spoke effect. Arguably the most effective development that has been made in improving the outcomes for lung cancer is CT screening; however, it still remains to be introduced in the UK despite good evidence for effectiveness.

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Conflict of Interest

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