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Lung cancer drug development: From traditional chemotherapy to targeted and immunotherapies

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Abstract. Lung cancer remains one of the deadliest types of cancer in the world, with the number of deaths due to lung cancer increasing dramatically year after year. In the same period, the approach to the treatment of lung cancer has changed dramatically over the past few decades, from systemic chemotherapeutic drugs-platinum-based drugs in the beginning to a wide range of newer therapeutic approaches such as targeted therapies and immunotherapies at the present time. This article reviews the development of drug therapy for lung cancer. By comparing the differences in mechanism of action and clinical side effects between traditional chemotherapeutic drugs and targeted drugs, we aim to highlight the importance of the development of new targeted drugs and new therapeutic means. In addition, the article also analyses the development and achievements of novel drugs targeting NSCLC with MET-14 exon mutations, and looks into the possible future therapeutic strategies, but there are some research gaps in combination therapy. Through an analysis of the development of lung cancer drugs, this paper aims to provide a more comprehensive perspective to provide guidance for the development and treatment of lung cancer drugs in the future, but there are still a lot of different efficacies brought about by the combination of drugs that have not been resolved, and future research can focus on the direction of the combination of therapies.

Keywords: Lung cancer, chemotherapeutic drugs, targeted therapies, drug development

1. Introduction

Malignant tumours are major diseases that pose a serious threat to human health. In 2020, there will be 19.29 million new cancer cases and 9.96 million cancer deaths worldwide. The number of new cases and deaths in China will be as high as 4.57 million and 3 million respectively. With aging, the cancer burden will further increase [1]. Among them, lung cancer is one of the deadliest malignant tumours globally, posing a serious threat to human health because of its excessively high mortality rate as well as the fact that it is not easy even to be detected, and lung cancer often leads to a low survival rate of the patients and is difficult to treat. In developing countries, lung cancer is the second most common cancer after breast cancer, while in developed countries, it is the fourth most common cancer. According to GLOBOCAN 2020, the incidence and mortality rates of new lung cancer cases per year globally are twice as high in men as in women, reflecting to some extent the gender differences in smoking behaviour. In China, the situation of lung cancer is particularly serious. It is not only the most common type of cancer but also the leading cause of cancer deaths. According to GLOBOCAN 2020, China accounts

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for approximately 37 per cent and 40 per cent of global lung cancer cases and deaths, respectively, ranking first in the world [2].

In summary, the treatment of tumour is an urgent problem faced by all countries, compared with the traditional oncology drugs such as cisplatin, "hurt the enemy a hundred, self-loss of a thousand" efficacy, oncology drugs need to be innovative drugs, First-in-class R & D is the focus of the world, the global share of innovative drugs in the 2010-2020 period in each country Between 2010 and 2020, the proportion of innovative drugs in the world is 71.2% in the United States, 17.3% in the European Union, 7.7% in Japan, and 3.8% in China [3]. It can be seen that China needs to further explore the innovative drug R&D in oncology. The main existing problems of innovative drug R&D, the current situation of oncology R&D, and the future direction of research and development need to be further clarified. The discussion of these issues is of great significance for the treatment of tumours in China.

This study will focus on the single aspect of lung cancer, comparing the advantages and disadvantages of traditional anti-lung cancer drugs and targeted drugs, as well as the achievements of China's newest targeted drugs, in order to deeply explore the development of lung cancer drugs and the solutions for such problems in the future.

2. Research and advances in lung cancer drugs

2.1. Platinum-based drugs drug development and mechanisms

Common lung cancer drugs are platinum-based drugs. Worldwide, cisplatin, carboplatin and oxaliplatin have all received official approval for clinical use and have become the drugs of choice for the treatment of various malignancies, including lung cancer. In the late 1960s, cisplatin was discovered and approved for cancer treatment in 1978 as the first generation of platinum-based anticancer drugs. It has shown therapeutic efficacy in a wide range of tumours including lung, ovarian and colorectal cancers. However, cisplatin is a non-specific treatment that, in addition to its killing effect on tumour cells, causes extensive systemic toxicities and may cause significant damage to normal tissues with prolonged use.

Therefore, based on the structure and mechanism of action of cisplatin, carboplatin, a second-generation platinum-based chemotherapeutic agent, was introduced into clinical use after more than a decade of research and development. Carboplatin contains a bis-platinum cyclobutane dicarboxylic acid ligand that allows for a lower rate of hydration and a higher biosafety, which greatly reduces systemic toxicity including hepatotoxicity, nephrotoxicity, neurotoxicity, and ototoxicity, and allows for the use of relatively large doses in the treatment of invasive tumours. However, the problem of resistance to platinum-based drugs remains a major challenge in chemotherapy. After a certain number of treatment cycles, the problem of resistance to cisplatin and carboplatin may arise. To overcome this problem, oxaliplatin was developed as a third-generation platinum-based drug. Unlike cisplatin and carboplatin, oxaliplatin, although similar in mechanism, does not cross over with the former two to produce resistance. Therefore, oxaliplatin can produce complementary effects with cisplatin in the clinic and is widely used in anticancer therapy [4].

