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A Review on Polymeric Nanoparticles Targeting Lung Cancer

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ABSTRACT

Lung cancer is one of the emerging diseases that contribute heterogeneously to an increased worldwide mortality rate. As it is silently established inside the lung, diagnosis at early stages is slightly difficult and often difficult to handle, leading to patient mortality**.** Even after increased progress in understanding the physiology of lung cancer, development in early detection, cancer treatment, and resistance development mechanisms, the survival rate and output continued to stay low for several patients. In the treatment of lung cancer, numerous surgical and non-surgical therapeutic techniques are used, including photodynamic therapy, radiotherapy, and chemotherapy. Most of these methods, however, are expensive, complicated, and have no patient compliance. Chemotherapy, which is widely used in cancer treatment, is associated with the lack of specific tumor targeting and minimal drug solubility, resulting in an inadequate quantity of the drug reaching the tumor site. To overcome these chemotherapy-related demerits, polymeric nanoparticles offer new opportunities for selective drug delivery to fight lung cancers. Biodegradability, biocompatibility, non-toxicity, sustained circulation and a broad payload range of a therapeutic agent are the main characteristics of this system. In this study, we reviewed polymeric nanoparticles used through selective drug delivery and inhalable nano-based drugs for the treatment of lung cancers. In addition, it explores promising strategies in this emerging area.

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INTRODUCTION:

Cancer is an evolving global issue to counter the fact that it is the world's next big cause of death (secondary to cardiovascular diseases).[1]The term cancer refers to cell diseases that suggesting unregulated proliferation, dedifferentiation (anaplasia), invasiveness, and metastasis potential (outspread to distant parts of the body).[2-4]The most commonly diagnosed cancers globally are lung cancer (attributing 11.6 % of the total number of cases, with an estimated 1.69 million deaths), breast cancer (10.9 %) and colorectal cancer (9.7 %), and the most prevalent type of cancer that leads to death is lung cancer (18.4 % of the total), stomach cancer (9.7 %) and liver cancer (9.2 % of the total).[5] Lung cancer is a diverse disease that results in the development of genetic and epigenetic changes in the epithelium of the lungs.[6] Almost all tumors are the result of continual exposure to tobacco smoke.[7-8] Lung cancer is mainly graded into non-small cell lung cancer (NSCLC) and small cell lung cancer, based on therapeutic and clinical aspects (SCLC). About 85 % among them are NSCLC, and the rest (15 %) are SCLC.[3] Recent carcinoma therapies also induce harmful long-term and short-term side effects, including cardiotoxicity, ulcers, nausea, and increased probability of developing other cancers, cytotoxicity to healthy cells, and can also cause a wide range of degenerative diseases. Direct delivery of chemotherapy to pulmonary tissues may result in toxicity, poor delivery performance, multidrug resistance, and severe side effects, as selective delivery to cancer cells is not permitted.[9] To curb these high mortality and morbidity statistics, novel, harmless and efficient therapies are therefore urgently needed. To increase the solubility and therapeutic effects of poorly water-soluble chemotherapeutics, nanotechnology has been used. In addition to enhancing the therapeutic efficacy of chemotherapeutic drugs, nanotechnology also reduces unspecific cytotoxicity, facilitates targeted delivery, sustained release of the drug, and inhibits drug resistance.[10, 11]Polymeric nanoparticles are the type of colloidal sub-micron pieces in which the various polymers are used to encapsulate the drug. These polymeric nanoparticles are used to target particular cancer cells or polymer nanoparticles by binding the ligand to them. Poly (glycolic acid) (PGA), poly (lactide-co-glycolide) (PLGA), poly (lactic acid) (PLA), poly(ε-caprolactone) (PCL), polyacrylic acid, chitosan, etc. are widely used polymers in the preparation of nanoparticles. Due to their regulated and sustained release properties and biocompatible nature, these polymers have become prominent.[10-13] In the treatment of lung cancer, polymeric nanoparticles have positive outcomes. Polyethylene-glycol-modified polylactic acid (PEG-PLA) taxane-loaded nanoparticles have greatly enhanced chemoradiation therapy in both *in vitro* and *in vivo*

