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Review Article

RECENT ADVANCES IN CHEMOTHERAPY OF LUNG CANCER USING NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Cancer is one of the most common diseases that results in a large number of fatalities worldwide. Lung cancer is the most chronic type of cancer in the world, according to the major types of cancer. Lung cancer is typically treated with a combination of medical procedures such as chemotherapy, surgical removal, and radiation therapy. Nanocarrier technologies are currently being employed widely to exploit and overcome the blockages caused by lung cancer. Because the goal of nano-carrier-loaded therapeutic drug delivery systems is to inhibit the proliferation of tumour cells, they have showed promise in treating lung cancer. Various techniques of nano drug delivery, such as liposomes, dendrimers, quantum dots, carbon nanotubes, and metallic nanoparticles, are reviewed in this review. Nano-carrier drug delivery systems appear to be a promising strategy, and as a result, fresh and more advanced paths in cancer therapies are predicted to open up.

Key words: Nanocarrier technologies, Lung Cancer, Treatment

INTRODUCTION

Cancer remains to be one of the major health problems in both developed and developing countries globally (Lozano *et al*., 2015). Hippocrates first introduced the term "cancer" in 370 BC and stated that these are abnormally growing cells due to chromosomal alterations (Lukong, 2017). On an approximate, around 1.6 million cancer cases have been reported in the United States alone each year (Bray et al., 2018).

There are more than 100 different types of cancers categorized by organ and tissues of origin. Of all these types, lung cancer is the leading cause of deaths, where, chronic smoking is considered to be the major cause, in addition to the other contributing factors. Interestingly, it has been reported that men and women are equally exposed to both direct and indirect smoking (Schaal and Chellappan, 2014). About 1.04 million cases

of lung cancer are recorded each year worldwide, with the highest prevalence observed in North America and Europe. According to the available statistical data, the 5-year relative survival rate for patients having lung cancer was a mere 13% in 1975, whereas, during 1996 to 2003, it increased to 16% (Mao *et al*., 2016).

Every year, the number of deaths due to lung cancers is far more than the other types of cancers; namely, breast, colorectal or prostate cancer to name a few. In developing countries, the percentage of people having lung cancers is exponentially high, as more than 50% of cases belong to the local population. Rapid development, urbanization and environmental pollution are the other major contributors, apart from smoking habits, that account towards the increased number of patients suffering from respiratory diseases (Jiang et al., 2016).

Lung cancer is categorised into two categories based on histological assessment, which are; i) Smallcell lung cancer (SCLC) and ii) Non-small cell lung cancer (NSCLC).In developing countries, NSCLC is very common, primarily due to smoking, and it accounts for at least 85% of cases of lung cancer, whereas, SCLC accounts for the rest of the 15% cases (Mitrou et al., 2016). NSCLC is further categorized into three sub-categories, i.e., a) Adenocarcinoma (AD), b) Large-cell carcinoma (LC) and Squamous-cell carcinoma (SQ) (Vendrell et al., 2017).

Global prevalence of lung cancer

Over the past few centuries, the prevalence of lung cancer has shifted from being a rare disease to a common disease worldwide. Lung cancer is the most commonly occurring cancer in men and the third most commonly occurring cancer in women. According to the American Cancer Society (ACS), in 2018 alone, it accounted for 234,030 newly diagnosed cases, representing 14% of all newly diagnosed cancer cases and 154,050 deaths, which is 1.4 folds higher than as seen in developed countries (American Cancer Society).

Traditional methods and the importance of nano-carriers in the treatment of lung cancer

Treatment of any cancer aims to remove or destroy the cancerous cells without killing normal cells. The most common traditional methods used for treatment include surgery, radiation, and chemotherapy which can be used either alone or in combination with each other. The most consistent and effective option to treat patients suffering from lung cancer is surgical resection. In 1933, the first resection of a tumour from the lung was reported by Graham via pneumonectomy,

and in the past two decades, this has been the principal procedure to treat lung cancer (Badrzadeh et al., 2016).

