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Nanoparticles Targeted Drug Delivery in Lung Cancer

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Abstract: *Lung cancer is one of the top most leading cancers in the world. Nano-scale size dependent properties of the nanoparticles revolutionized the targeted therapy for the lung cancer. Nasal drug delivery of the nanoparticle aid in enhancing the effect at targeted site. Vascularization, large surfaced area and rapid disposition of drug nanoparticles is encouraging toward the inhalable drug delivery. The main purpose of the review is to gather the recent literature work in the area of nanoparticle uses in lung cancer and work on the development of targeted drug deliveryples.*

Key Words: Lung cancer, Targeted Drug Delivery, Inhalable Nanoparticles, Nanocarriers, Nano-formulations

Introduction

Despite the modern advancement in the area of diagnosis along with treatment, the cancer of the lung is among the most common cancer leading to mortality in the world due to the breast and prostate cancer. Based on histological appearance, it is further classified in to the following three types; SCLC (Small cell lung cancer) that has a survival spam of 5 years is a very hostile type of lung cancer. Its causes mainly include smoking. NSCLC is purely related to genomic instability and not environmental factors and is more common in women. Large cell carcinoma has a higher growth rate making the treatment a challenging one (Essa *et al.*, 2020; Norouzi & Hardy, 2020).

Malignant cell formation in the tissue lung leads to NSCLC that can be grouped into pleomorphic, large cell carcinoma, adenocarcinoma, carcinoid tumor, squamous carcinoma and unclassified carcinoma. However, oat-cell carcinoma also explained as small cell carcinoma. Its nature is quite hostile and spread quickly into the bronchi or it can also metastasize throughout the body. (Norouzi & Hardy, 2020) Respiratory system, nervous system, bone liver and adrenal glands are the mainstream metastatic sites for lung cancer.

Chemotherapy, radiotherapy in combination with the surgery are the conventional treatment of the lungs cancer. To cure NSCLC, surgical resection can be the best strategy, but the surgery is not possible in every case. Now a days the anticancer drug using for lung cancer have issues of toxicity and selectivity. Chemotherapy option have issues with multidrug resistance ultimately leads to higher dose which result in severe adverse effect.

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Researchers are now trying to develop Nanomedicines that can overcome drug resistance and also enhance immunotherapy. Afatinib (Gilotrif), ramucirumab (Cyramza), and bevacizumab (Avastin) are the new treatment options for lung cancers. The siRNAs are a type of therapeutic agents have the property to target onco proteins and onco genes as well as those proteins that play a vital part in development of resistance to multiple drugs, so they can be of great use in Lung cancer treatment (Youngren-Ortiz & Chougule, 2017).

Nanoparticles focus on providing efficient therapeutic localization aiming directly to refine patient quality of life (Cryer & Thorley, 2019). Nanocarriers such as Liposome, dendrimer, polymeric micelle, carbon nanotube (CNT) has been used for drug delivery and improvement. CNTs are tubes composed of carbon having dimensions in nanometers and are widely used in fields due to their electrical properties and thermal conductivity (Sheikhpour *et al.*, 2020).

In designing nanoplatform based therapeutic targets, four steps are necessary i.e.

1. To select effectual therapeutic that has a range from small molecular drugs to larger nucleic acids.
2. Selecting a proper carrier
3. Implementing a target and drug delivery strategy
4. Singling out the imaging agent. (Paul *et al.*, 2019)

Nanoparticle Drug Delivery for Lung Cancer Therapy

The exceptionally proficient method in which the anti-cancer drugs are encapsulated in the nanocarrier and are delivered to the target site. By directing cellular event at nano scale, the targeted distribution of drug to cancer cells can occur. A large number of cells were needed to identify the presence of tumor, nanotechnology application could drastically bring down this necessity, empowering a whole lot earlier diagnosis/treatment regime. The nanoparticles (NPs) have its own distinctive characteristics including the characteristics small size, larger surface, and flexible surface characteristics. A few nanoparticles showed multifunctional capacities including theranostics applications.

This approach consists of carrier that is bound through the specific conjugation chemistry to the target moiety and a drug. Lipid, inorganic nanoparticle, polymer, may act as a carrier in nanocarrier-based methodologies. Antibodies, high affinity ligands and nucleic acids are included in target moiety.

