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The Role of Nanotechnology in Improving Drug Delivery For Lung Cancer

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Abstract

Lung cancer remains one of the deadliest cancers globally, highlighting the urgent need for effective treatment strategies, the aim in this research the potential of nanotechnology in revolutionizing lung cancer treatment, focusing on inhalation chemotherapy and targeted drug delivery systems. The research begins by outlining the characteristics and challenges of lung cancer, emphasizing the importance of early detection and personalized treatment approaches. It then delves into the application of nanotechnology in medicine, specifically highlighting the advantages of nanocarriers for drug delivery, through a field visit to the National Cancer Institute in Misrata, it was found that the total number of cancer cases reached 1,086 between January and June 2024, The number of male cases was 571, while female cases numbered 515. It is worth noting that there were 95 cases of lung cancer, 80 of which were among males and 15 among females, the most affected age group was those over the age of sixty, Data obtained from the institute indicated that the stage of disease detection for the majority of patients was either unrecorded or possibly unknown. It was also noted that the diagnosis of these cases was not accurate in determining whether the cancer was of the NACLC or SCLC type, The research also explores the development of inhalable formulations for lung cancer treatment, emphasizing the advantages of direct and non-invasive drug delivery to the lungs, leading to improved bioavailability and therapeutic index. The research concludes by highlighting the immense potential of nanotechnology in improving lung cancer treatment outcomes, emphasizing the need for continued research and development of sophisticated nanocarriers capable of effectively targeting and treating lung cancer. This advancement holds promise for improving patient survival rates and quality of life.

Introduction

Lung cancer, recognized as the most common and serious type of cancer, has spurred intense research efforts to develop effective therapeutic approaches. The past decade has witnessed significant advancements in drug delivery systems based on nanotechnology. This has led to a surge in interest among researchers in chemotherapy and targeted delivery via

nanocarriers, Nanocarriers, due to their unique properties, offer several advantages over conventional drug delivery methods. Their small size allows them to penetrate tissues and reach target cells more efficiently, enhancing drug accumulation at the tumor site. This targeted delivery minimizes systemic toxicity and improves therapeutic efficacy.

The global cancer burden is notable, with millions of new cases and deaths annually, Lung cancer stands out as a significant health issue, contributing significantly to cancer-related deaths. Table 1 displays information on cancer incidence and mortality in 2022, categorized by new cases and deaths, It emphasizes the dominance of lung cancer as the most widespread cancer globally in 2022, emphasizing the necessity for ongoing research and initiatives to tackle this worldwide health crisis[1].

***Source*: GLOBOCAN 2022.**

The table presents 2022 data on cancer incidence and mortality globally, Lung cancer had the highest new cases and deaths at 2,480,301 and 1,817,172 respectively, representing 12.4% of new cases and 18.7% of deaths. Female breast cancer followed with 2,308,897 cases and 665,684 deaths, accounting for 11.6% of cases and 6.9% of deaths, Colorectal cancer ranked third with 1,926,118 cases and 903,859 deaths (9.6% of cases, 9.3% of deaths), Prostate cancer was fourth with 1,466,680 cases and 396,792 deaths (7.3% of cases, 4.1% of deaths), Stomach cancer and liver cancer had 968,350 and 865,269 cases, and 659,853 and 757,948 deaths respectively, These statistics highlight the global cancer burden, where lung cancer leads in fatalities, while breast cancer shows lower mortality, possibly due to early detection and advanced treatment options. [1].

Causes of lung cancer: Cancer is a complex disease caused by uncontrolled growth and division of abnormal cells due to gene mutations, As a result of mutational changes, cancer cells exhibit certain characteristics including proliferation, resistance to signals that inhibit their growth and resistance to apoptotic signals that cause cell death, which make it difficult to treat the disease [3].

lung cancer is commonly related to smoking and is thus often classified as a social disease with an associated stigma attached. The majority (85 %) of cases of lung cancer are due to long-term tobacco smoking, These cases are often caused by a combination of genetic factors and exposure to radon gas, asbestos, second-hand smoke, or other forms of air pollution. Contrary to popular belief, lung cancer also affects non-smokers and about 10–15% of cases occur in people who have never smoked, For example, in women only 65% of cancer deaths are a result of smoking, with lung cancer killing more women than breast, ovarian and uterine cancers combined. Regardless of cause, death from lung cancer is high; with less than 10% of those diagnosed surviving for 5 years [2].

