Nanomedicine for Treatment of Lung Cancer

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Abstract Lung cancer is the second most common cancer and the primary cause of cancer-related death in both men and women in the United States and rest of the world. Due to diagnosis at an advanced stage, it is associated with a high mortality in a majority of patients. In recent years, enormous advances have occurred in the development and application of nanotechnology in the detection, diagnosis, and therapy of cancer. This progress has led to the development of the emerging field of "cancer nanomedicine." Nanoparticle-based therapeutic systems have gained immense popularity due to their bioavailability, in vivo stability, intestinal absorption, solubility, sustained and targeted delivery, and therapeutic effectiveness of several anticancer agents. Currently, a plethora of nanocarrier formulations are utilized including lipid-based, polymeric and branched polymeric, metal-based, magnetic, and mesoporous silica. In lung cancer, nanoparticle-based therapeutics is paving the way in the diagnosis, imaging, screening, and treatment of primary and metastatic tumors. The application and expansion of novel nanocarriers for drug delivery is an exciting and challenging research filed, in particular for the delivery of emerging cancer therapies. Some of the current progress and challenges in nanoparticle-based drug delivery systems for lung cancer treatment are discussed.

Keywords Nanoparticle • Drug delivery • Polymer conjugates • Therapy • Lung cancer

Abbreviations

DACHPt	(1,2-diaminocyclohexane) platinum(II)
EGF	Epithelial growth factor
EPR	Enhanced permeability and retention effect
GPs	Gelatin nanoparticles

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MSNs	Mesoporous silica nanoparticles
MTD	Maximum tolerated dose
MTX	Methotrexate
NSCLC	Non-small-cell lung carcinoma
PCL	Poly (ε-caprolactone)
PEG	Polyethylene glycol
PLA	Poly(D,L-lactic acid)
PLGA	Poly(D,L-lactic-co-glycolic acid)
PTX	Paclitaxel
RES	Reticuloendothelial system
SAR	Structure-activity relationship
SCLC	Small-cell lung carcinoma
SPIO	Superparamagnetic iron oxide

1 Background

Lung cancer is the second most common cancer in both men and women worldwide. It accounts for about 14 % of all new cancers with a dismal 5-year survival rate of only 15 % [1]. Recent data suggests that lung cancer is likely to overtake breast cancer as the main cause of cancer death among European women by the middle of this decade [2]. According to The American Cancer Society, an estimated 220,000 new cases of lung cancer has been diagnosed in the United States in 2013 (118,080 in men and 110,110 in women) of which 85 % of the cases are classified as non-small-cell lung carcinoma (NSCLC) [1], while the remaining cases are diagnosed as small-cell lung carcinoma (SCLC). Genetic and environmental factors, as well as their interaction, influence the risk of developing lung cancer. Although smoking is the main cause of lung cancer, risk also is increased by exposure to secondhand smoke; environmental exposures, such as radon, workplace toxins (e.g., asbestos, arsenic), and air pollution. Recent data suggest that the hazard ratios for lung cancer mortality are staggering: 17.8 for female smokers and 14.6 for male smokers [3].

Depending on the type of malignancy and stage at the time of diagnosis, lung cancer treatment often involves a combination of surgery, chemotherapy, and/or radiation therapy. However, due to the deficiency in early-stage diagnostics, most lung cancers are only detected at advanced stages, with local tumor invasion or distant metastasis and are not suitable for surgery. Therefore, a systemic chemotherapy treatment modality that addresses the majority of lung cancers is currently the mainstay of advanced lung cancer treatment regimens, aimed at extending survival and improving quality of life [3]**.** Standard first-line chemotherapy regimens for lung cancer include platinum-based drugs such as cisplatin and carboplatin. However, platinum-based chemotherapy is riddled with dose-limiting side effects including nephro- and cardiotoxicity, anemia, intestinal injury, and peripheral neuropathy as well as less serious symptoms of uneasiness, nausea, and fatigue [4]. To mitigate many of these untoward effects, platinum drugs are used in combination

with other anticancer agents resulting in increased therapeutic effectiveness and reduced dosage of each individual drug required to produce an observable therapeutic response. The recommended treatment for patients with advanced NSCLCs involves systemic platinum-based chemotherapy (e.g., cisplatin, oxaliplatin) combined with taxens (such as Paclitaxel or Docetaxel) or Gemcitabine [5]. However, the main problem associated with current therapies is their low efficacy due to unspecific toxicity to normal tissues, which precludes the use of curative doses. Additionally, the hydrophobic nature of the majority of the cancer chemotherapeutics makes them poorly water soluble and therefore limits their administration at high doses [6]. Thus, the unmet medical need is for more effective anticancer agents, especially for strategies that focus toxicity to tumor cells and away from normal tissues. This has led to development of methods to improve tumor-targeted delivery of chemotherapeutics that will result in increased drug efficacy with improved pharmacological properties and minimal toxicity to normal tissues remain a priority in cancer therapy.