Benefits of Nanoparticles

Uniform Distribution of Drug

They can generally, accomplish a homogenous distribution of drug dose within the lungs (alveoli). (Leach C, L. CG and Luskin A, 2009) They have the ability to bear nebulization forces in the aerosols. They can avoid muco ciliary clearance as well as mononuclear phagocytic system, thus prolonging the residence of the therapeutic agent within the lungs.

Enhanced Solubility/Dissolution Rate

The improved solubility of nanoparticle enhances the diffusion, permeability of drug thus they can easily be taken up by the target cells. The earlier chemotherapeutic agents (cisplatin, paclitaxel, gemcitabine) were lipophilic and have poor water solubility, thus nanoparticles can result in the increase of bioavailability fraction of lipophilic drugs. (Scherließ R and Etschmann C., 2018)

Sustained Delivery Release

Nanoparticles may act as drug reservoir and thus prolongs the release of drug in the lungs, causing the decrease in the dosing frequency.

Delivery of Macromolecules

Macromolecules liable to instability can be delivered by nanoparticles, as it provides protection from degradation. It can be used as a protective carrier and can deliver biotherapeutics to tumor cells in vivo.

Type of Targeting

Passive Targeting

The type of targeting in which the systemic circulation is targeted by the drug. In this type, the body immune response is involved that serves as a target to the drug or drug carriers.

In the tumor tissue, the endothelium becomes discontinuous and more inflamed than the other healthy tissues. Nano particles permeates through the leaky vasculature and contributes to accumulation in the cancerous tissue, called as Enhanced permeation and retention factor (EPR). Properties of nanocarrier such as small particle size may influence their circulation time and retention levels in the tumor tissues. (Alexis F et al., 2008; Folkman J and Long DM, 1964; Yokoi K, Tanei T and Godin B, 2014; Yokoi K et al., 2014; Gref R, 1994; Miller MA, Gadde S and Pfirschke C, 2015)

One approach is tumor activated prodrug therapy in which some drug administered as prodrug or inactive drug becomes highly active when it permeates through the leaky vasculature.

Matrix metalloproteinase- 2 causes the cleavage of bound form of albumin resulting in the release of doxorubicin. This approach can be used in the cure of malignant cancer. (Guo, Szoka and F. C., 2003)

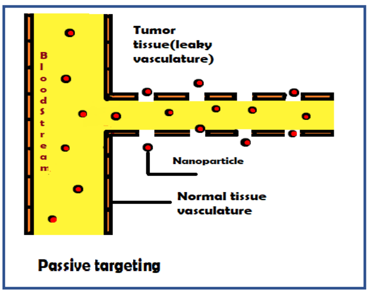

Figure 1

Active Targeting

It involves the conjugation of nanoparticles to the monoclonal antibodies that specifically targets the receptors on tumor tissue or cells. (Lammers et al., 2012: Xu S *et al.*, 2013; Yameen B et al 2014) Tissue antibodies (Monoclonal antibodies), protein(albumin), aptamers and folate molecules are candidates of active targeting.

Active targeting has been taken into advantage over passive targeting because it directs cell specific detection and killing of both primary and secondary tumor cells.

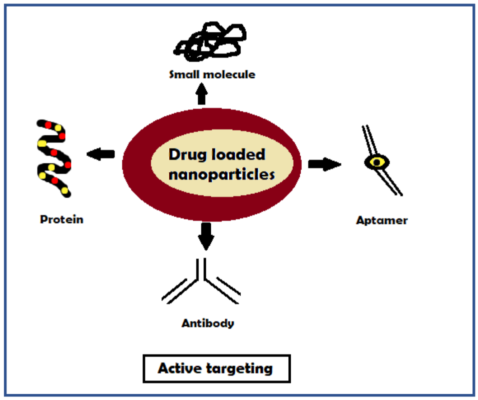

Figure 2

Type of Nanoparticlles

Lipid Based Nanoparticles

Liposomes

Liposomes are circular or globular vesicles made up of lipid bilayer, forming a core and shell. (Suarez S *et al.*, 2001). Lipid bilayer is arranged in such way that their hydrophobic head faces outward while hydrophilic tail faces inward. Thus, they are able to incorporate hydrophobic drugs as well as hydrophilic drugs.(Bozzuilo and Molinari, 2015). Their size ranges from 20nm to several micrometers. (O'Hara P and Hickey A, 2000). Their diameter depends upon the number of lipid bilayers. Thus, their small size improves their circulation in the blood and make tumor cell targeting easy. There are certain unique characteristics of liposomes that make them most extensively used as drug delivery system:

- The composition and structure of liposomes resembles the biological membranes.
- Liposomes can increase the solubility and penetrability of substances therefore many drugs and diagnostic agents are delivered with liposomes.