Stage-I lung cancer patients may be incompetent to bear surgery if their health condition is poor. Radiotherapy has provided relief to patients, who were incapable of undergoing surgery, however, the rate of cure is considerably low in comparison to surgical resection (Port et al., 2014). It is well known that radiotherapy causes damage to the surrounding cells, which in turn significantly leads to the loss in the functionality of the lungs. Thus, this approach may not be appropriate for those patients who have a severely compromised pulmonary system (Hirsch et al., 2014).

Novel drug delivery systems for treating lung cancer

There are different novel drug delivery systems that are developed for treating lung cancers (Mehta et al., 2014). Moreover, these novel drug delivery systems are further sub-divided into three categories as follows:

Liposomes

Liposomes consist of nano-scaled spherical vesicles which allows them to integrate hydrophobic and hydrophilic drugs in an aqueous centre and its outer appearance resembles the biological membrane (Gao et al., 2013). Liposomes have several unique features, viz; its non-toxic nature, the ability of its surface to get easily altered by external stimuli, physical stability, high-vascular density and retention time at the target site. The structure of a liposome comprises of cholesterol and phospholipids along with an aqueous core. Phosphatidylethanolamine and phosphatidylcholine are the most commonly used phospholipids. These liposomes are 0.05- 5µm diminutive synthetic vesicles. To obtain the desired size liposomes, one needs to follow the standard procedure and use the required constituents which can readily dissolve in aqueous media (Akbarzadeh et al., 2013).

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are a newly emerging surrogate to the traditional colloidal delivery system. SEM (scanning electron microscopy) and TEM (transmission electron microscopy) analysis have revealed the spherical shape of solid-lipid nanoparticles and their size, ranging from 50-1000 nm. The safety profile of SLNs was attributed to their biocompatible lipids that are highly tolerable by the lungs and body.

Therefore, they are highly recommended for pulmonary drug delivery, either as suspension or dry powder, without inducing inflammation. Solid-lipid nanoparticles contain solid lipid 0.1-30 % (w/w), which

readily gets mixed in the aqueous solution. About 0.5–5% of surfactants are added to increase the stability of solid-lipid nanoparticles . Solid lipid nanoparticles fall in the category of a nanoparticulate system containing lipids which remains solid at room temperature. These nanoparticles have various advantages like easy modification, biocompatibility with the lipophilic drug, targeted delivery of the therapeutic agents, enhanced drug stability, reduced toxicity and in addition, avoid the first pass effect in comparison to other colloidal carries (Naseri et al., 2015).

Nanostructured lipid carriers

There are few limitations of solid lipid nanoparticles like the expulsion of the drug during storage, the formation of crystals under the varied conditions and low payload capacity, which has led to the development of alternative approaches for targeted drug delivery called as nanostructure lipid carriers . This approach is an amalgam of solid and liquid lipids, that exhibits reduced drug expulsion during storage and has high payload capacity . These carriers form an occlusive layer over the surface, that reduces the water loss via trans-epidermal layer . Different nanostructured lipid carriers have been synthesized for anticancer therapy (Akhter *et al*., 2018).

Polymer-based nano-carriers

Polymeric nanoparticles

In the field of nanotechnology, polymeric nanoparticles have emerged as an effective strategy for treating cancers, as their composition and morphology can be changed according to the need . The polymer used for lung cancer treatment includes alginic acid, chitosan, gelatin, polycaprolactone, polylactide-co-glycolide, and polylactic acid. However, on supplementing these polymeric nanoparticles with sulfide bond, it regulates the release of the therapeutic drug . Cationic polymers are known for its cellular toxicity and elevated aggregation in lung capillaries because of their non-degradability and poor compatibility (Chen *et al*., 2016).

Polymeric micelles For controlled release and targeted delivery of hydrophobic anti-neoplastic therapeutic agents, polymeric micelles are commonly used. They are considered to be potential nanocarriers, as they are made up of a co-polymer hydrophobic core that allows the payload of the hydrophobic chemotherapeutic agent and hydrophilic shell for a hydrophilic chemotherapeutic agent (Xu *et al*., 2013).

Moreover, the hydrophilic shell increases the stability of these polymeric nano-sized micellar structures. The size of the micelles can vary from 20-100nm, which is applicable

for the delivery of hydrophobic therapeutic drugs, accommodating high payload, high drug permeability, long circulation time in blood stream, uniform distribution and deep tumor penetration of the drug (Qu *et al*., 2018).

