Medicon Medical Sciences
Volume 4 Issue 1 January 2023
Mini-Review

Emerging Nanotechnology Advances: Liposomal Formulations to Treat Non-Small Cell Lung Cancer: A Short Review

Gopika Ashokan, KB Sneed and Yashwant Pathak*

Taneja College of Pharmacy, University of South Florida, Tampa FL 33612, USA

***Corresponding Author:** Yashwant Pathak, Taneja College of Pharmacy, University of South Florida, Tampa FL 33612, USA.

Received: December 10, 2022; **Published:** December 19, 2022

Abstract

Lung cancer is one of the leading causes of death in the US and is caused mainly due to smoking. The number of patients that suffer from non-small cell lung cancer is around 85% of the total lung cancer population. Traditional treatment methods use radiation, chemotherapy, immunotherapy, surgery, and/or a combination to treat lung cancer. The issue with these traditional drugs is the non-specific toxicity caused at other healthy sites which causes side effects such as nausea, hair loss, etc. New advancements in science opened an avenue called nanodrug drug delivery system to make therapeutics 1-100 nm in size to increase bioavailability and specificity. In this review article, we discuss a promising nanodrug delivery system, liposomes, to target NSCLC for its treatment.

Keywords: Nanotechnology advances, Liposomes, Nano drug delivery systems, cancer cells, Abnormal cell growth, Lung cancer, Nanomedicine, Neo-adjuvant therapy

Introduction

Cancer is the second leading cause of death in the United States. The World Health Organization defines cancer as large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs [1]. Around 1.9 million new cancer cases and 609360 deaths are estimated to be diagnosed in the United States in the year 2022.

Lung cancer accounts for 236,740 new cases and 130,180 deaths [2]. There are two different types of lung cancer - small cell and non-small cell. Approximately 85% of the patients suffer from non-small cell lung cancer (NSCLC) and the rest from small cell lung cancer (SCLC). NSCLC is further categorized into adenocarcinoma, squamous cell carcinoma and large cell. The causes of lung cancer are mostly due to smoking, exposure to radon gas, secondhand smoking, exposure to asbestos, metals like chromium, arsenic, radiation, air pollution and diesel exhaust. The symptoms include continuous cough, blood-streaked sputum, bronchitis, shortness of breath and chest pain.

Nanomedicine is a branch of nanotechnology that uses materials that have the size between 1-100 nm. Nanomedicine can help in increasing bioavailability, efficacy, specificity and sustained release. The advantages of using nanoscale materials can be attributed to its high surface area to volume ratio. Several nano drug delivery systems have been developed to treat NSCLC. Nanodrug delivery system can be classified into liposomes, micelles, dendrimers, solid lipid nanoparticles and polymeric nanoparticles. In this review article, we will discuss the traditional treatment methods, challenges and liposomes as a solution to treat non-small cell lung cancer.

Tumor heterogeneity is one of the main challenges posed by cancer cells [3]. It may affect the efficacy of the drugs. Cancer cells undergo their own divergent evolution during metastasis and create a unique metastatic tumor at another site. It is important to keep in mind the heterogeneity to simultaneously target multiple sites and pathways while treating cancer. This challenge can be overcome by decorating the surface of the liposome with antibodies that target specific pathways.

Molecular mechanism of NSCLC

Mutations causing cancer resulted in resistance to cell death, cellular proliferation and angiogenesis [4]. A number of somatic mutations occur in NSCLC. The mutation frequency is observed higher in smokers compared to non-smokers. These mutations occur at gene encoding signaling protein level. The mutated genes are usually *EGFR, FRFR1, KRAS, PIK3CA, ERBB2, BRAF, ALK, ROS1, MAPK2K1, RET1, NRAS* and *AKT. TP53* mutation contributed to 50% of the mutations in adenocarcinoma.

Copy number mutations involve *NKX21-, TERT, MDM2, KRAS, EGFR, MET, CCNE1, TERC* and *MECOM. EGFR* mutation contributed to 22% of copy number alteration. *TP53, KEAP1, STK11* and *EGFR* play an important role in tumor initiation.