- They are made up of nontoxic lipids which are easily available and digestible.
- Their surfaces can be modified by adding PEG which will further improve therapeutic activity of drug, enhance stability, clearance and distribution.
- They have increased immunogenicity and hence are biocompatible. (Baleeiro RB *et al.*, 2016)

Solid Lipid Nanoparticles

SLNs came up with the solutions of the delivery of the drugs that are water insoluble, they are replacing the liposomes, emulsions and polymeric NPs and they can be prepared using a solid core by the methods of homogenization, emulsifier evaporation and double emulsion methods. (Hanif SNM and Garcia-Contreras L, 2012 ; van Dissel *et al.*, 2014) They contain 0.1-30% w/w solid lipid and 0.5-5% surfactant that provides stability.(Naseri N *et al.*, 2015; de Jesus MB and Zuhorn IS, 2015)

They are usually solid at temperature 37C and show diameter of less than 80 nm after filtration.(Kisich KO et al., 2011).Their diameter can be increased through fabrication resulting formation of micro and macro particles, however crystalline nature can be a barrier. (Muttil P *et al.*, 2010). They are widely used in the cure of the lung s cancer. (Tonnis WF *et al.*, 2012).)

Polymer Based Nanoparticles

Polymeric Nanoparticles

(PNPs) are the colloidal solid particles of size ranges from 50 to 300nm, synthesized from biodegradable natural or synthetic polymers.(Babu *et al.*, 2013). Their smaller size increases the penetrability through the capillaries thus improve the target delivery of drugs. They are most widely used as nanocarrier for anticancer because their properties can be modified by changing polymer composition and morphology. (Maiolino S et al., 2015; Alexis F *et al.*, 2008). They can entrap, encapsulate and dissolve drug substance in the polymer or drug may be embedded between polymeric matrixes. PNPs provide protection against macrophages and also restricts the interaction of active moiety with healthy cells. PNPs exist in two forms (i) nanospheres (ii) nano capsules. When the drug is dispersed or conjugated with polymer or adsorbed on the surface then such PNPs are knowns as nanospheres. When the liquid core of oil or water, surrounded by solid shell contain the drug inside its cavity then such PNPs are called as nano capsules.

FDA has approved PEG and PLGA polymers as more effective against carcinomas, for their therapeutic applications.(Videira M, Almeida AJ and Fabra À, 2012). Sustained release biodegradable polymers can be prepared by adding disulfide bonds.(Uday SK *et al*, 2013).

Dendrimers

Dendrimers are nanocarriers that connect molecular chemistry to the polymer science. They are highly branched polymeric NPs. They are termed as dendrimer which is a Greek word meaning tree as their polymeric NPs are arranged in such a way that their arms arise from the core like a tree branch. (Fried *et al.*, 2004). Thus, dendrimer has a hydrophobic core of branched polymeric NPs and exterior of multivalent functional groups. Thus, they can carry nonpolar and uncharged drugs as well as charged polar compounds through electrostatic interaction of these compounds with terminal functional groups.

Polymeric Micelles

Polymeric micelles are prepared in aqueous medium upon the spontaneous arrangement of the amphiphilic surfactants resulting in the core shell structure, where the non-polar part of amphiphilic surfactant forms the core while polar part of amphiphilic surfactant forms the shell. But this preparation process is not practical at drug loading levels thus physical incorporation of drug by encapsulation methods is used. Their modifiable properties make them potential candidates as nanocarriers for anticancer drug delivery.