Symptom of lung cancer:

The most frequent symptoms described in the literature (although with variations according to the study in question) are persistent cough, hemoptysis, chest pain, dyspnea, cervical or supraclavicular lymphadenopathies, weight loss, metastatic pain, fatigue and fever [4].

type of lung cancer:

lung cancer is divided into two main types according to the characteristics of the disease and the response to therapy (Figure 2- 2).

1- Non-small cell lung cancer (NSCLC) can be located in the mid-chest, but it is also found in other parts of the lung. According to the current World Health Organization classification.
2- small cell lung carcinomas (SCLC) is typically more centrally located in lungs [5].

Accounting for about 85% of all lung cancer cases, NSCLC is the most common of the two types while the remaining 15 % are small cell lung cancer [6], Clinical staging and identification of the histological type are essential to finding the best therapeutic strategy for treating such patients. Therefore, the classification of lung cancer into SCLC and NSCLC was necessary for treatment of patients with lung cancer in hospital routine practice [7].

treatment of lung cancer:

Standard treatment for cancer includes combinations of surgery, radiation and chemotherapy, Other treatment options include hormonal therapy and targeted therapy (including immunotherapy such as monoclonal antibody therapy), The choice of therapy depends upon the location, grade of the tumor and the stage of the disease. Over the last decade a number of potent anticancer drugs have been developed with various mechanisms of action such as blocking nucleic acid biosynthesis, interfering with gene transcription, causing cell cycle arrest, inducing apoptosis, and inhibiting angiogenesis [8].

The conventional therapies for the management of lung cancer include chemotherapy and radiation therapy, as well as a combination of both. The different kinds of traditional treatment modalities for lung cancer management are shown in Figure (2-4) [7]

Metastatic cancer, such as lung cancer, can be managed with various treatment approaches, including systemic therapy (chemotherapy, biological therapy, targeted therapy, and hormonal therapy), local therapy (surgery, radiation therapy), or a combination of these modalities, The selection of treatment options is influenced by factors such as the primary cancer type (size, location, and number of metastatic tumors), the patient's overall health and age, and the cancer stage, Treatment goals may aim for a cure (complete eradication) or focus on palliative care to alleviate pain and improve the quality of life for the patient, It is reported that more than one type of therapy is prescribed to enhance the effects of the primary therapy and is referred to as adjuvant therapy, Examples of such therapy include chemotherapy or radiotherapy, which are administered after surgical removal of tumors to destroy any remaining unwanted cells. [9].

Materials and Methods

Nanotechnology:

Nanotechnologies are the design, characterization, production, and application of structure, devices, the systems by controlling shape and size at the nanometer scale. [10]

Nanotechnology in medicine and healthcare

Nanomedicine is the term used to refer to the applications of nanotechnologies in medicine and healthcare. Specifically, nanomedicine uses technologies at the nanoscale and Nano-enabled techniques to prevent, diagnose, monitor and treat diseases. Nanotechnologies exhibit a significant potential in the field of medicine, including in imaging techniques and diagnostic tools, drug delivery systems, tissue-engineered constructs, implants and pharmaceutical therapeutics, and has advanced treatments of several diseases, including cardiovascular diseases, cancer, musculoskeletal conditions, psychiatric and neurodegenerative diseases, bacterial and viral infections, and diabetes.[2.10]