(A549 lung tumor xenograft model).[14]Different types of lung cancers are depicted in Figure No .1. [15]

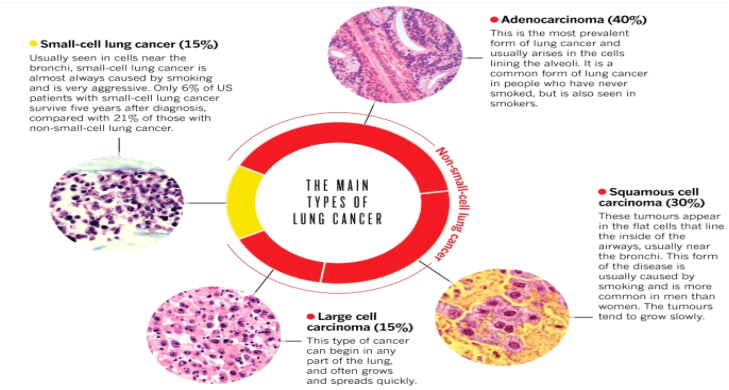

Figure No. 1: Different types of lung cancer

CONVENTIONAL LUNG CANCER TREATMENTS AND THEIR LIMITATIONS:

a. Surgery: In almost 20 % of NSCLC cases, early-stage I and II and selected patients with stage IIIA, surgery is the favored alternative for cancer treatment.[16] Surgery can enhance outcomes during the early stages of lung cancer in combination with chemotherapy and radiation therapy. It is an operating procedure to remove the tumor physically if the tumor is not resettable. The health status of patients is very important to decide whether they can handle the procedure or not. Initially, testing to confirm the existence of NSCLC begins, and then further studies are conducted to examine the stage and location of the tumor to determine whether it has spread to the degree that surgical operations will not cure the disease. CT scans and positron emission tomography are commonly performed for assessment. The minimally invasive procedures are pneumonectomy, video-assisted thoracoscopic surgery (VATS), and VATS lobectomy, for lung cancer surgery, these are rarely done for the removal of the entire lung.[17]

b. Radiation Therapy: By destroying their DNA with the aid of energy beams associated with high power, the main purpose of radiation therapy is to kill cancer cells. NSCLC patients who are made unavailable for surgery are often preceded by curative-intention chemotherapy. In addition, patients who do not respond to operation or chemotherapy, such as NSCLC in stage IV, become part of palliative care. The most popular method of intervention that is used for lung cancer is external-beam radiation therapy. This can be either radiosurgery which involves very few high-focused doses of radiation therapy fractionated over long periods involving low doses. Stereotactic ablative body radiotherapy (SABRT) is

an innovation in external beam radiation therapy, where high-dose radiation is reliably administered within the body to an extracranial target. A single dose or a few fractions may be used to do this.[18]

c. Chemotherapy: The usage of drugs became a vital part of treating lung cancer, i.e. chemotherapy, to kill cancer cells. This improves survival and is the first line of treatment in advanced NSCLC, enabling the patient to tolerate/resist treatment.[19] The main treatment for advanced NSCLC patients that are inadequate for surgery is chemotherapy, frequently accompanied by radiation therapy. A single drug or a combination of medicines in cycles, along with recovery, is required for the treatment. The duration of rest or rehabilitation, given that the medication works on days or weeks after the first delivery, allows body control. However, in certain cases, chemotherapeutics are prescribed daily. Drugs frequently used in chemotherapy for the treatment of lung cancer include carboplatin (Para platinum), cisplatin (Platinum-AQ or Platinum), docetaxel (Taxotere), etoposide, cisplatin-containing gemcitabine hydrochloride (Gemzar), cisplatin-containing paclitaxel, paclitaxel albumin stabilized formulation of nanoparticles (Abraxane, also known as albumin-containing paclitaxel or nab-paclitaxel) (Navelbine). Sometimes, when combination therapy is needed, cisplatin or carboplatin plus an extra drug is used. The first-line treatment of stage IV NSCLC is cytotoxic combination therapy. In the case of advanced lung cancer, initial chemotherapy does not normally work for the use of a single chemotherapy medication such as Docetaxel, Pemetrexed, following either immunotherapy or targeted therapy.[20]