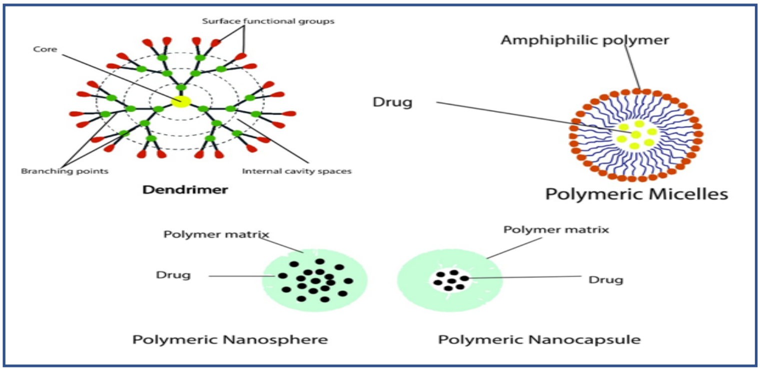

Figure 3

Table 1. Advantages of Various Nanoparticles

Nanocarrier	Advantages	References
Liposome	• Reduces the toxicity of the loaded drug • Increases the efficacy and therapeutic index of loaded drug • Protects drug from external factors • Can carry both hydrophobic and hydrophilic drugs	(Shinghai, A. K., Anwekar, H., & Patel, S., 2011)
Solid Lipid Nanoparticle	• Does not need organic solvents • Biodegradable • Biocompatible • Facilitates control drug release • Cost effective	(Mukherjee, S., Ray, S., & Thakur, R. S., 2009)
Polymeric NP	• Small quantity is sufficient • Highly stable • Can easily be synthesized • Facilitates both sustain and control drug release • Can cross blood brain barrier (BBB)	(Kaundal, B., Sardoiwala, M. N. & Choudary, S. R., 2018)
Dendrimer	• Improves bioavailability of loaded drugs • Enhanced capacity to load drugs • Easy modification • Enhanced penetration through biological membranes	(Chis, A. A., et al., 2020)
Polymeric Micelle	• Increased blood circulation time • PEGylated polymeric micelles prevent their uptake by macrophages of RES • Some of the modulated polymeric micelle prevent drug efflux	(Wakaskar, R. R., 2017)
Metallic NP	• Highly stable • High biocompatibility • Easy large-scale production using aqueous solvents (by avoiding organic solvents)	(Klębowski, B. *et al.,* 2018)
Magnetic NP	• Highly stable in both acidic and basic medium • Does not require organic solvent • Targeted drug delivery through magnetic field guidance	(Zhou, C. *et al.,* 2018)

Metal Based NPS

They are nanosized entities made up of common metals like gold, silver, zinc, iron, titanium in size range of 1-10nm. Their small size gives large surface area for incorporating large drug doses. Most commonly discussed examples are nanogold, nanosilver, metal oxides and quantum dots (fluorescent semiconductor material used as label for imaging purpose). Recently gold nanoparticles appeared as favorable candidate for targeted drug delivery in cancer therapy, because they are non-toxic, biocompatible and immunogenic. (Rasool *et al.*, 2015).Graphene based nanoparticle also gained attention because of their physicochemical properties. (Rahman *et al.*, 2015)

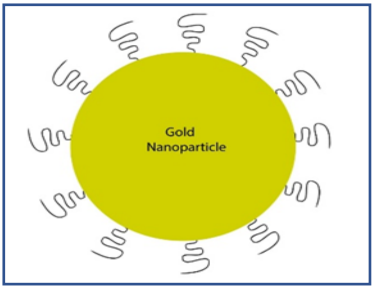

Figure 4

Magnetic Nanoparticles

Magnetic nanoparticles have two components, one is magnetic material like iron, nickel, cobalt while other one is functional chemical substance. Magnetic nanoparticles are those NPs whose properties can be managed by magnetic field. In magnetic NPs either magnetic sphere holds the drug, or it is embedded as magnetic discs.

Magnetic nanoparticles have coating that may be of a biocompatible polymer or recently introduced inorganic materials like silica. They are conjugated with some molecules like carboxylic group, biotin, avidin, iron oxide in order to become functional. Iron oxide conjugated magnetic nanoparticle is most commonly used because they are biocompatible and biodegradable.

Like other nanoparticles they target specific site in the body actively or passively through ligands and produce magnetic effect at the site of action. (Stocke NA *et al.*, 2015; Zhang L *et al.*, 2010). Magnetic nanoparticles are super paramagnetic. They are small sized ranges >25nm. They are used as intratumoral drug delivery system and pose hypothermic effect that may leads to tumor cell death (necrosis).(Babu *et al.*, 2013).