Classification of existing inhalation formulations

Compared with traditional routes of drug administration, inhalation-based lung cancer treatment offers promising prospects due to its direct and non-invasive drug delivery to the lungs, elimination of first-pass metabolism in the liver, targeted effects, and reduced potential for systemic toxicity[11.12], Integration of nanosystems like lipid nanoparticles (LNPs), polymer nanoparticles, or inorganic nanoparticles with inhalation-based drug delivery further enhances the bioavailability, stability, and lung-targeting residence of anticancer drugs, thereby

improving the therapeutic index of cancer treatment [13], However, it is crucial to note that not all drugs are suitable for inhalation-based administration[11], The efficacy of drugs greatly depends on the size, lipophilicity, and surface modifications of nanoparticles. To ensure that nanoparticles are not cleared by respiratory airflow, mucus, or alveolar macrophages, it is essential to control the surface cationic charge and achieve a lung residence time by constructing nanoparticles with a calculated logP<0 and a size range 100-150 nm, which represents an optimal choice for pulmonary delivery, Currently various inhalable formulations have been developed, including drug nanoparticles, nanocarrier delivery systems, and antibody-drug conjugate systems incorporating nanoparticles. [14.15]

Nanoscale drug particles, created by processing raw materials into particles of nanometer dimensions, are formulated for delivery to the respiratory tract through inhalation devices like dry powder inhalers and nebulizers [16], With sizes ranging from 1-100 nm, these particles offer a larger surface area-to-volume ratio and enhanced biological activity, effectively increasing the contact between the drug and the respiratory mucosa, thereby prolonging the residence time within the airways [17], the construction of nanoscale particles helps in effectively avoiding impaction in the upper respiratory tract and enables deeper deposition into the lungs, while also evading engulfment by alveolar macrophages [18], Local administration via inhalation devices has shown efficacy in preclinical models of lung cancer, with a focus on small molecular drug compounds [19.20], Concurrently, several monoclonal antibodies (mAbs) such as bevacizumab and trastuzumab have gained approval for intravenous administration in treating non-small cell lung cancer (NSCLC) [21.22].

Shepard *et al* [23] developed a physically stable and biologically active dry powder formulation of bevacizumab, an anti-VEGF monoclonal antibody (mAb), with aerosol characteristics suitable for deep lung tissue penetration, maintaining excellent stability for at least 6 months at room temperature. The bioactivity of the anti-VEGF mAb remains unaffected by the manufacturing process, resulting in a 10-fold reduction in the effective dose compared to the intravenous injection control group, Maillet *et al* [24] demonstrated the use of a cloud of cetuximab aerosol particles for local lung cancer treatment, utilizing both mesh and jet nebulizers while preserving their immunological and pharmacological characteristics. They also conducted pharmacokinetic analyses showing rapid accumulation of mAb concentrations in normal and cancerous lung tissues after aerosolization, with concentrations twice as high as those achieved through intravenous administration[25], Brunaugh *et al* [26] optimized aerosol conditions in particle engineering processes to assess the impact of freeze-drying on mAb stability and aerosol performance, demonstrating the feasibility of inhaled mAb dry powder formulations, Cortez-Jugo *et al* [27] introduced a portable acoustic microfluidic device capable of nebulizing epidermal growth factor receptor mAbs into a fine aerosol mist with a mass median aerodynamic diameter of approximately 1.1 μm, ensuring stable and active delivery for deep lung deposition.

Nanoparticle drug delivery systems (NDDS) are advanced delivery systems that utilize nanotechnology in their preparation. These systems utilize nanoparticles as carriers to encapsulate drugs either internally or on their surface, enabling precise drug delivery to target tissues or cells through targeted and controlled release mechanisms. NDDS offer several advantages. Firstly, due to their small size, nanoparticles can easily cross biological barriers, enhancing the bioavailability and therapeutic effectiveness of drugs. Secondly, NDDS allow for targeted delivery by utilizing surface modification or specific bioactive ligands, ensuring accurate drug delivery to diseased tissues or target cells while minimizing harm to normal cells

[28], Moreover, NDDS facilitate controlled drug release, extending their presence in the body and providing more stable and sustained drug effects.[29].

Types of nanoparticles

To date, several nanoparticles and nanomaterials have been investigated and approved for clinical use. Some common types of nanoparticles are discussed below [2].