d. Photodynamic Therapy (PDT): In Comparison with other treatment approaches. PDT is an innovative trend for effective and efficient cancer treatment, having several advantages. PDT is economic and reduces the need for regular and long-term treatment. The first-generation photosensitizer is Porfimer sodium, which is commonly used for the diagnosis of lung cancer. Most PSs show autofluorescence, making it easy to monitor and observe absorption within the body. The organic photosensitive agent, the PDT, is (Porphyrin, Texaphyrin, and Chlorine). When the photosensitizers are introduced with the aid of the external light with a particular wavelength into the particular site, they elevate to excite to the ground state. It remains in the field triplet state where oxygen plays a major role. Oxygen is more highly reactive because of this singlet, which helps to kill the cancer cells. Further, PDT can be monitored by light near-infrared (NIR) radiation; PS can be radiated and the drug released once in the area of interest of the tumor, thereby minimizing toxicity to normal tissues.[21]

POLYMERS USED IN POLYMERIC NANOPARTICLES:

a. Polyethylene Glycol (PEG): Polyethylene glycol (PEG) is used to enhance the solubility of water-insoluble cancer drugs. Conjugation with PEG has modified the nanoparticle surface of hydrophobic drugs. The positive impacts of conjugation are improved solubility, extended circulation time, and targeting of specific cancer cells through improved permeation and retention (EPR) effects. The conjugation approaches associated with PEG are of two generations:

1. First-generation, chemically known as randomization PEGylation and

2. Second-generation, or targeted approach; (i.e., site-specific PEGylation).[22]

b. Poly-lactic acid (PLA): PLA is used in the supply of drugs and tissue engineering due to its slow degradation and fast processing. It is commonly synthesized in two forms, lactic acid poly-condensation as well as lactide ring-opening polymerization, with 2 stereoisomers (i.e., D-and L-lactic acids) that are optically active, it is possible to obtain four different polymers, including one homopolymer.[23]

c. Poly (lactide-co-glycolide) (PLGA): PLGA is a lactide and glycol ideal copolymer that involves polymerization with ring-opening. It blends the properties of each of these monomers, because of the presence of both polys (lactide-co-glycolide) PLA and PGA (PLGA). The PLGA characteristics can be changed by modifying the PLA and PGA ratios. Few parameters can be customized, such as degradation period, time of retention, pH solubility, and temperature. PLGA's sol-to-gel properties allow scientists to explore its potential.[24]

d. Polyalkyl cyanoacrylate (PACA): The biggest challenge to cancer management is the cellular resistance of many lipophilic medications. Unique pathways born at the tumor site may be involved in the cellular resistance theory or may have been associated at the action site with drug problems. Nano-sized particles of poly alkylic cyanoacrylate (PACA) overcome the multidrug-resistance (MDR) phenomenon at both non-cellular and cellular locations. Currently, in phase II trials, PACA nanoparticles are in usage. PACA nanoparticles with charged DOX display the greatest susceptibility to cancers in contrast to PLGA, PCL, and various other nanoparticles with charged doxorubicin (DOX).[22]

e. Poly (ε-caprolactone) (PCL): It is indeed one of the polyester sequence polymers that consist of repeating units of hexanoate. PCL is formulated by polycondensation of 6-hydroxyhexanoic acid. The PCL is slow to degrade, and the time for degradation is up to several months, particularly in comparison with certain other polyesters such as PLA, PGA, and PLGA sequence polymers. PCL is therefore commonly used for the controlled release of various biomedicines and certain other chemotherapeutic agents. [22]