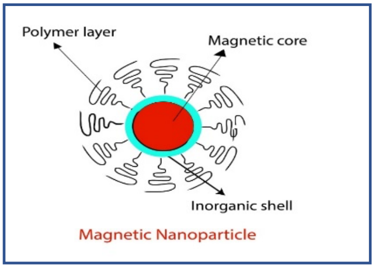

Figure 5

Nanoparticle Delivery VIA Pulmonary Route for Lung Cancer Treatment

Pulmonary delivery of drug has become an important route of administration after the achievement of insulin in inhalable form. It allows the localized delivery of chemotherapeutic agent to the affected tumor cells orally or via nasal route.

One approach in the treatment of lung cancer is to administer the drug via intravenous route leading to significantly less fraction of drug to the targeted area. This allows considerably low drug concentration at targeted region. A high dose is required to attain the therapeutic concentration of the drug at target site. The adverse effects are associated with such a high dose thus, there is a dire need to investigate localized treatment for lung cancer.(Sriraman SK, Aryasomayajula B and Torchilin VP, 2014; Bahl A and Falk S, 2001; Tannock I, 1978)

Localized (Inhalable) Chemotherapy

The inhalation treatment which locally delivers the chemotherapeutic agent to the affected tumor tissues, hence lowering the systemic side effect along with increase in efficacy.

The following are the advantages of inhalable chemotherapy:

Bioavailability of Drug

The drug metabolizing enzymes in the lungs are limited in number as compared to liver or GIT. Therefore, by using inhalable route of administration it causes an increase in the bioavailability of drugs.(Goel *et al.*, 2013) Moreover, it avoids the first pass effect.

Non-invasive Route of Administration

It avoids puncturing of skin, provides comfort to the patient, which makes it a better alternative to parenteral route of administration of chemotherapeutic drugs.

Rapid Onset of Action

Due to large surface area of the peripheral lung and high blood perfusion, it promotes higher absorption rate, reduces the frequency of dose administered and rapid onset of action.(Goel, et al., 2013)

Bio-distribution of Drug

Inhalation promotes the accumulation of large amount of dug in the lungs unlike parenteral administration and in this way biodistribution of the drugs can be altered.(Gagnadoux F *et al.*, 2008; Labiris NR and Dolovich MB, 2003; Sharma S *et al.*, 2001; Hershey AE *et al.*, 1999; Koshkina NV *et al.*, 2001)

Drug Deposition in the Lungs

A large fraction of the drug is deposited in the lymph nodes through the lymphatic circulation. Thus, inhalation plays a significant role in the treatment of metastatic lymphatic cancer.

The distribution and deposition of the drug in the aerosols can be affected by the respiratory disease e.g., cystic fibrosis, COPD bronchiectasis caused by lung cancer.

Irreversible Cell Injury

Cytotoxic effect of the drug may lead to irreversible cell injury which is reduced by the localized inhalable route of chemotherapy.

Effective Option for Lung Cancer Treatment

It involves the localized adverse effects including glottis and cough which are not complex and easily treatable which makes it a better option for effective treatment of lung cancer.

Barriers to Inhaled Drug Delivery

Before employing the inhalation treatment, certain barriers needed to be considered in the effective lung cancer therapy. Mucociliary and macrophage clearance are the main barriers which are needed to be overcome first. Mucociliary system is responsible for the clearance of any foreign particle that enters the airways. In the alveoli, macrophages sweep the foreign particle that get deposited in the alveolar sacs.

Inhalable Nanoparticulate Powders

The deposition of the particles in the lungs depends on its major properties that includes particle size, size distribution, surface morphology, hygroscopicity, electric charge and density. The disease state and the breathing pattern also impart the deposition in the lungs. The smaller particles deposit in the airways by diffusion and the large particles is due to inertial impactions. Nasal route is the chosen for the delivery of vaccine due to the ease of delivering, large surface of absorption, low enzyme degradation and high vascularity of the nose. Superiority on liquid formulations and the enhancement of the systematic availability is the major advantage of the inhalable formulation for nasal drug delivery. Those nanoparticles that have a size larger then 20nm will cross the membrane through transmucosal roue by endocytosis, receptor-mediated or carrier mediated transport process.