Liposomes

Liposomes are spherical vesicles with particle sizes ranging from 30 nm to several microns, that consist of lipid bilayers. Liposomes can be used to incorporate hydrophilic therapeutic agents inside the aqueous phase and hydrophobic agents in the liposomal membrane layer. Liposomes are versatile; their surface characteristics can be modified with polymers, antibodies and/or proteins, enabling macromolecular drugs, including nucleic acids and crystalline metals, to be integrated into liposomes, Poly ethylene glycol (PEG), ylated liposomal doxorubicin is the first FDA-approved nanomedicine, which has been used for treatment of breast cancer, and it enhances the effective drug concentration in malignant effusions without the need to increase the overall dose [4].

Dendrimers are macromolecules with branched repeating units expanding from a central core and consists of exterior functional groups, Polyamidoamine dendrimer-DNA complexes (called dendriplexes) have been investigated as gene delivery vectors and hold promise in facilitating successive gene expression, targeted drug delivery and improve drug efficacy, dendrimers are promising particulate systems for biomedical applications, such as in imaging and drug delivery, due to their transformable properties [30,31].

Carbon nanotubes

Carbon nanotubes are cylindrical molecules that consist of rolled-up sheets of a single-layer of carbon atoms (graphene), They can be single-walled or multi-walled, or composed of several concentrically interlinked nanotubes, Due to their high external surface area, carbon nanotubes can achieve considerably high loading capacities as drug carriers.[32]

Metallic nanoparticles

Metallic nanoparticles include iron oxide and gold nanoparticles. Iron oxide nanoparticles consist of a magnetic core (4-5 nm) and hydrophilic polymer, Metallic nanoparticles have been used as imaging contrast agents in laser-based treatment, as optical biosensors and drug delivery vehicles. [33]

Polymeric nanoparticles

Polymeric nanoparticles are versatile nanoparticles used for delivering anticancer drugs due to their adaptable design that meets various application requirements, Typically, biocompatible and biodegradable polymers are chosen as starting materials in design protocols to prevent or minimize systemic inflammation and facilitate material removal post drug release, The particle formation process is crucial in polymeric nanoparticle design, as the drug is integrated into the biocompatible polymer to ensure a uniform drug distribution within the particle, This uniform distribution is essential to ensure each particle contains the same drug content while reducing drug leaching from the particle. Polymeric nanoparticles exhibit significant potential in delivering both hydrophobic and hydrophilic drugs. In the realm of lung cancer treatment, a few polymeric nanoparticles have been developed with some already having filed for patents. [8]

Discussion and Results

During a field visit to the National Cancer Institute in Misrata, Libya, statistics from January to June 2024 revealed that the total number of cancer patients across different cases was 1086,

with 571 male patients and 515 female patients. Specifically, there were 95 cases of lung cancer, with 80 male patients and 15 female patients. It is worth noting that the number of male cases is significantly higher than female cases, which contradicts international studies in this field regarding this disease, furthermore, the age group most affected by this disease had an average age above 60 years, aligning with global studies. It is essential to mention that the majority of detected lung cancer cases have unknown stages of detection and the type of cancer cells. This information significantly impacts treatment options.

Notably, Non-Small Cell Lung Cancer (NSCLS) is present in cases across various age groups, characterized by a higher cure rate compared to others.

Statistics indicate that most cases of lung cancer identified at the National Cancer Institute in Misrata, Libya, have not had their detection stages and cancer cell types precisely determined. The file suggests that Non-Small Cell Lung Cancer (NSCLS) is present in various age groups, with a higher cure rate compared to other lung cancer types.

Table 1: Lung Cancer Tops Global Cancer Prevalence in 2022

Cancer Type	New Cases (Number)	New Cases (%)	Deaths (Number)	Deaths (%)
Lung Cancer	**2,480,301**	**12.4%**	**1,817,172**	**18.7%**
Female Breast Cancer	2,308,897	11.6%	665,684	6.9%
Colorectal Cancer	1,926,118	9.6%	903,859	9.3%
Prostate Cancer	1,466,680	7.3%	396,792	4.1%
Stomach Cancer	968,350	4.9%	659,853	6.8%
Liver Cancer	865,269	4.3%	757,948	7.8%

Source: GLOBOCAN 2022.