With the development of personalized medicine, polymeric micelles have gained attention for their role in passive targeted therapy for cancer. Modifications to the surface peptides of these polymeric micelles improve their efficiency for precision targeting. For example, a study reported on integrin-associated polymeric micelles that are found to actively target the tumor cells (Gao et al., 2015). The major benefit of this approach is, its biodegradable nature for drug delivery systems which can be used for both cancer and ocular drug delivery.

Dendrimers

Dendrimers are synthetic branched polymeric and bifurcated macromolecules, of size ranging from 10-100 nm. Generally, they are globular in shape and have functional groups on their surface which makes them excellent candidates for drug delivery. Dendrimers are synthesized chemically with a regulated polymeric reaction involving electrostatic and hydrophobic interaction. The surface of these nanocarriers can be fine-tuned, and biodegradability can also be improved. These nanocarriers have emerged as a useful tool in cancer therapy because of its symmetrical shape, biocompatibility, easy biodegradability, high payload, and multiple conjugation point that aid in surface modification. The potential of this nanocarrier has been well-reported in the literature (Szymański *et al*., 2011).

Effective adsorption of peptide conjugated dendrimers has been reported in an athymic mouse model bearing lung cancer that revealed the real potential of this nanocarrier system in treating lung cancer . Moreover, PEGylated dendrimers exhibited promising applications when used as an aerosol-inhaled drug delivery model (Somani *et al.*, 2018). Substantial improvement has also been recorded for doxorubicin delivery via dendrimers.

Inorganic nanoparticles

Magnetic nanoparticles

This type of nanoparticles gets affected by surrounding magnetic fields and reach the target site in the body either by an active or passive strategy, because of their ligands. The FDA has approved the usage of magnetic nanoparticles along with chemotherapy, which is a giant leap in treating cancers. Magnetic nanoparticles are made up of super paramagnetic material of size >25 nm. These nanoparticles are either biodegradable or

non-biodegradable. Non-biodegradable magnetic nanoparticles are coated with specific material which causes the leaching of the magnetic core and facilitates its excretion through the kidneys. When an external magnetic field is applied to these magnetic nanoparticles, they exhibit thermic effects which trigger cellular apoptosis above 42°C and direct killing at 45°C (Revia and Zhang. 2016).

Cisplatin, being a hydrophobic drug, needs a special carrier to improve its antitumor activity. Therefore, a functionalized nanoparticle of Fe3O4 associated with PEG-PLGA copolymer has been developed which shows the improved antitumor activity of cisplatin in lung cancer. It has been found that Iron-oxide nanoparticles conjugated with gold improves the bio-availability of nanocarriers and are considered safe for treating lung cancers (Orel *et al*., 2015).

Carbon nanotubes

Carbon nanotubes are hydrophobic-tubular structures made up of carbon atom between 4 nm to 100 mm diameter and can vary according to the arrangement of graphene molecules. Intrinsically, these carbon nanotubes are insoluble in any organic solvents or aqueous solutions and toxicity induced by these in a biological fluid is a major challenge that needs to be addressed. Chemical modification improves the biocompatibility, reduces toxicity and transforms them into water-soluble nano-carriers (Kudr *et al*., 2017).

Carbon nanotubes have a large surface area. The graphene cavity of carbon nanotubes can accommodate high payloads and has distinct mechanical, electron emission and optical properties which make them a candidate of interest. This nanocarrier has high penetration power as it mimics the structure of a fine needle and the functionalized surface is an additional advantage which improves tumor targeting (Kausar *et al*., 2016).

Quantum dots

Lately, nanofabrication has enabled researchers to synthesize nano-sized colloidal particles possessing atom-like properties, known as quantum dots (QDs) . These QDs are considered to be a novel approach for treating lung cancers. As the surface modification of these nanoparticles enhance the biocompatibility and solubility, which makes it a superior fluorescent probe in comparison to organic fluorophores (Chinen *et al*., 2015).