f. Chitosan: It is a randomly distributed cationic, biodegradable, and non-toxic polysaccharide of (1,4)-linked N-acetyl-D-glucosamines and D-glucosamines. Different types of chitosan nanoparticles and their derivatives are prepared for tumor treatment. Examples include chitosan-modified bile acid, PEGylated chitosan, chitosan liposomes, and many others.[25] Chitosan-based nanomaterials are unique carriers for the targeted delivery of chemotherapeutics at the precise target site. Successful cancer therapy requires effective continuous delivery of tumor tissue for an extended period, which is done by using modified chitosan nano vehicles.[24]

g. Albumin: It is involved in aggressive targeting as well as passive targeting. The entire pharmacokinetic profile of anticancer agents is modulated by the extraordinarily long half-life of albumin. Due to the versatility in its chain, Albumin also displays the EPR effect.[20]

h. Gelatin: It is one of the most extensively used polymers in the production of polymeric-based nanoparticles. The biodegradability and biocompatibility of gelatin nanoparticles are the major benefits of gelatin nanoparticles above other polymeric nanoparticles. For the processing of gelatin nanoparticles, the water-oil emulsion method is employed frequently. Compared to the traditional formulation of the medication, gelatin nanoparticles demonstrate regulated release.[26]

Currently marketed polymeric nanoparticles targeting lung cancer, their mechanism of action, and common side effects are mentioned in Table No. 1.

Table No. 1: Marketed polymeric nanoparticles targeting lung cancer, their mechanism of action, and common side effects

Drug	Year of FDA approval	Mechanism of action in lung cancer	Side effects
Atezolizumab[27]	2016	Inhibition of the interaction between PD-L1 and PD-1 receptor Induction of T-cell antitumor activity	Fatigue Diarrhea Nausea
Methotrexate[28]	2014	Inhibition of the synthesis of purine nucleotides Suppression of DNA synthesis Inhibition of cell proliferation Inhibition of ALK, hepatocyte growth factor receptor	Hepatotoxicity Osteonecrosis Soft tissue necrosis
Paclitaxel[29]	2012	Fusion with β-tubulin Stabilization of microtubules Inhibition of cell cycle at mitotic phase	Neutropenia, Nausea and vomiting Arthralgia
Crizotinib[30]	2011	Inhibition of ROS1 Suppression of growth Induction of apoptosis	Pneumonitis Bradycardia Vision disorders

INHALABLE NANOPARTICLES (INPS) BASED LUNG CANCER THERAPY:

a. Polymeric nanoparticles: In recent times, the delivery of chemotherapeutics by inhalable nanocarriers has attracted increasing interest owing to its ability to interact closely with drugs and continue to maintain their release, along with their capability to target cancer tissues in the lungs. They can also be converted into aerosols efficiently, and nebulization forces can withstand extremely high resistance.[31]

b. Gene delivery: Polymeric nanocarriers are less harmful, non-immunogenic, extremely stable at normal room conditions, also convenient for the huge production process, hence acts

as a substitute to viral vectors for gene delivery purposes. The most frequently used polymer i.e., polyethyleneimine (PEI) since it promotes the absorption and endo-lysosomal escape of polyplexes within the gene delivery. In addition, its positive burden enables the fusion with the phospholipids, which are loaded negatively, and in turn improve transfection. Depending upon the molecular weight and structure, the efficiency of PEI is affected in terms of cytotoxicity.[31]

c. Co-delivery of drugs and genes: Polymer-based nanoparticles were being used in the delivery of respiratory drug and gene compositions. The combined effect of drug and gene delivery showed delayed drug tolerance, less toxic effects, and synergistic effects. Medicines are normally polymer-conjugated or stuck (PEI). Electrostatic interaction complicates the genes. Cis-aconite anhydride and tert-Butyl carbamate have been used as pH sensible linkers to facilitate the release of pH-responsive polyplex chemotherapy. A Schematic diagram of pulmonary delivery of polymer-based nanoparticles for the treatment of lung cancer is represented in Figure No. 2.[32]

