Lipids and Polymers Targeted Therapies

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Solid lipid nanoparticles are just a solid core of lipids formed by one of the following techniques at 37 °C: high-pressure homogenization, double emulsion, high-shear homogenization, or emulsifier evaporation. The lipid core can be then functionalized using a PEGylated layer or by alternate adsorption. Solid lipid nanoparticles either have one drug incorporated inside their core during fabrication, or they may contain more than one drug. In general, both hydrophobic and hydrophilic drugs can be inserted. For instance, solid lipid nanoparticles are characterized by biocompatibility, low toxicity, good stability, and enhancement of entrapped lipophilic drugs.

Polymeric nanoparticles can be identified as an interaction of two opposite polymeric materials that form a cross-linked network and condensed core. This core can be further functionalized by a PEGylated layer or coated by a lipid monolayer. Hanafy et al. optimized hybrid polymeric lipid nanoparticles by using chitosan-oleic acid after blocking its free fatty acid. This strategy reduced the cytotoxicity that can be generated by oleic acid. Hybrid polymeric lipid nanoparticles can be co formulated in the shape of micelles by using polymer self-assembly, while drugs can either be attached during fabrication or inserted after fabrication. Recently, polymeric materials in the shape of hydrogel materials, mucoadhesive materials, and stimuli-responsive polymers have been developed. Polymeric nanoparticles are characterized by controlled drug release, stability inside cells, and easy and cost-effective formulation. However, the disadvantage of polymeric NPs is mostly associated with the type of organic solvent used during fabrication and the polymer cytotoxicity.

Keywords: Lung Cancer - Targeted therapies- Liposomes- ; Lipid nanoparticles- Polymeric nanoparticles

1. Introduction

Lung cancer is the most frequently diagnosed cancer in the world and a common reason for cancer-related deaths [1]. For patients diagnosed with this type of cancer, the 5-year survival rate is approximately 17.8%[2]. Lung cancer can be divided into three main subtypes according to microscopic evidence and histological profiles: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumor, accounting for 85%, 10–15%, and less than 5% of cases, respectively[3]. Among the three subtypes of lung cancer, NSCLC is the most common one diagnosed in non-smokers. It appears in women more than men, and it is more frequently discovered in younger people than other type of lung cancer[4]. This type can be subdivided, according to World Health Organization (WHO), into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[5].

Adenocarcinoma is a popular type, representing around 40% of all total diagnostic cases. It usually occurs in smokers and nonsmokers[6]. It arises from small airway epithelial cells that form the lining of the lung and alveolar cells: the mucus secreting cells[7]. Furthermore, it grows slowly and can spread outside the lungs. Adenocarcinoma is characterized histologically by the presence of glandular/acinar growth, papillar differentiation, or a single-layer of wallpaper-like spread along the alveolar septum and bronchioles[8]. Squamous-cell carcinoma is derived from the squamous cell type located at the airways of the epithelial cells. These cells line the bronchial tubes in the center of the lungs. This type is mostly associated with smoking tobacco, and it represents 30% of all lung cancer patients[9]. It is histologically identified by the presence of keratinization or intercellular bridges.

Large cell carcinoma comprises 5–10% of lung cancer patients. It arises from the central region of the lungs, the area nearest to the lymph nodes, and the wall of the chest[10]. It usually grows and spreads rapidly, which makes its treatment challenging. Large cell carcinoma, also called non–small cell cancer, has a poor prognosis[11].

SCLC represents 25% of all invasive cancer types worldwide, and it is found exclusively in smokers[12]. It originates from neuroendocrine cell precursors. Thus, it is attributed to endocrine and neurologic paraneoplastic syndromes (Eaton Lambert syndrome, inappropriate antidiuretic hormone secretion, and Cushing's syndrome)[12]. Moreover, it is characterized by its worse clinical course than that of NSCLC[13][14]. Additionally, it can be resistant to both chemotherapy and radiotherapy courses[15][16].

The last type of lung cancer is lung carcinoid tumor. It originates from neuroendocrine cells, which is are special cells located in the lungs. The growth of this type of cancer is typically very slow and it rarely spreads (see Figure 1)[17].