2 Nanoparticle Drug Delivery for Lung Cancer Therapy

One highly efficient way of delivering drugs to diseased sites is encapsulation of anticancer agents in nanocarriers. The major clinical advantage of nanocarrier-based strategies over free drugs is specific delivery of large amounts of chemotherapeutic agents by favorably altering their pharmacokinetic properties, resulting in increased tumor localization, improved antitumor effects, and decreased nonspecific toxicities [7–9]. In recent years, various nanoparticle formulations including liposomes and polymers, which are designed to efficiently deliver anticancer drugs and nucleic acids such as DNA & siRNA to metastatic lung cells and bear the potential to become candidates for the next-generation therapy for advanced-stage lung cancer [10, 11]. Typically, nanocarrier-based approaches include a carrier, a targeting moiety that is bound to the carrier via specific conjugation chemistry, and a drug. Carriers may be composed of lipids, polymeric nanoparticles, inorganic nanoparticles, or dendrimers. Targeting moieties may include high affinity ligands, antibodies and nucleic acids, and they may be conjugated to the carriers utilizing a variety of chemistries.

2.1 Lipid-Based Nanoparticles

The major classes of lipid-based nanoparticles for drug delivery applications are liposomes and micelles. Liposomes are vesicles composed of a phospholipid bilayer commonly used to deliver chemotherapeutic drugs. Hydrophobic agents are incorporated in the lipid bilayer and hydrophilic drugs are encapsulated in the inner aqueous core. The physical structure of lipid-based nanocarriers primarily defined by its phospholipids composition, which determines the chemophysical features, such as size, shape, curvature, and charge [12]. Varying the lipid compositions and reducing

the number of lipid bilayers changes the surface charge, reduces the size of the liposomes to nanometer scale with the aim to prolong their in vivo circulation time and enhance tumor localization. Lipid-based nanocarriers have become a favorable platform for delivery of anticancer drugs mainly due to their non-toxic, biodegradable, and biocompatible nature [10, 13]. Particularly promising are liposomes containing surface-grafted lipid derivatives conjugated with polyethylene glycol (PEG) [8, 14]. These sterically stabilized liposomes (also called "Stealth" liposomes) have long circulation times in the blood as a consequence of reduced uptake by the reticuloendothelial system (RES) [7, 9]. A variety of chemotherapeutic agents, such as doxorubicin and vincristine, have been encapsulated in PEGylated liposomes and validated in preclinical models in vitro and in vivo [8, 15–17]. PEGylated liposomes achieve a higher drug load in tumors due to a passive targeting process, which exploits the "enhanced permeability and retention effect" (EPR), resulting from increased vascular permeability inherent to many solid tumors [14, 18]. PEGylated liposomal doxorubicin (Doxil/Caelyx) has been approved for use in acquired immunodeficiency syndrome–related Kaposi's sarcoma, and refractory ovarian and breast cancers, and several other liposomal anticancer agents are currently under clinical investigation (http://clinicaltrials.gov).

Lipid-based nanoparticles represent a promising delivery system for drugs and genes for the treatment of lung cancer. For the last two decades, cisplatin is the drug of choice for the treatment of NSCLC. Furthermore, only three platinates—cisplatin, carboplatin, and oxaliplatin— have been successfully used in the clinics [19]. However, cisplatin is implicated in the development of nephrotoxicity in 20 % of patients receiving high doses [4] . In order to reduce the systemic toxicity of cisplatin and improve therapeutic efficacy, Lipoplatin, a liposomally encapsulated cisplatin was developed for various cancer indications, including non-small cell lung cancer and pancreatic cancer [20]. Furthermore, these researchers also demonstrated Lipoplatin exceed the size cutoff for clearance by the kidney [21] and therefore exhibited limited cisplatin-associated nephrotoxicity compared to standard therapy [22]. Exciting and promising data were announced from a randomized Phase III study on Lipoplatin™ in the treatment of non-squamous non-small cell lung cancer (NSCLC). This study used Lipoplatin in combination with paclitaxel as first line treatment against non-squamous NSCLC and compared response rates and toxicities to a similar group of patients treated with cisplatin plus paclitaxel. This study has demonstrated statistically significant increase in tumor response rate in the Lipoplatin arm (59.22 %) versus the cisplatin arm (42.42 %) while also reducing most major toxicities of cisplatin, especially nephrotoxicity [22].