Although inhaled delivery has the clear pharmacokinetic advantages as compared to the systemic delivery. The use of dry inhalable nano powder NPs could efficiently accumulate in the lung cancer via passive or the active targeting hence the concentration at the target site will increased. The major problem faced by the use of inhalable NPs is the exhalation of drug before reaching to the site of action due to its nano size. Powder nano drugs give advantages especially in the case of water soluble, protein and the peptide drug which does not stand the shear produced during the inhalation. Effervescent technology can impart an active release mechanism of the drug and it is the promising technique for the dispersion of the nanoparticles. These nanoparticles achieve deep lung deposition; however, no drug is found in any other organ.

Inhalable Nanoparticles Droplet

Nanoparticles delivered by pulmonary route often produced in the form of inhalable droplets. Respiratory droplets are generally existing in two sizes,that determine the distance travelled by them. Usually, inhalable droplet of size >5um reaches only upper respiratory tract while droplet of size 5um reaches the lower respiratory tract and inhalable NPs droplets belong to this category. Inhaled NPs droplets are more suitable than the simple drug droplets as they have more FPF (fine particle fraction).(Joshi N *et al.*, 2014; Hu L, Jia Y and WenDing, 2010). But storing NPs suspension may affect physicochemical properties of formulation including aggregation of particles, hydrolysis of polymers and drug degradation. Despite the barriers faced by pulmonary drug delivery, there are many devices available to deliver NPs inhalable droplets including nebulizer and pressurized metered dose inhalers (pMDIs), which convert NPs suspension into inhalable droplets.(Zhou Q et al., 2014; Atkinson J *et al.*, 2009). Different types of nebulizers are available e.g., jet nebulizer and ultrasonic nebulizer. Nebulizers contain both the compressed air and liquid, it made them to pass through narrow opening of nozzle and enters the wide area of nebulizer cup. This result increased air volume with decreased pressure which further covert the liquid into droplets.

ebulizers are not portable owing to their large size but pMDIs are portable and can easily be handled by the patient. pMDI utilizes pressurized propellants that atomize the drug solutions and make them to suspend in compressed propellent while nebulizer does not require any external force to make fine droplets. But there are drawbacks associated with pMDI like dosing error because of mishandling by the patient and low efficiency as only 10% of droplets emitted by the pMDI reaches the deep lungs. There are concerns associated with these devices, like they may affect the physical integrity of nanocarriers, and many studies are being performed to prove these concerns wrong.

Challenges for NPS Mediated Pulmonary Drug Delivery

- Retention of NPs in the tumor and residence time at the targeted site is bit challenging and complicated.
- Any deviation in the physicochemical parameters including, interaction of particle with living environment, protein adsorption on nanoparticle, aggregation behavior leads to poor therapeutic delivery of drug.
- There are limited number of rules for the testing of nanoparticles, based on safety, manufacturing etc. Additionally, these NPs testing is quite cumbersome and complex.

Clinical Nanoformulations for Lung Cancer Therapy

Clinical studies are done to find new treatment that are moresafe, effective, and have better therapeutic effects than the previous treatments. Many nanoformulations of therapeutic moieties have been studied for their efficacy against lung cancer, until now, very few got clinical approval, and many are undergoing clinical trials. Nab-Paclitaxel is the first approved nanoformulation for lung cancer as combination therapy by FDA in 2012. The previous Paclitaxel has been widely used chemotherapeutic agent which belong to family of taxane, a plant alkaloid. It is antimicrotubular agent,that interferes with microtubules which is a structural unit of cell that helps in the cell division. But unlike other antimicrotubular agents that inhibit microtubule, Paclitaxel stabilizes microtubule and prevent it from breaking up during mitosis (cell division). That ultimately leads to cell death or tumor death. But paclitaxel has some serious adverse effects like hypersensitivity reactions which are associated with its solvent Cremophore EL. Crempohre El and ethanol are added to the commercial preparation of paclitaxel as solvents to increase its aqueous solubility. These adverse effects are avoided by administrating small doses of paclitaxel for about 3h through IV route. In addition, corticosteroids and antihistaminic agents are also given prior to paclitaxel administration. But now with advances in nanotechnology, Nab-Paclitaxel has been introduced which is albumin bound nanoformulation of paclitaxel that has overcome the shortcomings of previous formulation of Paclitaxel by eliminating Cremophore EL including ; (a) higher doses of paclitaxel can be administered (b) reduced infusion time of 30/40mins (c) elimination of prior administration of corticosteroids and antihistamines (d) Enhanced delivery of drug at target tumor site via better transportation across endothelial cells by following albumin transport pathway. Another nanoformulation of Paclitaxel, Genexol PM has also been clinically approved in South Korea for NSCLC and breast cancer. It is the polymeric micellar nanoformulation of Paclitaxel. It is composed of Paclitaxel and Methoxy poly (ethylene glycol)-b-poly (D, L -lactide). It has proved to be less toxic with more administered dose as compared to paclitaxel. As compared to Nab-Paclitaxel, it does not require albumin donor. One of the challenges, faced by chemotherapeutic agents include their exposure to plasma proteins and pleural fluid proteins that adsorbed on the surface of drugs. This protein layer accelerates mononuclear phagocytosis system (MPS) mediating clearance of NPs, which results in increase uptake of NPs by liver and spleen that leads to reduced NPs concentration at targeted tumor. But the PEG coating in Genexol inhibit this nonspecific protein interaction by adding hydrophilicity and stearic hindrance that prevent MPS clearance and increased concentration at target site.