Nanotechnology and cancer treatment

Staggering numbers of individuals suffer from cancer worldwide, highlighting the need for an accurate detection method and novel drug delivery system that is more specific, efficient and exhibits minimal side effects, Anticancer treatments are often regarded as superior if the therapeutic agent can reach the specific target site without resulting in any side effects, Chemical modifications of the surface of nanoparticle carriers may improve this required targeted delivery, one of the best examples of modifications at the surface of nanoparticles is

the incorporation of PEG or polyethylene oxide, these modifications enhance not only the specificity of drug uptake, but also the tumor-targeting ability, Incorporating PEG avoids the detection of nanoparticles as foreign objects by the body's immune system, thus allowing them to circulate in the bloodstream until they reach the tumor, Additionally, the application of hydrogel in breast cancer is a prime example of this innovative technology, Herceptin is a type of monoclonal antibody used in breast cancer treatment by targeting human epidermal growth factor receptor 2 (HER2) on cancer cells. A vitamin E-based hydrogel has thus been developed that can deliver Herceptin to the target site for several weeks with just a single dose, due to the improved retention of Herceptin within the tumor, the hydrogel-based drug delivery is more efficient than conventional subcutaneous and intravenous delivery modes, thus making it a better anti-tumor agent. Nanoparticles can be modified in several ways to prolong circulation, enhance drug localization, increase drug efficacy and potentially decrease the development of multidrug resistance through the use of nanotechnologies.[34.35]

Conclusion

This review addresses lung cancer, its causes, symptoms, and treatments, along with statistics from the National Cancer Institute in Misrata, focusing on the role of nanotechnology in enhancing therapeutic efficacy. Lung cancer represents a significant global burden as the leading cause of cancer-related deaths worldwide. According to the National Cancer Institute, 95 cases of lung cancer were reported from January to June of this year, with 80 cases among men and 15 among women, Despite advancements in surgery, radiation, and chemotherapy, targeted therapies remain essential, Nanotechnology shows promise by offering unique properties for targeted drug delivery, reducing toxicity, and improving effectiveness, many nanocarriers such as liposomes and metallic nanoparticles have potential in lung cancer treatment, Challenges remain in nanoparticle dispersion, necessitating further research for optimal design and delivery methods. Ultimately, nanotechnology-based drug delivery systems hold immense promise for enhancing lung cancer treatment and patient outcomes.

Although the National Institute for Cancer Treatment in Misrata is the largest cancer treatment center in the central region of Libya, it will not be able to utilize this technology in the near future due to the following reasons:

- The high cost of acquiring the technology.
- The lack of appropriate treatments that can be used in conjunction with this technology.

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استخدام تقنية النانو في توصيل العلاج لسرطان الرئة

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الكلمات المفتاحية:
سرطان الرئة غير صغير الخلايا.
سرطان الرئة صغير الخلايا.
تقنية النانو تكنولوجي.

الملخص

يضل سرطان الرئة أحد الأمراض القاتلة عالمياً، حيث تتضح الحاجة إلى إيجاد دواء عاجل مشدداً على طريقة إيصال الدواء للمريض عن طريق الأدوية التي تؤخذ عن طريق الاستنشاق، مؤكداً على أهمية اكتشاف المريض في وقت مبكر، حيث يعتبر سرطان الرئة أكثر أنواع السرطان التي تصيب الرجال أكر من النساء، حيث أجريت هذه الدراسة في المعهد القومي لعلاج الأورام في مدينة مصراتة في الفترة ما بين يناير إلى يونيو 2024م، تم من خلالها إحصائية عدد حالات السرطانات عامةً في هذه الفترة حيث كانت 571 ذكور، 515 إناث، وكان عدد حالات سرطان الرئة 95 حالة، منها 80 رجال و15 نساء، خصوصاً في عمر الستين، ويوجد منه نوعان هما: **N.S.C.L.C** سرطان الرئة غير صغير الخلايا، و **S.C.L.C** سرطان الرئة صغير الخلايا.
حيث تحاول هذه الدراسة إظهار الدور الخفي لتقنية النانو تكنولوجي في إيصال الدواء للمريض دون استخدام الجراحة، إلا أن تشتت جزئيات النانو داخل جسم المريض يمثل تحديًّا كبيراً.