RTK/RAS/RAF pathway, PI3K-mTOR pathway, p53 pathway, cell cycle, chromatin pathways and RNA splicing pathway showed alternation in the biochemical reactions. *PI3KCA* and *STK11* genes are associated with PI3K pathway biochemical alteration. SWI/SNF multiprotein complex mutation is observed in lung carcinoma that affects the chromatin remodeling pathway. Understanding these mutations is important for targeting the checkpoint inhibitors for therapeutic purposes.

Traditional Treatment Strategies

Surgery

Stage I and stage II patients are treated with surgical resection. Lobectomy, where a single lobe is resected, is performed in patients with early-stage NSCLC. The surgical approach to treat NSCLC differs from one patient to another.

Neoadjuvant therapy

Neo-adjuvant therapy is useful to treat early treatment of metastasis and down staging the tumor. This allows for the tumor to be completely resected and improves tolerability.

Adjuvant therapy

After surgery that can get rid of most of the cancer the sites to which the tumor may have metastasized can fail. Adjuvant therapy is used in such cases. It mostly comprises of a cisplatin-based combination regimen. There are reports that indicate survival benefits of adjuvant therapy in patients with stage II and stage IIIA cancer [5].

Chemotherapy

Platinum doublet like carboplatin or cisplatin with gemcitabine, vinorelbine, paclitaxel or docetaxel is indicated as standard treatment methods for patients with metastasis [6].

Targeted therapy

Monoclonal antibodies and tyrosine kinase inhibitors (TKI) can be used to target Epidermal Growth Factor Receptor (EGFR). Erlotinib, gefitinib and Osimertinib are some examples of EGFR TKIs [7].

Liposomal drug delivery system to treat NSCLC

Parvathaneni et al [8] showed pirfenidone-loaded liposomes were effectively taken up by the cancer cells and showed significant cytotoxicity. The research group was able to synthesize a liposomal formulation of size 211.8 ± 12 nm with near to 100% drug en-

trapment. Due to its positively charged surface, they were quickly internalized by the cells. The drug delivery system reduced cellular interaction, migration and single-cell tumor development. Park et al [9] synthesized pH sensitive liposomes that were loaded with doxycycline and docetaxel that targets the folate receptor B. The liposomes used the acidic tumor environment to their advantage and released docetaxel that was cytotoxic to the tumor. Folate helped in cellular internalization. Doxycycline had a synergistic effect with docetaxel that helped in decreasing cell proliferation, migration and angiogenesis. Kong et al [10] developed a multifunctional liposome with multiple layers loaded with drugs Vinorelbine and Dioscin. Matrix Metalloprotease enzymes cleave the peptide attached to the surface of the liposome and expose cell-penetrating peptide. After internalization, dioscin helps inhibit tumor metastasis and neovascularization. Vinorelbine had cytotoxic effects on the tumor cells. A combination of dioscin and vinorelbine showed dose-dependent cytotoxicity. Animal studies also showed inhibitory effects on tumor growth due to the multifunctional liposomes. Liposomes can be used to encapsulate hydrophobic and hydrophilic drugs. Karpuz et al [11] encapsulated hydrophobic paclitaxel and hydrophilic vinorelbine in their radiolabeled liposomes. The liposomal formulations were used to diagnose and treat NSCLC cell lines. The radiolabeled liposomes acted as an effective alternative to conventional imaging techniques and treatment strategies. Application of Tyrosine Kinase inhibitors and immunotherapy are reported to be successful in treating NSCLC. Epirubicin, an isomer of doxorubicin, is an anticancer drug which has lower toxicity than doxorubicin. Kong et al [12] co-delivered RPV-modified epirubicin and doxorubicin loaded liposomes. The liposomes had an approximate size of 100 nm. The RPV peptide helped in enhancing the cellular drug uptake. Results indicated that the RPV-modified liposomes with epirubicin and dioscin showed cytotoxic effects and inhibited formation of vasculogenic mimicry channel. The biodistribution studies showed higher accumulation in tumor site compared to liver, spleen and kidneys and necrosis of tumor cells were observed in tumor bearing mouse. Sawant et al [13] developed inhalable Osimertinib loaded liposome and found that it had lower IC50 value compared to free drugs. They found out their liposomal formulation was able to stop tumor migration and colonization. Their 3D tumoroid studies showed tumor growth inhibition after treatment with the liposomal formulation. The formulation showed aerosolization performance with fine particle fraction of 82%. Zhang et al [14] used inorganic nanoparticles that are sensitive to pH to develop a sustained release nanoliposome. Gefitinib and bevacizumab were encapsulated in the liposomes to offer anti-cancer activity. MnO_2 had pH and glutathione responsiveness which increased the anticancer efficacy. The liposomes showed biocompatibility in vitro and inhibited tumor growth in vivo. Thymoquinone, an anti-cancer drug, has poor solubility in aqueous solution. Khan et al [15] constructed a polyethylene glycol (PEG) coated liposome encapsulation thymoquinone. Molecular docking shows it has high affinity to Hsp90 protein. The encapsulation efficiency of liposomes was 96% with a size of 120nm. The liposomes had high cytotoxic effects compared to free drug. In vivo data suggest a 9-fold increase in the LD_{50} of liposomes compared to free thymoquinone.