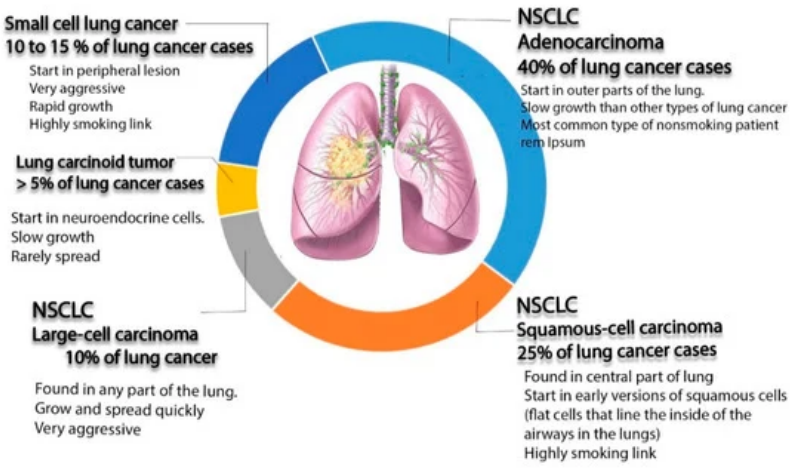

Figure 1. Schematic diagram illustrating different types of lung cancer (non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumors, as well as non-small cell lung cancer).

Here, we try to highlight the development and application of nanoparticles in lung cancer treatment, mainly those made of liposomes, lipids, and polymer materials. Many nanoparticle-based therapies have been developed for the treatment of metastatic NSCLC, such as liposomes, polymeric nanoparticles (NPs), albumin NPs, Lipid NPs, inorganic NPs, and metal NPs. However, few have been translated successfully into clinical trials. In our current study, liposomes, solid lipid nanoparticles (SLNPs), polymeric nanoparticles (PNPs), and hybrid polymeric materials were studied, and they are summarized in Table 1, Table 2 and Table 3, while the successful nanoparticles that moved into clinical trials are outlined in Table 4.

2. Clinical Studies of Pulmonary Nanoparticles Can Be Finally Driven into the Industry Market

Clinical trials represent strategy-based scientific research that attempts to evaluate the influence of a new therapeutic molecule on human health outcomes. It includes several steps, as follows: Phase I—the study of new therapeutic molecules on a small group of volunteers; Phase II—monitoring and evaluation of safe drugs on a large group of volunteers; Phase III—the study of safe drugs in different groups of volunteers located in different regions and countries; and Phase IV—monitoring of safe drugs after obtaining approval for their use in a wide population over long time frame[18]. During the clinical trial process, each drug is given a particular description according to its status, as summarized in Table 4. For instance, it is “recruiting” when several participants are invited to contribute to the study, while “active” status means the study is underway. On the other hand, when the investigation is finished, there is no need for any participants. The status of the drug is changed to “completed”. “Terminated” status means that the study has stopped and will not be started again[19]. In the current review, we have described the use of several nanochemotherapeutic agents to treat lung cancer, and recently, they have reached clinical trial status. Irinotecan liposome injection has obtained a “recurring” status and is being investigated in comparison with topotecan in patients with small cell lung cancer after treatment with a platinum-based first-line therapy (Phase 3; 2018–2022 study). Many studies have completed the clinical study process, such as Cholesterol-Fus1 in non-small-cell lung cancer[20] and the liposomal form of Lurtotecan as OSI-211 to treat recurrent small cell lung cancer[21]. Stimulating Targeted Antigenic Responses To NSCLC (START) was a phase III trial of the MUC1-antigen-specific cancer immunotherapy tecemotide, following chemoradiotherapy for unresectable stage III NSCLC[22] and a liposomal formed of Lurtotecan [7(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20-(S)-camptothecin dihydrochloride] was combined with cisplatin to treat patients with advanced or metastatic solid tumors. A phase II trial of this combination showed that three of 25 patients with breast cancer and two of 23 patients with NSCLC had partial responses[23].

Table 4. Clinical trial studies of lung cancer therapies using lipid nanoparticles.