Taxanes are another class of the most widely used anticancer drugs [23]. However, the hydrophobic structure of a typical taxane molecule such as paclitaxel (PTX), a diterpenoid centered around a bulky and fused taxane ring with multiple hydrophobic substitutions limits its solubility. Historically, it was formulated using Cremophor EL to enhance its solubility in physiological fluids. However, this resulted in hypersensitivity reactions and associated with serious side effects complicating its systemic delivery and efficacy [24]. In order to circumvent this problem, liposomal-paclitaxel formulations were developed to enhance therapeutic efficacy. It has been demonstrated in both pre-clinical animal models and human clinical trials that

liposomal-paclitaxel formulations significantly increase a maximum tolerated dose (MTD) of PTX which outperform that for Taxol®. Liposomal PTX formulations are in various stages of clinical trials. LEP-ETU (NeoPharm) and EndoTAG®-1 (Medigene) have reached the phase II of the clinical trials. Lipusu® (Luye Pharma Group) has already been commercialized [25] in China. In 2010, a phase I clinical trial in China assessing liposomal paclitaxel in combination with cisplatin as first-line chemotherapy for patients with advanced NSCLC with regional lymph-node metastasis [26].

Another class of lipid-based nanoparticles are micelles which are self-assemblies of block copolymers that have gained increasing popularity as tumor-targetable nanocarriers since they were first used as drug vehicles in the late 1980s [27–29]. These micelles, which are several tens of nanometers in size and have a characteristic core shell structure consisting of a drug-loaded hydrophobic core and poly(ethylene glycol) (PEG) hydrophilic shell, are long-lived in the bloodstream and effectively accumulate in solid tumors after intravenous injection [30]. The critical features of polymeric micelles for their function as drug vehicles, including size, drug loading and release, and specific binding to the target cells, can be modulated by engineering the constituent block copolymers. At present, micelle formulations incorporating doxorubicin, paclitaxel, SN-38, cisplatin, and (1,2-diaminocyclohexane) platinum(II) (DACHPt) are undergoing clinical trials [30] and four of these have advanced to Phase II studies [31, 32]. These clinical studies have revealed that polymeric micelles reduce side effects from the incorporated drugs and are effective against various intractable tumors, such as lung cancer and triple-negative breast cancers [33], indicating their clinical potential.

Recently, increasing attention has also been paid to another potentially useful property of nanocarriers to achieve subcellular drug targeting [30]. Subcellular drug targeting of nanomedicine could enhance the pharmacological activity of the loaded drugs through improved subcellular drug distribution [34]. Drug vehicles designed to release active drugs in acidic organelles, such as the endosome and lysosome, can circumvent recognition by the drug efflux pump (for example, P-glycoprotein) through internalization by endocytosis, thus overcoming multidrug resistance in cancer cells [35, 36]. This approach is particularly appealing for platinum agents such as cisplatin and oxaliplatin which can be engineered by harnessing a structure-activity relationship (SAR). Employing such a strategy, a novel nanoplatinate was designed inspired by the mechanisms underlying cisplatin bioactivation. This novel lipid-based platinum (Pt) complex self-assembled into a nanoparticle, which releases cisplatin in a pH-dependent manner. The nanoparticles exhibited significantly improved antitumor efficacy in terms of tumor growth delay in breast and lung cancers, and resulted in reduced systemic and nephrotoxicity [37].

2.2 Polymer Conjugates as Nanocarriers

Polymeric nanoparticles are synthesized from polymers. Polymer-based nanomedicine, an arena that entails the use of polymeric NPs, polymer micelles, dendrimers, polymersomes, polyplexes, polymer–lipid hybrid systems, and polymer–drug/protein

conjugates for improvement in efficacy of cancer therapeutics, has been widely explored. Biodegradable polymers such as poly(D,L-lactic acid) (PLA), poly(D,L-lactic-co-glycolic acid) (PLGA), and poly (ε-caprolactone) (PCL), polycaprolactone, and poly-alkyl-cyanoacrylates, gelatin, albumin, chitosan, and their copolymers diblocked or multiblocked with poly(ethylene glycol) (PEG) have been commonly used to form polymeric nanoparticles (NPs) to encapsulate a variety of therapeutic compounds. These include polymeric micelles, capsules, colloids, dendrimers, etc. [38]. Polymeric NPs can be formulated by self-assembly of block copolymers consisting of two or more polymer chains with different hydrophobicity. Drug release rates from the polymeric NPs can be controlled by modifying polymer chemical and physical properties.

