ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

Application of nano drug delivery system in targeted treatment of lung adenocarcinoma bone metastasis

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Abstract: *Nanomedicine delivery, as a multi-lineage and multi-functional designable targeted therapy technology, highlights potential research value in the field of nanomedicine. Nanotechnology can deliver drugs to lesions through specific targeted sites, improve drug efficacy and selectivity, as well as diagnosis through disease marker molecules, and allow integrated nanotechnology to integrate diagnostic and therapeutic functions, enable real-time and accurate diagnosis of the disease and simultaneous treatment, while monitoring efficacy and adjusting the dosing regimen, which provides a brand-new possibility exploration in the diagnosis or treatment of human chronic diseases and malignant tumors. In this paper, the characteristics of lung adenocarcinoma and its current treatment methods are analyzed by literature review and research statistics, and the design concept, targeted therapy mechanism, drug release mode of nanomedicine delivery system (NDDS) and its preclinical and clinical research progress in the treatment of lung adenocarcinoma are further described, and the challenges faced by nanomedicine in clinical translation are discussed. We provide new perspectives in improving cancer treatment options and developing more effective nanomedicines.*

Keywords: *Nanomedicine delivery system NT (Nanotechnology), Targeted therapy, Lung adenocarcinoma bone metastasis*

1. Introduction

With the continuous progress of scientific and technological and medical screening as well as medical and radiation oncology treatment, people pay increasing attention to the prevention, control treatment of lung diseases. However, lung cancer remains the most common cause of cancer death worldwide, with adenocarcinoma being the most common histological subtype of primary lung cancer[1].Although traditional chemotherapy and radiotherapy are able to inhibit tumor growth to some extent, they also cause damage to normal cells[2] .On the other hand, because lung adenocarcinoma itself has some occult many lung adenocarcinomas are diagnosed at an advanced stage[3], at this time if cancer cells spread to other organs, it will cause difficulties in treatment. In addition, resistance to chemotherapeutic agents has always been a problem that biomedical workers continue to explore and study[4], and lung cancer patients may have multiple genetic mutations, which complicates targeted therapy. Although immunotherapy has achieved good results in the treatment of lung adenocarcinoma and brought new hope to patients with lung adenocarcinoma, some patients are not suitable for immunotherapy due to individual differences. For example, patients with EGFR/ALK driver gene positive or low or negative PD-L1 expression may not respond well to immunotherapy[5],[6], and with the development of nanotechnology, nanomedicines have shown great potential and advantages as targeted drug delivery systems in lung cancer treatment. Nanomedicines can address classical chemoresistance by modulating components, functionalizing surfaces, encapsulating various active therapies, and combining multiple treatments using a single nanoparticle platform, and can reactivate the immune system and inhibit tumor growth by directly targeting the immunosuppressive microenvironment. For example, it attenuates hypoxia and downregulates the expression of immunosuppressive PD-L1 molecules through nanomodulators and activates immune cells to prevent

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

the proliferation of tumor cells[7],[8].Based on the rapid development of nanomedicine science and nanodelivery technology, multidisciplinary cooperation and the gradual deepening of the application of artificial intelligence technology, this paper leads to the exploration of brand-new possibilities for the detection and treatment of cancer in the future nanodelivery technology in the treatment of lung adenocarcinoma and even other diseases in the form of multifunctionality, diversification and cell individualization[9].

2. Characteristics of lung adenocarcinoma

Lung adenocarcinoma (LUAD) is a common type of thoracic tumor with poor prognosis and high mortality. The exact pathogenesis is not yet fully understood, but a potential factor in lung adenocarcinoma development may be associated with DNA methylation, leading to changes in chromosome structure[10].It causes abnormal proliferation or qualitative change of normal lung tissue and even metastasis to other organs of the body, of which metastasis to bone tissue is common. According to Don X Nguyen et al.[11], they concluded that activation of the WNT/TCF pathway is a determinant of brain and bone metastasis during lung adenocarcinoma progression, and that the WNT/TCF target genes HOXB9 and LEF1 are mediators of chemotactic invasion and colony growth, and their unique signaling program enhances the ability of lung adenocarcinoma cells to colonize bone and brain. In Huang L et al[12] study, among the cancer driver genes they detected, the first five mutations in EGFR (7/15), TP53 (7/15), ROS1 (3/15), IDH2 (2/15), and SYNE1 (2/15) were mutated in patients with lung adenocarcinoma, while EGFR (7/15), TP53 (5/15), ADGRL3 (2/15), APC (2/15), and KMT2C (2/15) were mutated in patients with bone metastases, and KMT2C gene alternans were only observed in bone metastases compared with patients with lung adenocarcinoma, indicating that the difference in oncogenic gene mutations between lung adenocarcinoma and bone metastases may be biomarkers to predict cancer spread, which provides a new idea for early intervention and targeted therapy of lung adenocarcinoma.