Cisplatin has been widely used as a chemotherapeutic agent against variety of solid tumors like, breast, testicular, ovarian and lung cancer. But there are numerous side effects associated with it including nephrotoxicity. There is also tumor cisplatin resistance and cisplatin nonselective distribution among healthy and tumor cells that limit its usage as anticancer agent. So clinical studies are going on to overcome these shortcomings by forming nanoparticles of cisplatin or nanoformuations of cisplatin using different types of nanoparticles like liposomes, polymeric NPs and polymeric micelles etc. Despite, many clinical studies not a single nanoformuation of cisplatin got approved while lipoplatin (liposomal cisplatin) has shown promising results in preclinical studies and entered into clinical trials. Clinical studies are also going on to find Doxil, a liposomal doxorubicin, to find its efficacy against SCLC and NSCLC. Doxil is already an FDA approved NP therapeutic agent for many cancer treatments like ovarian cancer, multiple myeloma and AIDS- related Kaposi sarcoma. So currently, many clinical studies are going on and further efforts are needed to find safety profiles of nanomedicines under clinical trials. (Mohammad Norouzi and Pierre Hardy, 2015)

Table 2. Nanoformulations for Lung Cancer Treatment

Product	Formulation	Indications	Company	Clinical Stage
Nab-Paclitaxel (Abraxane)	Albumin bound paclitaxel	NSCLC	Celgene Co.	FDA approved
Genexol PM	Paclitaxel loaded polymeric micelle	NSCLC	Samyang Biopharmaceuticals	Approved in Korea

Lipoplatin	PEGylated liposomal cisplatin	NSCLC	Regulon Inc.	Phase II/III
Doxil	PEGylated liposomal doxorubicin	SCLC and NSCLC	Johnson & Johnson	Phase II
Tecemotide	Liposomal vaccine	NSCLC	Oncothyreon Inc.	
CRLX101	Cyclodextrin PEG based polymer conjugated camptothecin	SCLC	Cerulean Pharma	Phase II

Conclusion and Future Perspective

Lung cancer is one of the life-threatening disease conditions worldwide, with millions of cases reported annually. There are many challenges encountered by oncologist and other health care professionals regarding its diagnosis, mitigation and treatment. Conventional treatment involving chemotherapy contributes to systemic toxicity, adverse drug effects and drug resistance. Nanoparticle drug delivery is the modern application, considered for the targeted delivery of chemotherapeutic drugs. Many types of nanoparticles (liposomes, SLNs, dendrimers, polymeric Np) have been developed to increase in the efficacy and therapeutic index of the drug. Pulmonary route is the most promising drug delivery approach in the field of Nano formulations. Due to higher concentration of drug at targeted site and minimal side effects, it is becoming more and more important nowadays. Inhalable nanoparticles can cross the membranes and uniform distribution of the drug can be achieved. However, particles are deposited on the upper and lower part of respiratory tract on the basis of their size. Many Nano formulations are undergoing clinical trials, while Nab Paclitaxel is one of them to get a clinical approval. Hence, we hope soon many exciting opportunities in nanomedicines awaits us and each challenge in this field would take us toward improvement and betterment.

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