With regard to the mechanism of action of platinum drugs, it is generally accepted that cisplatin is first transported into tumour cells via copper transporter protein 1 (CTR1). Upon entering the cell, cisplatin passes through an activation process known as chloride ligand displacement, which involves the replacement of the chloride ligand by a water molecule or a small sulfur-containing molecule. Inside the cell, the concentration of chloride ions is about 4 mM, much lower than the extracellular concentration of 100 mM, and this low concentration promotes the formation of cationic hydrates such as cis-[Pt(NH3)2Cl(OH2)]+ and cis-[Pt(NH3)2(OH)2]2+.

Compared to cisplatin, carboplatin and oxaliplatin have more stable ligands that are less susceptible to hydrolysis. In addition, these drugs hydrate and react with ammonia much faster than cisplatin. For example, after 4 hours of contact with erythrocytes, transplatin reacts with 70% of glutathione, whereas cisplatin only reacts with 35% of glutathione. This high activity of transplatin makes it likely that it will rapidly become inactive before it reaches its target, which can compromise its anticancer effect. In the cytoplasm, platinum-based drugs undergo a series of chemical reactions that react with DNA to trigger

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DNA damage by interfering with its structure through the formation of internal and cross-strand cross-links of DNA.The most nucleophilic site in DNA is the N7 position of guanine, which is the primary site of action of platinum-based drugs [4]. These DNA damages block the growth cycle of tumour cells and may lead to their apoptosis.

In general, it appears that the anti-cancer mechanism of cisplatin works primarily by binding to DNA and forming crosslinks. Nevertheless, it has been reported that only 1-10% of cisplatin actually enters the cell nucleus and interacts with the DNA, and while this is sufficient to stop the rapid proliferation of tumour cells and induce their death, most of the rest is harmful to the rest of the body, making the development of targeted therapies a preferred area of research in various countries.

2.2. The rise of targeted therapies and mechanisms of action

In view of the efficacy of platinum drugs, which is "one hundred injuries to the enemy and one thousand injuries to the self", targeted drugs are designed to target specific molecular markers in order to improve the therapeutic effect and reduce the damage to normal cells, and countries have invested a lot of energy in research and development.

Lung Specifically speaking, targeted drugs for lung cancer are drugs designed for specific molecular targets in lung cancer cells, which work to block or inhibit tumour growth, proliferation and metastasis. In the late 1990s, researchers identified mutations in the epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC), and this discovery led to the development of targeted therapies to address these specific mutations, and the first generation of EGFR inhibitors was born, which significantly enhanced the effectiveness of treatment compared to traditional drugs, such as gefitinib and erlotinib.

Shortly thereafter, scientists also identified the phenomenon of positive lymphoma kinase (ALK) and c-ros oncolytic virus 1 oncogene homologue (ROS1) gene rearrangements, which led to the development of targeted drugs such as crizotinib, which is specifically targeted at lung cancer patients carrying these gene rearrangements, thus further enhancing the accuracy and effectiveness of treatment. When it comes to crizotinib, it is also one of the earlier targeted drugs introduced into China [5]. Below is a list of targeted drugs that have been introduced into China [5]. The following is the mechanism of action of Crizotinib: Crizotinib inhibits the activity of positive lymphoma kinase and intermediate lymphoma kinase by binding to their ATP binding sites, interrupting the phosphorylation process and blocking the downstream transmission of kinase signals. In tumour cells, ALK, ROS1 and MET promote cell growth and inhibit cell death by initiating signalling pathways such as MAPK/ERK, PI3K/AKT and STAT. Crizotinib inhibits these pathways, limiting the proliferation of tumour cells and promoting apoptosis [5].

3. Comparison of conventional platinum drugs and targeted drug

3.1. Cisplatin drugs

There are many platinum drugs such as cisplatin, carboplatin and oxaliplatin, here we will take the drug cisplatin for studies, according to the study more than 90% of cisplatin's excretion is done through the kidneys, after a patient receives a standard dose of cisplatin intravenously about 25% of the cisplatin will be cleared within 24 hours along with a 50% clearance within 5 days. This mechanism of excretion then leads to cisplatin accumulation in the kidneys, which can lead to nephrotoxicity. This nephrotoxicity is demonstrated in 28-36% of patients treated with a 50 mg/m2 dose of cisplatin. Patients may experience acute oliguric or non-oliguric renal insufficiency within 2 to 6 days of cisplatin overdose, and patients may continue to suffer chronic renal failure for more than two years at a dose of 20 mg/m2 per day. We can assess nephrotoxicity by monitoring increases in blood urea nitrogen (BUN), creatinine, and serum uric acid as well as decreases in creatinine clearance and electrolyte imbalances. Also at the time of treatment, in order to reduce the patient's response to the monohydrate form of cisplatin, the facility will recommend that the patient receive a 3-6L daily infusion to moderate the nephrotoxicity to the body [5].