3. Lung adenocarcinoma treatment

In the latest guidelines issued by the World Health Organization (WHO)[13], lung cancer is divided into two subtypes according to histological classification characteristics: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for more than two-thirds of the total cases, with high occult nature, and most patients (84%) have advanced disease at the time of diagnosis and treatment[3].At present, the treatment of non-small cell lung cancer (NSCLC) is mainly based on the pathological type and stage of lung tissue and the patient 's physical condition, and scientific personalized treatment options are adopted, including surgical treatment, radiotherapy, chemotherapy, immunotherapy, traditional Chinese medicine treatment, and drug targeted therapy. It is worth noting that, according to Howlader N et al[14], from 2013 to 2016, the population mortality rate of non-small cell lung cancer in the United States decreased dramatically, and the survival rate increased substantially after diagnosis and treatment, and the reduction in its morbidity and mortality may be related to the approval and use of targeted therapy. Some LUAD patients can benefit from specific agents that target multiple genetic loci, such as EGFR, ALK, ROS1,etc[15],because targeted drugs tend to identify carcinogenic sites in the body, targeted therapy specifically acts on the lesion at the cellular and molecular levels to kill tumor cells[16].The main mechanisms of action include preventing or shutting down chemical signals that control the growth and division of cancer cells[17],[18], destroying the protein structure in cancer cells, thereby causing cancer cell death[19], inhibiting the angiogenesis of feeding cancer cells[20], and stimulating the immune system to attack cancer cells to induce anti-tumor responses [21].According to Khalil et al[22], up to 50% of lung adenocarcinoma patients have EGFR mutations, most commonly in-frame exon deletions and the missense mutation L858R, resulting in a tyrosine kinase (TK) domain that is provoked and drives tumorigenesis. In the last five years (2018–2023), EMA has authorized the use of targeted therapy for four other molecular biomarkers in advanced NSCLC. These include the NTRK fusion targeted by larotrectinib and entrectinib, RET fusion targeted by selpercatinib and pralsetinib, KRAS G12C mutation targeted by sotorasib, and MET exon 14 skipping mutation targeted by tepotinib and capmatinib[23].In addition, Sun Z et al[24] concluded that serum miR-4433a-3p levels were significantly correlated with clinical stage, and miR-4433a-3p could be used as a biomarker for early diagnosis and monitoring treatment outcomes in lung adenocarcinoma. Although drug-targeted therapy for NSCLC provides a good treatment option for many patients, significant challenges remain as most NSCLC patients experience the development of drug resistance and disease progression[25].Many

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

researchers have carried out various explorations and studies on the development of drug resistance and drug toxicity of targeted drugs. In recent years, due to the rise of nanotechnology, Nanodelivery systems have made breakthrough progress in targeted therapy of cancer. According to Gao F et al[26], hyaluronic acid (HA) -modified nanoparticle hollow manganese dioxide (HMnO2) was used to encapsulate and deliver enzalutamide and MK-8776, and HMnEampampH was found to have a more significant tumor growth inhibition effect than simply adding enzalutamide and MK-8776 without carriers. In addition, Zhang M et al[27] prepared a targeted drug delivery system using mesoporous silica nanoparticles (MSN) and found that after MSN-HA/Dox was preferentially absorbed by cancer cells through receptor-mediated endocytosis, the drug release further enhanced the efficacy by replacing desulfobiotin with intracellular biotin. Nanoparticles (NP) are colloidal carriers ranging in size from 1 to 1000 nm, and the main advantages of using NPs to participate in drug delivery in targeted cancer therapy are high specificity, efficiency, stability, and low overall toxicity[28], and have received much attention because of their good characteristics in cancer therapy, and many nanocarriers are used for drug delivery, including metal and inorganic nanoparticles, polymer nanoparticles, viral nanoparticles, liposomal nanoparticles, and biomimetic nanoparticles.