Study Title	Conditions	Status	Assigned Number
Study of Irinotecan Liposome Injection (ONIVYDE®) in Patients With Small Cell Lung Cancer	**Small Cell Lung Cancer**	**Recruiting**	**NCT03088813**

Study Title	Conditions	Status	Assigned Number
Irinotecan Hydrochloride Liposome Injection (LY01610) For Small Cell Lung Cancer	Small Cell Lung Cancer	Recruiting	NCT04381910
Paclitaxel Liposome for Squamous Non-Small-cell Lung Cancer Study (LIPUSU)	Squamous Non-small-cell Lung Cancer	Active, not recruiting	NCT04381910
Phase I Study of IV DOTAP: Cholesterol-Fus1 in Non-Small-Cell Lung Cancer	Lung Cancer	Completed	NCT00059605
BLP25 Liposome Vaccine and Bevacizumab After Chemotherapy and Radiation Therapy in Treating Patients With Newly Diagnosed Stage IIIA or Stage IIIB Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery	Lung Cancer	Active, not recruiting	NCT00828009
Efficacy and Safety Study of OSI-211 (Liposomal Lurtotecan) to Treat Recurrent Small Cell Lung Cancer	SCLC and Carcinoma, Small Cell	Completed	NCT00046787
Study of Tecemotide (L-BLP25) in Participants With Stage III Unresectable Non-Small Cell Lung Cancer (NSCLC) Following Primary Chemoradiotherapy	Non-small Cell Lung Cancer	Completed	NCT00960115
Liposomal Lurtotecan Plus Cisplatin in Treating Patients With Advanced or Metastatic Solid Tumors	Head and Neck Cancer, Lung Cancer, Ovarian Cancer	Completed	NCT00006036
Study of Autologous CIK Cell Immunotherapy Combination With PD-1 Inhibitor and Chemotherapy in Advanced NSCLC	Non-small Cell Lung Cancer	Recruiting	NCT03987867
A Study of FF-10850 Topotecan Liposome Injection in Advanced Solid Tumors	Advanced Solid Tumors	Recruiting	NCT04047251
TUSC2-Nanoparticles and Erlotinib in Stage IV Lung Cancer	Lung Cancer	Active, not recruiting	NCT01455389
Doxil Topotecan, Doublet Cancer Study	Small Cell Lung Cancer, Pancreatic Cancer, Head and Neck Cancer	Completed	NCT00252889
TUSC2-nanoparticles (GPX-001) and Osimertinib in Patients With Stage IV Lung Cancer Who Progressed on Osimertinib Alone	Carcinoma, Non-Small-Cell Lung	Not yet recruiting	NCT04486833
Intrathecal Pemetrexed for Recurrent Leptomeningeal Metastases From Non-Small Cell Lung Cancer	Leptomeningeal Metastases	Completed	NCT03101579
Inhaled Doxorubicin in Treating Patients With Primary Lung Cancer or Lung Metastases	Lung Cancer, Metastatic Cancer	Completed	NCT00004930
VX-710, Doxorubicin, and Vincristine for the Treatment of Patients With Recurrent Small Cell Lung Cancer	Lung Cancer	Terminated	NCT00003847
Topotecan Hydrochloride and Doxorubicin Hydrochloride in Treating Patients With Relapsed or Refractory Small Cell Lung Cancer	Recurrent Small Cell Lung Carcinoma	Completed	NCT00856037
Inhaled Doxorubicin in Treating Patients With Advanced Solid Tumors Affecting the Lungs	Lung Cancer, Malignant Mesothelioma, Metastatic Cancer	Completed	NCT00020124
Effects of STM 434 Alone or in Combination With Liposomal Doxorubicin in Patients With Ovarian Cancer or Other Advanced Solid Tumors	Ovarian Cancer, Fallopian Tube Cancer, Endometrial Cancer, Solid Tumors	Completed	NCT02262455
An Open-label, Phase I/IIa, Dose Escalating Study of 2B3-101 in Patients With Solid Tumors and Brain Metastases or Recurrent Malignant Glioma.	Brain Metastases, Lung Cancer Breast Cancer	Completed	NCT01386580
Radiation Therapy Plus Combination Chemotherapy In Treating Patients With Limited Stage Small Cell Lung Cancer	Lung Cancer	Completed	NCT00003364
A Phase II Study of Doxorubicin, Cyclophosphamide and Vindesine With Valproic Acid in Patients With Refractory or Relapsing Small Cell Lung Cancer After Platinum Derivatives and Etoposide	Small Cell Lung Carcinoma	Completed	NCT00759824

Study Title	Conditions	Status	Assigned Number
Combination Chemotherapy Followed by Radiation Therapy in Patients With Small Cell Lung Cancer	Lung Cancer	Completed	NCT00002822

Data retrieved from the US National Institutes of Health website (http://clinicaltrials.gov/) on 21 August 2011[19].

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