Conclusion

Liposomal drug delivery systems can be used to carry both lipophilic and hydrophilic drugs. The liposomes are shown to release the drugs in a controlled and sustained manner to increase the bioavailability of the drugs in the system. The liposomal surface can also be decorated with targeting moieties to increase the specificity of the drug delivery system, thus reducing the side effects of naked drugs due to non-specificity. In conclusion, the liposomal drug delivery system is an effective way to treat non-small cell lung cancer.

References

1. Cancer, World Health Organization (2022).
2. Cancer Facts & Figures 2022, American Cancer Society (2022).
3. Wang X and Adjei AA. "Lung cancer and metastasis: new opportunities and challenges". Cancer and Metastasis Reviews 34.2 (2015): 169-171.
4. Testa U, Castelli G and Pelosi E. "Lung Cancers: Molecular Characterization, Clonal Heterogeneity and Evolution, and Cancer Stem Cells". Cancers 10.8 (2018): 248.
5. Pignon JP., et al. "Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group". In Database of Abstracts of Reviews of Effects (DARE): Quality-Assessed Reviews. Centre for Reviews and Dissemination (UK) 26.21 (2008):

3552-9.

6. Soria JC., et al. "Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer". New England journal of medicine 378.2 (2018): 113-125.
7. Duma N, Santana-Davila R and Molina JR. "Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment". Mayo Clinic Proceedings 94.8 (2019): 1623-1640.
8. Parvathaneni V., et al. "Systematic Development and Optimization of Inhalable Pirfenidone Liposomes for Non-Small Cell Lung Cancer Treatment". Pharmaceutics. MDPI AG 12.3 (2020): 206.
9. Yong Il Park., et al. "pH-sensitive multi-drug liposomes targeting folate receptor β for efficient treatment of non-small cell lung cancer". Journal of Controlled Release 330 (2021): 1-14.
10. Kong L., et al. "Tumor Microenvironmental Responsive Liposomes Simultaneously Encapsulating Biological and Chemotherapeutic Drugs for Enhancing Antitumor Efficacy of NSCLC". International journal of nanomedicine 15 (2020): 6451-6468.
11. Merve Karpuz., et al. "Design and in vitro evaluation of folate-targeted, co-drug encapsulated theranostic liposomes for non-small cell lung cancer". Journal of Drug Delivery Science and Technology 57 (2020): 101707.
12. Kong L., et al. "RPV-modified epirubicin and dioscin co-delivery liposomes suppress non-small cell lung cancer growth by limiting nutrition supply". Cancer Sci 111 (2020): 621-636.
13. Sawant SS., et al. "Pulmonary delivery of osimertinib liposomes for non-small cell lung cancer treatment: formulation development and in vitro evaluation". Drug Deliv. and Transl. Res 12 (2022): 2474-2487.
14. Jisong Zhang., et al. "The combination of MnO2@Lipo-coated gefitinib and bevacizumab inhibits the development of non-small cell lung cancer". Drug Delivery 29.1 (2022): 466-477.
15. Khan A., et al. "Safety, Stability, and Therapeutic Efficacy of Long-Circulating TQ-Incorporated Liposomes: Implication in the Treatment of Lung Cancer". Pharmaceutics 14.1 (2022): 153.

Volume 4 Issue 1 January 2023