Large absorption spectra, high photo bleaching, and photo stability are few peculiar characteristics of these QDs . QDs show redundant cycles of fluorescence and

excitation with a narrow range of emission spectra. Generally, QDs comprise the elements of group II-VI/III-V. Groups II-IV includes elements like cadmium–telluride, cadmium–selenide, zinc–selenide, and zinc sulfide. Whereas, groups III-V include the elements like gallium arsenide, gallium nitride, indium arsenide and indium phosphide (Lewinski *et al.*, 2008).

Inhalable chemotherapy of lung cancer

Compared to systemic chemotherapy, inhalation treatment locally delivers the chemotherapeutic agent to tumor tissues thereby enhancing its efficacy and lowering its systemic side effects. Moreover, inhalable therapy avoids first pass metabolism and increases patients' comfort towards treatment since being needle-free. Also, systemic chemotherapy has been associated with side effects and drawbacks that are not even chemotherapy-related. For instance, i.v. paclitaxel (PTX) has been associated with hypersensitivity reaction and neurotoxicity attributed to the solubilizing mixture of Cremophor EL and dehydrated alcohol. Such toxicities are dose-limiting and could lead to therapy failure

Inhalable particulate DDSs for lung cancer therapy

Unfortunately, inhalable lung cancer therapy is hampered by several potential drawbacks that have hindered its clinical applications. Inhalation of chemotherapeutics increases their concentration locally in the lung which increases the risk of pulmonary toxicity. Also, elimination of the therapeutic agent is immediately initiated once it has been deposited in the lung. This rapid decay often requires multiple daily inhalations, which inevitably affects the patient compliance. Furthermore, traditional inhalation therapy does not enable drug targeting to specific lung tumor sites. To overcome these drawbacks associated with "conventional" inhalation therapy of chemotherapeutic drug solutions, "intelligent" pulmonary drug delivery systems have emerged (Al-Hallak *et al*., 2010). In the following sections, we will thoroughly discuss the outcomes brought by different micro- and nano-size drug delivery

Inhalable nanocarrier-based lung cancer therapy

Pulmonary delivery of chemotherapy via inhalable nanocarriers has gained more attention in recent years due to their ability to highly associate with drugs and sustain their release, in addition to their ability to target cancer tissues in the lungs. They also have the ability to be efficiently transferred into aerosols, and highly endure nebulization forces (Beck-Broichsitter *et al.*, 2012). Moreover, nanocarriers can avoid

mucociliary clearance and lung phagocytic mechanisms, thus prolonging the residence of the therapeutic agent within the respiratory tract.

Polymeric nanocarriers

Cancer nanotechnology research is greatly progressing in the last years. Polymers either synthetic or natural have been extensively utilized for tumor-targeted drug delivery (Elzoghby *et al.*, 2017). Polymeric nanoparticles (NPs) have been widely utilized for the aerosol delivery of chemotherapeutics, genes, or their combinations for lung cancer therapy.

Pulmonary delivery of chemotherapeutics

Chemotherapeutic drugs could be physically entrapped within inhalable biodegradable polymeric nanocarriers. Gelatin-based NPs (GNPs) have demonstrated powerful anti-tumor activity against A549 lung adenocarcinoma cells (IC50= 1.2 μg/mL) via the pulmonary delivery of cisplatin (CIS) compared to free CIS solution (IC50= 2.54 μg/mL). The droplet of nebulized aerosol of GNPs demonstrated mass median aerodynamic diameter (MMAD) of 0.5–5 μm thus suitable for deep lung deposition resulting in higher drug accumulation in lung following inhalation in mouse (Elzoghby, 2013).

Pulmonary gene delivery

As alternative to viral vectors for gene delivery purposes, polymeric nanocarriers (polyplexes) are less toxic, non-immunogenic, highly stable during storage, and facile for large scale production (Nayerossadat *et al*., 2012). Polyethyleneimine (PEI) has been the most commonly used polymer for gene delivery as it facilitates the uptake and endolysosomal escape of polyplexes. Moreover, its positive charge facilitates the fusion with the negatively charged nuclear envelope phospholipids which in turn enhances transfection. However, the efficiency of PEI is faced with its cytotoxicity which is dependent on its molecular weight and configuration (Kim *et al*., 2015). PEI-based polyplexes were synthesized for the aerosol delivery of interleukin 12 (IL-12) gene for the treatment of osteosarcoma lung metastases