3.1. Advanced nanoparticles for targeted treatment of lung adenocarcinoma

The existence of metal nanoparticles in nature is broadly divided into pure metals (such as Au, Ag, Cu, etc.), oxides (such as Fe3O4, TiO2, MnO2, ZnO, etc.) and metallothionein compounds. Metal nanomaterials can not only be used as a chemotherapeutic agent, but also have strong stability, specific targeting high loading capacity, triggered release and other characteristics, which play an important role when used as drug carriers, not only promoting radiosensitivity and remodeling the immune microenvironment, metal nanoparticles can also deliver RNAi molecules to participate in gene-assisted therapy[29].According to Li L et al[30], CuS nanoparticles were synthesized by a simple chemical method, coated with two layers of hydrophilic polymers, and their therapeutic potential against the lung adenocarcinoma cell line SPC-A-1 was examined in vitro and in vivo using a mouse cancer model, well illustrating that CuS nanoparticles are potential phototherapy agents in the treatment of cancer. In addition, iron oxide nanoparticles have been found to inhibit tumor growth by inducing pro-inflammatory macrophage polarization in tumor tissues to increase M1 macrophages[31], as well as using Prussian blue/calcium peroxide nanocomposites as precursors to mediate iron mineralization in tumor cells, promoting the early differential diagnosis of medical imaging between lung adenocarcinoma and benign nodules, while introducing oxidative stress to activate apoptosis and iron death pathways, thereby inhibiting the growth or metastasis of tumor cells[32].Tian H X et al[33] also confirmed that HSAPt (IV) assembled into nanomedicines (human serum albumin-encapsulated tetravalent Pt, HSAPt (IV)) with high administration capacity, low drug toxicity and strong anti-tumor effects by in vitro and in vivo experiments, and found that HSAPt (IV) could also activate iron apoptosis by affecting intracellular iron homeostasis in the treatment of non-small cell lung cancer (NSCLC).Some inorganic nanoparticles also have high drug-loading capacity, biocompatibility, and versatility, and stimulus-responsive inorganic nanomaterials also have various functionalized coatings that can be used to achieve programmable nanomedicine delivery, including UiO-66 framework, zeolite imidazolate frame-8 (ZIF-8), and a combination of MIL-101, terephthalic acid, and chromate[34].Although inorganic nanoparticles are relatively simpler to prepare and functionalize than polymer particles, and have advantages over polymer particles in size and shape control[35], their potential toxicity and metabolic problems cannot be ignored. At present, metal and inorganic nanomaterials as targeted drug delivery systems for the treatment of lung adenocarcinoma are still in preclinical trials, how to further improve the pharmacokinetics and overcome their potential toxicity is a question worthy of in-depth study. Naturally polymeric nanomaterials, of course, are biodegradable and non-toxic, such as chitosan, cellulose, alginate (ALG), amino acids, and proteins (e.g., gelatin and albumin), and are commonly used materials for drug delivery to targeted tissues based on their good physicochemical properties and biocompatibility[36].While most synthesized nanoparticles are often prepared from polymer materials such as polyalkyl cyanoacrylate (PACA)[37], polyethylene-nyamide (PEI)[38], and poly (lactic-glycolic acid) PLGA[39], drugs can also be transported in a variety of ways. However, how to adopt appropriate purification technology, including the size of the laboratory, the availability of materials, economy and productivity are all factors that need to be monitored and considered. According to Ko Zoczek et al[40], the use of polymeric micelle-mediated semi-sandwich ruthenium (II) complex and fluoroquinolone-derived phosphanes for lung adenocarcinoma treatment can not only reduce the systemic cytotoxicity of ruthenium complex, but also effectively accumulate drugs in human lung adenocarcinoma (A549 tumor cell line) and improve drug activity. In addition, it has been confirmed that dihydroartemisinin aggregated gelatin and hyaluronic acid (HA) nanoparticles