Polymer nanoparticles have been shown to enhance the chemo- and radiotherapeutic efficacy of anticancer agents [39]. Abraxane, an FDA-approved albumin-based nanoparticle carrying paclitaxel, is indicated for first-line treatment of locally advanced or metastatic NSCLC in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy [39]. Polyethylene glycol- (PEG-) modified polylactic acid nanoparticles loaded with taxanes have significantly improved the efficacy of chemoradiation therapy in both in vitro and in an A549 lung tumor xenograft model [40]. Other research groups have developed a cremophor free nanoformulation of paclitaxel and cisplatin using block copolymers of PEG and polylactic acid for the treatment of lung cancer [41]. One such polymeric NP is Genexol-PM, a PLGA-b-methoxyPEG NP encapsulating paclitaxel, which has received regulatory approval in South Korea for clinical use and is currently undergoing phase II clinical trials for a number of cancer indications, including patients with advanced NSCLC, in the United States [38]. Results are awaited for a phase II trial of Genexol-PM and Gemcitabine in patients with metastatic lung cancer (http://clinicaltrials.gov/show/NCT01770795). PEG–polyglutamic acid block copolymer micelles loaded with cisplatin demonstrated remarkably prolonged blood circulation and accumulation in solid tumors (Lewis lung carcinoma cells) about 20-fold higher than free cisplatin. The micellar system was found to confer both sufficient stability to ensure prolonged circulation in the bloodstream and sustained drug release kinetics upon accumulation at the delivery site. Treatment with micelles led to complete tumor regression with no significant body weight loss, whereas free drug treatment resulted in tumor survivals and approximately 20 % of body weight loss at the equivalent dose [41]. Polymer nanoparticles have been extensively used in studies aimed at delivering targeted chemotherapeutics to lung cancer. Gelatin nanoparticles (GPs) were grafted with biotinylated epithelial growth factor (EGF) molecules for targeting lung cancer. These nanocarriers demonstrated increased cellular uptake on A549 lung adenocarcinoma cells in vitro and in vivo aerosol administration to cancerous lung in a mouse model [42].

Dendrimers are synthetic, repeatedly branched polymeric macromolecules having numerous extensions from central core, resulting in a tree-like structure. The structure of dendrimers and modifiable surface functionality allow for either encapsulation/conjugation of therapeutic agent, in the core or on the surface, making them attractive carriers for anticancer therapeutics [43]. Poly(glycerol-succinic acid)

dendrimers were explored as potential carriers for camptothecin [44]. The anticancer activity of the camptothecin-encapsulated dendrimer formulation was examined using human breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (HT-29), non-small-cell lung carcinoma (NCI-H460), and glioblastoma (SF-268) [45]. A recent study illustrated the use of dendrimer-targeting peptide conjugates as a carrier for drugs towards NSCLC. These dendrimer-peptide conjugates when administered to a lung tumor-bearing athymic mouse model were efficiently taken up by the cancer cells demonstrating their potential as a drug carrier for the treatment of lung cancer [46]. In a related study, a newly designed PEGylated dendrimer nanoparticle showed promising application as an aerosol-inhaled drug delivery modality. The smaller dendrimer particles are reported to enter the blood stream via inhalation while larger particles are sequestered in the lung for an extended period of time. In the future, this method of controlled drug delivery to the lungs could provide an alternative to injectable drug systems [46, 47].

2.3 Other Nanoparticle Systems

Recent years have seen tremendous progress in the design and study of metal-based nanomaterials of gold and silver, geared towards biological and biomedical applications. Most notable among these being the noble metal gold nanoparticles where the surface-plasmon resonance-enhanced optical properties of colloidal gold nanoparticles directed towards recent biomedical applications with an emphasis on diagnosis and therapy of cancer, including lung cancer [48, 49]. Recently, gold nanoparticles have also successfully been tested as sensors for discriminating and classifying different lung cancer histologies. The sensor was able to distinguish between normal and cancerous cells, SCLCand NSCLC, and between two subtypes of NSCLCs [50]. Gold nanoparticle conjugates of methotrexate (MTX), a drug with high water solubility and low tumor retention, have shown high tumor retention and enhanced therapeutic efficacy in a Lewis lung carcinoma mouse model [51].