Hybrid lipid-polymer nanoparticles

Lipid–polymer hybrid NPs (LPHNs) have gained a great attention for delivery of anti-cancer drugs. This system combined the advantages of biodegradable polymer core (such as structure integrity and physical stability) and biodegradable liposome shell (such as high cell affinity and cell uptake). In addition, they are characterized by high loading for hydrophilic and hydrophobic

drugs in lipid or polymeric region [36]. In lipid-coated NPs (LNPs), hydrophilic drugs could be incorporated in the core by using hydrophilic polymers whereas the shell was composed of hydrophobic lipid. In the study of Hitzman et al, LNPs were comprised of hydrophilic nanocore of 5-FU/poly-glutamic acid (400-600 nm) crosslinked together via both hydrogen and hydrophobic bonding. This nanocore was spray-dried with a hydrophobic lipid shell of tripalmitin/cetyl alcohol with total LNP diameter of 0.9-1.2 μm . LNPs exhibited prolonged release of 5-FU compared with liposomes and polymeric microspheres may be mediated by the poly-glutamic acid core-imparted viscosity. The rate of 5-FU release from hybrid LNPs was also dependent on the lipid shell thickness and NP diameter (Hitzman *et al.*, 2006).

Inorganic nanocarriers

Some limitations restrict the pulmonary application of metal NPs due to their toxicity to the lung tissues. This toxic effect could be controlled by the exposure time, size and concentration of inhalable metals. By controlling those factors, they could be applied for diagnosis and lung cancer treatment. Magnetic NPs (MNPs) are of great interest for sitespecific drug delivery to the pulmonary system. Magnetic hyperthermia is an alternative technique to chemotherapy for tumor ablation mainly by generation of heat when magnetic components which include superparamagnetic iron oxide NPs (SPIONs) are exposed to an interchanging magnetic field (Sukumar *et al.*, 2013).

Actively-targeted inhalable nanoparticles

Targeting lung cancer cells could be achieved via two main approaches: passive and active targeting. The passive tumor targeting mechanism during systemic delivery of drugs is carried out via enhanced permeation and retention (EPR) effect. However, active targeting mechanism via receptor-mediated endocytosis is more specific to cancer tissues than EPR effect which guarantees additional targeting to tumor sites (Danhier, 2016). Active targeting could be achieved via targeting either cancer cells or tumor vascular endothelium. On the other hand, localized direct delivery of drugs to lungs via inhalation enables passive targeting even if NPs are not particularly targeted to lung cancerous cells (Minko et al., 2004).

Dry powder inhalable microparticles

Pulmonary drug delivery via nebulization as a liquid-based delivery system provides several advantages. These include production of large amount of aerosolized drug droplets over long period of time with least patient collaboration thus suitable for children and elderly especially in chronic disorders such

as lung cancer. However, many obstacles face their wide use including long administration time, poor stability and tendency of drug leakage before reaching site of action. Therefore, dry powder inhalers (DPIs) as a solid-based delivery system can overcome problems encountered with nebulization offering several benefits (e.g, propellent free, easy to handle, easy to operate as well as improved long term stability). The aerosolization performance of DPIs could be evaluated via various parameters including fine FPF and MMAD. Aerodynamic diameter (dae) is a major clue that expects deposition of inhalable particles. Particles with dae> 1 µm are very fine and could be easily exhaled while particles with dae< 5 µm are easily stucked at oropharynx and deposit at upper airways. Therefore, to ensure efficient delivery of inhaled particles deeply into lungs, particles should possess dae of 1–5 µm (Goel *et al.*, 2013).

Conclusion

Nanoparticle-based medicine has limitless promise, with new applications for cancer diagnosis, detection, imaging, and treatment being developed all the time. These methods are already addressing significant difficulties with traditional anticancer medicines, such as nonspecific targeting, low therapeutic efficiency, unfavorable side effects, and drug resistance, while also outperforming their predecessors in terms of early metastatic detection. Nanoparticles are good vehicles for the treatment of lung cancer because of their capacity to be customized for a personalised medicine strategy. A combinatorial strategy is used in a number of nanoparticle-based experimental therapies for lung cancer, balancing the design with targeting and tracking moieties as well as anticancer drugs.

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