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

can enhance the apoptosis of lung adenocarcinoma A549 cells[41].Since the emergence of COVID-19, gene therapy and mRNA vaccines have made breakthrough progress, nucleic acid drugs have become increasingly prominent in the biomedical field, but the efficacy of nucleic acid drugs in the body is very low in the absence of appropriate vectors, and it needs to be considered that vectors selectively deliver nucleic acid drugs to the cytoplasm of target cells to play a role is a very worthy of exploration and research. For such problems, viral nanoparticles (VNP) have to be elicited, which cover a variety of natural nanomaterials derived from plant viruses, phages, and mammalian viruses[42], and their structures are symmetrical, multivalent, and monodisperse, with better stability of the capsid, strong protection against nucleic acids, and strong resistance to temperature and pH, so they can be well used for tissue targeting and drug delivery. Currently, there are viral nanoparticles including icosahedral plant viral nanoparticles[43]], spiral plant viral nanoparticles[44], and rod-shaped plant viruses and filamentous phages[45].According to Li Y et al[46], they constructed an oncolytic virus-like nanoparticle OVFN, which can selectively deliver nucleic acid drugs into the tumor cytoplasm through membrane fusion in response to the slightly acidic environment of the tumor and show significant tumor ablation ability in melanoma models. In addition, multifunctional viruses interact with nanoparticles and other functional additives, and the resulting bioconjugates may have antiviral and antibacterial activities[47].In recent years, liposomal nanoparticles (LNPs) have also made great breakthroughs in targeted drug delivery, and have been tested in clinical applications[48],[49], and the main advantage of LNPs is the versatility of lipid bilayers, which are delivery carriers based on lipid composition and can not only be functionalized by the targeted part, but also chemical diversity, high loading capacity, and intrinsic biodegradability are very conducive to drug delivery[50], in addition, LNPs can seal various types of RNA and protect nucleic acid payloads from degradation to introduce nucleic acid loads into the cytoplasm, which can not only avoid the occurrence of immune responses, but also be used as adjuvants during vaccination. Lipid-based platforms, such as nanoliposomes, provide a large number of nanomedicines that have been approved for cancer therapy[51], with 56% being lipid-based nanomedicines as of 2022, and the rest include protein-based (38%) and metal-based nanomedicines (6%)[52].In the study by Gao C et al[53], they linked SN38 prodrug (SN38 to cell penetrating peptide (CPP) TAT through polyethylene glycol (PEG) linker to form SN38 prodrug (TAT-PEG-SN38) and curcumin co-loaded into liposomes, and this co-delivery system showed better anti-proliferation and cell cycle arrest in A549 cells than single drugs compared with single drugs, with significant efficacy in targeted therapy of lung cancer. Notably, nanoliposomal formulations of irinotecan play a great role in targeted therapy for malignancies such as esophageal, pancreatic, gastric, and colorectal cancers and will be further used in patients with advanced solid tumors through clinical trials[54],[55].In the treatment of lung adenocarcinoma, biomimetic nanoparticles also need to be mentioned, which also have high specific surface area, good surfactant and biocompatibility, and they also show great potential in drug delivery, imaging and treatment. In addition to liposomes, biomimetic nanoparticles can also specifically recognize and bind to tumor cells through surface modification or size regulation, thereby increasing the concentration of drugs at the tumor site, reducing toxic side effects on normal tissues, and effectively inducing cancer cell apoptosis and inhibiting tumor growth and metastasis[56].In a study by Wang W et al[57], they proposed an inhalable biomimetic protein corona-mediated nanoreactor that enhanced iron death treatment in lung adenocarcinoma, which increased drug accumulation 2.6-fold, lipid peroxide production 3.2-fold, and accelerated iron death to achieve enhanced anti-tumor effects. As mentioned earlier, a potential factor in the development of lung adenocarcinoma may be associated with DNA methylation, and in response to this problem some researchers reversed DNA methylation-induced miRNA silencing by biomimetic nanoparticle-mediated gene delivery, which can effectively induce lung cancer cell apoptosis and inhibit the progression of lung adenocarcinoma[58].