Magnetic nanoparticles have been extensively investigated and applied in diagnosis and treatment of various cancers. Theranostic nanoparticles concurrently facilitate imaging and delivery of therapeutic agents. Magnetic hyperthermia is a noninvasive therapeutic approach for lung cancer that entails the heat-induced ablation of desired tumor tissue. When subjected to alternating currents the magnetic material, such as superparamagnetic iron oxide (SPIO), nanoparticles generate sublethal heat that causes local tissue damage. In one study, the tumor-targeted SPIO nanoparticles were highly effective in the hyperthermic destruction and inhibition of tumor growth in a mouse model of NSCLC [52].

Mesoporous silica nanoparticles (MSNs) have been increasingly used in anticancer drug delivery research due to their dynamic capacity for drug loading, controlled drug release property, and multifunctional ability. The first report on in vivo applicability of Mesoporous silica nanoparticles (MSNs) was published by the Mou group in 2008 [53]. Multifunctional mesoporous silica nanoparticles have been used

for intracellular labeling and animal magnetic resonance imaging studies. Human lung cancer cells primarily take up MSNs by endocytosis [54]. A tumor targeted MSN-based drug delivery system was developed for inhalation treatment of lung cancer. The system was capable of effectively delivering inside cancer cells anticancer drugs (doxorubicin and cisplatin) combined with two types of siRNA targeted to MRP1 and BCL2 mRNA for suppression of pump and non-pump cellular resistance in NSLC, respectively. Targeting of MSN to cancer cells was achieved by the conjugation of LHRH peptide on the surface of MSN via poly(ethylene glycol) spacer [55].

3 Challenges and Future Perspective

The past decade has witnessed tremendous growth and development of drug delivery technology utilizing nanoparticle systems. Nanocarriers have emerged as an important treatment modality for therapeutic intervention in clinical oncology. Different types of nanocarriers have established excellent therapeutic potential at both preclinical and clinical development stages. Some of the challenges being faced in the nanomedicine area are the bridging of rapidly developing novel ideas and translating them into clinical practice. Towards this end, safety of nanocarriers is an important consideration which needs to be assessed before proceeding to clinical study. One of the hurdles is in synthesizing nanoparticle drug delivery systems having appropriate properties such as size and charge to carry effective drug/gene payload, and ability to target to the right place. Non-uniform size distribution, undefined structure/shape, poor biocompatibility, and improper surface chemistry are possible risk factors in the biological environment. For highly effective drug delivery to the lungs using nanotechnology, it is crucial for these delivery systems to overcome a number of obstacles including immune reaction, rate of clearance from circulation, efficiency in targeting, and ability to cross biological barriers in order for these nanoparticle systems to enter the clinics. Understanding the mechanism of action and the biological behavior of nanoparticles is imperative to achieve the highest drug delivery efficiency. Identification of physicochemical parameters are absolutely critical in determining the particle-particle interaction within a biological environment, aggregation tendencies, adsorption of proteins on nanoparticle surface, and intracellular trafficking of nanoparticles are some of the important considerations to keep in mind.

From the regulatory stand point, nanoparticle-based therapy must overcome the same hurdles faced by any new drug: optimal design of components and properties, reproducible manufacturing processes, robust assay development and analytical methods for sufficient characterization, favorable pharmacology and toxicity profiles, and demonstration of safety and efficacy in clinical trials. Unlike standard drugs which are composed of a single active agent, nanoparticles are complex in nature with multiple active components that can affect the pharmacokinetics and pharmacodynamics. Such complexity necessitates the need for regulatory agencies to develop an exhaustive list of tests and a streamlined approval process to proactively

address the emergence of new products based on new technologies and facilitate nanomedicine delivery to the clinic.

In conclusion, nanoparticle-based medicine has infinite potential with novel applications continuously being developed for use in cancer diagnosis, detection, imaging, and treatment. The ability of nanoparticles to be tailored for a personalized medicine strategy makes them ideal vehicles for the treatment of lung cancer. Going forward, the development of different strategies to selectively deliver drugs to lung tumors and lung metastases is dependent on understanding the tumor biology, tumor microenvironment, and the interaction between the tumor cells and the nanoparticles. Particulate nanocarriers and polymer conjugates have increased the arsenal of drugs available to oncologists. These are currently based on passive tissue targeting, mainly by the enhanced permeation and retention (EPR) [18], and not active cellular targeting. New strategies utilizing a specific cell surface receptor as a way to target these nanocarriers into lung tumors or lung metastases are showing great promise and need to be scaled up to be able for translation into the clinic. In addition, new class of drugs, from the RNA family, including small interfering RNAs, microRNAs mimic, or anti-miRs, could effectively be used to modulate the function of specific gene or family of genes and are expected to be the next generation of pathway-specific medicine [11]. 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.

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