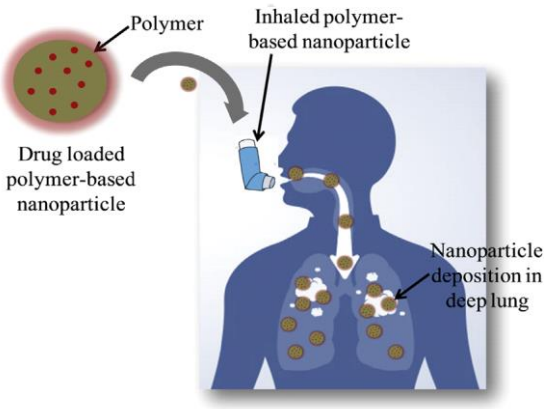

Figure No. 2: Pulmonary delivery of polymer-based nanoparticles for the treatment of lung cancer

RATIONALE FOR DEVELOPMENT OF INHALABLE NANOPARTICLES (INPS) BASED LUNG CANCER THERAPY:

a. Size of particles: Nano-sized particles are known to be effective in treating cancer. A critical function is played in assessing the efficacy of the treatment-specific spectrum of particle size, while the organ may remove some, or an alveolar macrophage may engulf some of them. Nanoparticles with a particle size of less than 10 nm, for example, are likely to be removed via the reticuloendothelial system (RES), i.e., the glomerular capillary of the lymph

nodes, spleen, liver, and kidney. Whereas nanoparticles ranging more than 100 nm were cleared by macrophages within the alveoli.[32]

b. Enhanced permeability and retention: The preservation of the active ingredient within affected cancer cells using tumor lymphatic drainage plays an important role concerning the EPR effect. Considering the vascular cut-off pore with vasculature tumor size varying from 10 nm to 1000 nm depending on the form and stage of cancer, it was shown that there are certain variations between tumors and healthy cells. Whereas ordinary vascular cells have particle permeability of less than 2 nm. At a particle size of 10 - 100 nm, a targeted tumor-based animal model was found to be successful.[32]

c. Surface properties: The pharmacokinetics of the anti-cancer medication in tumor cells affects nanoparticles' superficial properties. Ingestion by phagocytosis with macrophages could be avoided by coating hydrophilic polymer layers like polyethylene oxide, polyethylene, and poloxamine. It was noted that tumor cells with higher binding activity between tumor cells and particles could easily penetrate nanoparticles with positive charges. In addition, zeta potential values above ± 30 mV are substantially improved by the stability of suspended nanoparticles, while particle aggregations are reduced.[32]

ADVANTAGES AND APPLICATIONS OF POLYMERIC NANOPARTICLES IN THE TARGETED DRUG DELIVERY FOR LUNG CANCER THERAPY:

- Nanoparticles have many drug delivery benefits, including two important characteristics: small size and the use of biodegradable materials. Due to its small size, inflammatory sites such as the intestinal tract and liver can penetrate through microcapillaries, tumors, or endothelium. Due to its well-suited intravenous drug delivery, NPs has many advantages over large micro particles.[33]

- Several formulations and medications are being used in the therapy of pulmonary tumors including anti-cancer drugs, nucleic acids, cellular immunity activators, antibodies, pharmaceutical combinations, the colony-stimulating factor of granulocyte-macrophage, and human recombinant inhalation interleukin-2; screened for clinical authorization.[34-36]

- In terms of biocompatibility, amphiphilic block copolymer-based NPs have been stated that hydrophobic anticancer drugs are readily trapped with high trapping efficiency into the center of these NPs and protect against enzymatic degradation, but due to the acidic environment, the drug is mostly released within the tumor tissues. To resolve scale-up,

reproducibility, and cost concerns, natural polymers such as albumin and gelatine play an important role and are more preferable.[37]