3.2. Basis and mechanism of nanoparticle drug design in targeted treatment of lung adenocarcinoma

The research progress of various nanomaterials in targeted therapy of lung adenocarcinoma is discussed above. It can be known that most of the studies are still in the preclinical experimental stage or embryonic stage, and the reason is that the application mechanism of nanoparticles in the body is complex. The first is the targeted drug transport mechanism of nanoparticles, which mainly includes passive targeting and active targeting. Passive targeting: It mainly depends on the size effect of nanoparticles and the biological characteristics of tumor tissue. Tumor tissue usually has high vascular permeability and poor lymphatic reflux, which allows nanoparticles to accumulate in tumor tissue by enhancing the osmotic retention effect (EPR effect)[59].However, the efficiency of passive targeting is limited because most of the drug particles will be distributed to other organs, such as liver, kidney, spleen, lung, etc. And recent studies have shown that this passive mode of transport is not completely

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

accurate. It has been found that the entry and retention of NPs also relies on active transport mechanisms, i.e., cell-dependent processes, i.e., active transport and retention (ATR) principles[60].Active targeting: By modifying specific ligands, such as antibodies, peptides, etc., on the surface of nanoparticles, using ligand tumor cells or receptor binding overexpressed by tumor vessels, the proportion of nanomedicines reaching the targeted target site is increased[61], and drugs can also be released after drug carriers are guided to tumor tissues through external magnetic field forces[62].In addition, biomimetic membranes, VLPs, DNA nanomachines and other biogenic nanomaterials have received much attention in recent years, they have a variety of biological activities, have been widely used in the research and development of a variety of cancer nanomedicines, and have shown great prospects for clinical translation[63],[64], and in the nanotargeted therapy of lung adenocarcinoma, the application mechanism of nanoparticles mainly includes the following aspects:

Targeted drug delivery: Nanoparticles can be designed with specific ligand structures, loaded with anticancer drugs, and then bind specifically to receptors on the lung cancer surface to deliver drugs into lung cancer cells[65].

Control drug delivery and release: Nanoparticles can release drugs in two ways, one is to inhibit the delivery of drugs to healthy non-cancer cells, and the other is to directly deliver drugs to the tumor site, reducing the leakage of drugs to normal cells[66]. In addition, they can promote the controlled release of therapeutic agents by encapsulating drugs in nanoparticles, allowing them to be released in a gradual and controlled manner, thereby improving drug efficacy and reducing drug toxicity[67].

New forms of existing drugs: Nanoparticles are revolutionary drug delivery forms for existing drugs due to their unique properties. Nanoparticles act as colloidal drug carriers, providing a multi-functional and effective way to transport drugs within the body[68]. These colloidal drug delivery systems consist of particles ranging in diameter from 10 to 1,000 nanometers. These small sizes allow nanoparticles to interact with biological systems at the molecular level, thereby enhancing their efficacy and potential applications[69],[70].

Overcoming drug resistance: Nanocarriers can enhance the solubility and stability of drugs, thereby increasing the bioavailability of drugs in the body and allowing them to reach their target sites more effectively. By using nano drug-delivery system, drugs can more easily enter cells, increasing their accumulation within cells and effectively countering the drug resistance of tumor cells[71]. Furthermore, nanoparticles can not only evade the rapid clearance mechanisms within the body, such as the phagocytosis of the reticuloendothelial system (RES), and prolong the circulation time of drugs in the body[72]. Moreover, because nanoparticles are small, they can more easily penetrate biological barriers, such as the blood-brain barrier of tumor tissue, and increase the concentration of drugs in the affected area, thereby achieving a highly efficient nanoscale drug delivery system with programmable size changes, allowing drugs to act more precisely on the affected area, reducing toxicity to normal cells, and lowering the development of drug resistance[73],[74]. Usually, multidrug resistance is often associated with drug pumps on the cell membrane of tumor cells such as P-glycoprotein[75], which can pump drugs out of the cell, and nanocarriers can reverse resistance by preventing drugs from being pumped out or inhibiting the activity of these pumps. They can also achieve combined drug delivery and therapy by combining different treatments, such as regulating drug efflux and regulating apoptosis threshold[76],[77],[78], effectively improving the efficacy of drugs and overcoming drug resistance. Even though most chemotherapeutic drugs have high hydrophobicity and may be diluted in the body, nanodrug delivery systems can increase their solubility[79],[80],[81], thereby increasing their effect on tumor cells.

Improving protein and gene delivery: siRNA plays a crucial role in effectively blocking cancer proteins or inhibiting mutations of inhibitory proteins, suppressing proteins related to multidrug resistance, and activating immune cells related to tumors[82], but naked siRNA molecules are easily degraded by enzymes in the body's environment[83]. Nanocarriers can protect proteins and genes from enzymatic degradation and degradation in the body, prolong their circulation time in the body, and reduce their instability and inactivation in the body's changing environment by encapsulating or adsorbing proteins and genes[84],[85]. However, it is still worthwhile to emphasize the need to choose better experimental materials and further improve pharmacokinetics to overcome the inherent toxicity of the drug.

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

3.3. Research progress of nanomedicine as targeted drug delivery system in the treatment of lung cancer

Currently, nanometer-based therapies are more often undergoing clinical or preclinical trials. Nanotechnology in oncology involves the use of precisely engineered materials to develop new therapies and devices to reduce toxicity and improve the efficacy and delivery of treatments. Notably, Doxil ® and Abraxane ® are the best-known nanomedicines that have been approved by the FDA several years ago and have been successfully used in clinical practice[86], and two nanomedicines have already been clinically approved for lung cancer treatment, Abraxane and Genexol-PM[87]. At the NIH National Library of Medicine, the National Center for Biotechnology Information, 109 research results have been used in cancer treatment and has completed clinical trials of nanomedicine (Figure1.png)[1]. Of note, the search identified only one study with completed clinical trials for the treatment of non-small cell lung cancer (as shown in Table 1).

Table 1: One study with completed clinical trials for the treatment of non-small cell lung cancer.

NCT Number	Study Title	Conditions	Interventions
NCT00553462	Carboplatin and Paclitaxel Albumin Stabilized Nanoparticle Formulation Followed by Radiation Therapy and Erlotinib in Treating Patients With Stage III Non-Small Cell Lung Cancer That Cannot Be Removed By Surgery	Lung Cancer	DRUG : carboplatin DRUG: erlotinib hydrochloride DRUG paclitaxel albumin stabilized nanoparticle formulation RADIATION: radiation therapy

The basic principle is to use carboplatin and paclitaxel albumin stable nanoparticle preparation to further prevent the growth of tumor cells by killing cells or preventing cell division, plus radiotherapy using high-energy X-rays to kill tumor cells, combined use of drug erlotinib can make tumor cells more sensitive to radiation therapy, so carboplatin and paclitaxel albumin stable nanoparticle preparation combined with radiotherapy and erlotinib can kill more tumor cells. In the study by Bazhenova et al[88], they found that nanoparticle formulations allowed larger doses of cisplatin equivalents without clinically significant neurological, otologic, or nephrotoxicity and patients were able to receive longer treatment times. Activity was observed in heavily pretreated platinum-exposed lung cancer patients, most patients showed tumor regression or stable disease, and in Kim D W et al[89] study, they also first stated that Genexol-PM, a Cremophor EL (CrEL) polymer-free micelle formulation of paclitaxel plus cisplatin combination chemotherapy, showed significant antitumor activity, with relatively low incidence and severity of toxicity despite higher paclitaxel doses. It further illustrates that nanotechnology is very prominent in reducing drug toxicity in lung cancer treatment. In addition, some nanocarriers can also achieve specific drug release in diseased areas in response to specific stimuli in the tumor environment, such as pH, enzyme activity, or temperature changes[90].Therefore, nanodelivery systems can not only reduce drug side effects and drug resistance, but also help to improve drug efficacy and provide new strategies and hopes for cancer treatment.