- One of the benefits of pegylated / glycopegylated PNPs is that they have a longer shelf life to be able to produce loaded drugs at a lower frequency. The PGLA-conjugated nano-drug Opaxio was used as maintenance therapy and as the FDA-approved radiosensitizer for non-small-cell lung cancer (NSCLC) treatment.[37]

- Cellular therapy, drug delivery, immunoassay, and magnetic resonance imaging contrast enhancement, are applications for iron oxide nanoparticles.[38] As one of the applications for targeted drug delivery, magnetic nanoparticles prepared by coacervation using Poly(L-lysine) microspheres are characterized.[39]

- The use of biodegradable materials (PLGA and PLA) in the formulation of NP enables the sustained release of drugs within the target site, particularly effective for intracellular target drugs, for days or even weeks.[40]

CHALLENGES AND LIMITATIONS INVOLVED IN DRUG DELIVERY OF POLYMERIC NANOPARTICLES TO LUNG CANCER THERAPY:

- It is not free of restrictions, considering various applications in nanomedicine for cancer therapeutics over traditional therapeutic strategies. Another downside is the occurrence of unintended NP encounters within the body that lead to unforeseen effects, such as unwanted penetration into the blood-brain barrier (BBB). It is important to select efficient and suitable targeting ligands for selective tumor targeting, while certain surface proteins present in normal cells are overexpressed in most cancers, which does not guarantee selectivity. The manufacture of nano-drugs on a large scale is another barrier.[41] It seems to be a challenging task to resolve these challenges, but it can be made possible by targeted efforts.

- Drug-delivery nanotechnology and the advancement of nano carrier-based systems as an alternative technology to resolve the gaps are somehow the reach and obstacle for researchers around the globe. One of the challenges is the safe operation issues associated with nanocarriers, which should be carefully evaluated before a trial. Nanocarriers have proven to be an effective therapeutic modality for therapeutic intervention for clinical oncology.

- Despite enormous developments such as passive targeting, leaky vasculature extravasation has always been the primary mechanism on which cancer-targeting depends. The key difficulty lies in the tiny size of particles in the delivery of tumor-targeted drugs.[42]

- By using new strategies such as cell surface-specific receptors, nanosystems in lung cancer or lung metastases display tremendous promise as a target to be scaled up for effective translation into clinical settings. One of the evolving routes specific to next-generation medicines is modulation of a specific gene or gene family function and promotion of new RNA family substances such as siRNAs, microRNA mimics (miR-Mimics), or ant miRNAs.[43]

The various polymeric NPs targeting lung cancer under clinical trials are tabulated in Table No. 2).[44-47]

Table No. 2: Polymeric NPs targeting lung cancer under clinical development

Polymeric NPs	Targeting ligand	Therapeutic agent encapsulated	Indication	Clinical status
BIND-014 (NCT01300533)	Small molecule	Docetaxel	Solid tumors	Phase II
Atu027 (NCT01808638)	Protein kinase N3	siRNA	Solid tumors	Phase II
CRLX-101 (NCT01380769)/ NCT00333502)/ (NCT02010567)	Passive	CPT	Non-small cell lung cancer/rectal/renal cell carcinoma	Phase II

CONCLUSION:

In this review, we discussed different types of polymeric NPs utilized for delivering drugs to target tissues and organs, their specific activation against target cells, such as cancer cells, controlled delivery of anticancer agents, and their effective improvement towards therapeutic performance.[44] Due to the process of easy production, biodegradability, and biocompatibility polymeric NPs have been widely used as carriers. However, low investment and high cost of fabrication of targeted drug delivery systems decrease the use of NPS. Thus, an affordable

method must be chosen to have the ability to scale up the procedure. Finally, polymeric NPs provide a good perspective for the treatment of cancer with high potential and advantage toward a traditional method but needs further studies *in vivo* and provide clinical standards. In the future multifunctional properties composed with a simple design of PNPs with complex features will be the subject of research.[45]

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