4. Challenges in clinical transformation of nanomedicine

Nanodelivery technology is very promising in the development of cancer therapy, however, it still faces the limitations of cost, production, pharmacokinetics and toxicology in clinical practice. If the cost of raw materials and production process is too high, it is easy to cause test stagnation during the study process, resulting in empty ideas and unable to carry out further. Second, the cost of raw materials and production processes is too high, which can lead to very expensive products. It is estimated that the commercialization process of a new nanomedicine can cost $1 billion if it lasts more than 10 – 15 years[91]. Therefore, it is necessary to assess the population and practical feasibility of nanomedicines for the main target indications before considering their introduction into development.

[1]*Figure 1 contains more content and is displayed in the form of hyperlinks*. If you need further information, you can visit the official website of the original data https://clinicaltrials.gov/ct2/results?term=nanoparticle&cond=Cancer&Search=Apply&recrs=b&recrs=a&recrs=d&recrs=c&age_v=&gndr=&type=&rslt=information, you can visit the official website of the original data https://clinicaltrials.gov/ct2/results?term=nanoparticle&cond=Cancer&Search=Apply&recrs=b&recrs=a&recrs=d&recrs=c&age_v=&gndr=&type=&rslt=

ISSN 2706-6819 Vol.6, Issue 10: 1-11, DOI: 10.25236/IJFM.2024.061001

In addition, there are challenges in the manufacturing process, industrial production, and batch-to-batch quality control of nanomedicines, and these factors affect the consistency and reproducibility of drugs, which require rapid, precise, and reproducible nanoparticle library synthesis techniques as well as rapid contributing Multidisciplinary cooperation in oncology, imaging, pharmacy, nanoscience, materials science and applied science of artificial intelligence technology. In terms of safety issues, due to the consideration of changes in the biological distribution of drug molecules, the occurrence or biocompatibility of the body's immune response, and the safety of excipients, these issues need to be addressed through early preclinical pharmacokinetics and biodistribution studies, and preclinical safety studies in larger animals. The reason is that because the efficacy of nanomedicine varies between animal models and human patients, tools and techniques need to be developed to evaluate and address variability in nanomedicine performance between patients.

5. Conclusion

Although the unique role of nanotechnology in cancer therapy has achieved technical achievements, it also faces challenges in clinical translation and clinical application and requires a deeper understanding of nano-biotechnology. Nanotechnology provides multiple benefits in precision drug delivery, including improved drug efficacy and selectivity, as well as diagnosis through disease marker molecules, and allows integrated nanotechnology to integrate diagnostic and therapeutic functions and enable real-time and accurate diagnosis of the condition and simultaneous treatment, while monitoring efficacy and adjusting the dosing regimen. It has been shown that nanomedicine delivery systems inhaled through the lung can improve the efficacy of drugs in the treatment of lung cancer[92],[93], can also change the pharmacokinetics through PEGylation technology and other surface modifications, and can improve the accumulation of drugs at the tumor site with the help of EPR effect and active targeting technology[94],[95]. Nanomedicine delivery systems have shown great potential and diverse research directions in targeted therapy for lung adenocarcinoma. It is estimated that over the past two decades, more than 1,500 patents have been filled in and dozens of clinical trials have been completed in the field of nanomedicine[96]. In the future, with the deepening of multidisciplinary cooperation and the application of artificial intelligence technology, nanodelivery technology will be displayed in a multifunctional, diversified and cellular personalized manner in the treatment of lung adenocarcinoma and even other diseases[9], and the detection and treatment of cancer will usher in a brand-new possibility of exploration.

Data availability

All the data used in this paper are from the references cited in this paper, among which, Table 1, Table 2 from https://clinicaltrials.gov/ct2/results? term=nanoparticle&cond=Cancer& Search=Apply& recrs= b&recrs=a&recrs=d&recrs=c&age_v=&gndr=&type=&rslt= public data.

Acknowledgement

First of all, I would like to express my heartfelt thanks to all the people who helped me in this paper. My heartfelt thanks and thanks to my teacher. With the advice and encouragement of my supervisor, Mr Yan Zhang, I have a deeper understanding of these studies. Studying under his guidance and supervision is my great honor and joy. In addition, I am honored to have benefited from his personality and diligence, which I will cherish all my life.

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