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Vomiting and nausea are also common symptoms for patients, and the vast majority will still experience these symptoms despite the use of prophylactic antiemetic medication. However, these symptoms usually begin within 1-4 hours of treatment and can last up to 24 hours. Delayed nausea and vomiting may also occur for up to two weeks if high doses of cisplatin are used. Diarrhoea, loss of taste or metallic taste, pancreatitis and mucositis may also occur. It has been shown that cisplatin may exacerbate gastrointestinal toxicity when combined with other antineoplastic agents. An overdose of cisplatin can also lead to hepatotoxicity, ototoxicity, and many other toxicities [6].

3.2. Targeted agents

Crizotinib has shown excellent therapeutic efficacy in a number of clinical trials, particularly in patient populations that do not respond well to conventional chemotherapy. This targeted agent has been particularly effective in NSCLC patients who carry specific genetic mutations, significantly prolonging their progression-free and overall survival.

Specifically, in patients with NSCLC carrying a positive lymphoma kinase (ALK) rearrangement, crizotinib was able to improve their progression-free survival to between 7 and 11 months, a much longer period than the 4 to 6 months that would have been achieved with chemotherapy alone. This data suggests that crizotinib is able to control disease progression more effectively over a longer period of time than conventional chemotherapy regimens. Although it is a drug that is toxic, and crizotinib as a targeted drug has side effects, such as it can cause visual disturbances in patients, which can leave them with blurred vision and sensitivity to light; it may trigger arrhythmias in the heart; and it may cause nausea, diarrhoea and constipation [5]. Crizotinib is also easier for healthcare professionals to manage due to its milder side effects compared to conventional drugs.

In conclusion, targeted drugs not only provide new hope for patients who are less effective with traditional treatments, but also increase the likelihood of their recovery through targeted therapies, while at the same time reducing the side effects of the drugs on the human body, thus becoming an important treatment option in the field of lung cancer treatment.

4. Further research advances

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4.1. Mechanisms targeting met-14 exon mutations

In NSCLC patients with MET exon 14 alterations, crizotinib Although crizotinib has some efficacy, it has a relatively low ORR (the proportion of patients experiencing a complete or partial remission after receiving treatment), which is low compared to the approximately 60-80% ORR achieved with other NSCLC-driven gene-targeted therapies, but the overall efficacy is relatively low.

MET is a transmembrane tyrosine kinase receptor which, upon binding to hepatocyte growth factor (HGF), triggers a dimerisation process and induces intracellular phosphorylation of multiple tyrosine residues. This process activates a series of important downstream signalling pathways such as Ras-MAPK and PI3K-Akt, which in turn promotes cell proliferation, growth, migration and neovascularization. Similar to other tyrosine kinase receptors, the degradation of MET is regulated by the E3 ubiquitin ligase c-Cbl. The structural domain of exon 14 of MET close to the membrane is an important negatively regulated region containing a cysteine protease-sensitive cleavage site and a tyrosine site bound to the E3 ubiquitin ligase c-Cbl (Y1003), both of which are involved in the ubiquitination and subsequent degradation of the MET Protein ubiquitination and subsequent degradation processes. When the splice donor and acceptor sites of exon 14 are mutated, this may lead to exon jumping, resulting in the deletion of the membrane proximal structural domain containing the E3 ubiquitin ligase c-Cbl, which prevents the ubiquitination and degradation of MET proteins and reduces their degradation rate, thus increasing the stability of METs and the sustained activation of downstream signals, which may ultimately trigger tumorigenesis. Current studies have shown that there

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are various forms of jump mutations in exon 14 of MET, including point and deletion mutations, as well as the very rare Y1003 site mutation [7].

4.2. Drug mechanisms of targeted therapeutic agents against jump mutations in exon 14 of met and developmental

Met gene mutations have emerged as a key therapeutic target in NSCLC due to aberrant activation of the HGF/c-Met signalling pathway. Different sites of action in this signalling pathway have led to the classification of targeted therapeutic agents into three main types: anti-HGF monoclonal antibodies (mAbs), anti-c-Met mAbs, and small molecule tyrosine kinase inhibitors (TKIs). Anti-HGF and anti-c-Met mAbs interrupt downstream signalling mainly by binding to extracellular HGF or c-Met and blocking the interaction between HGF and c-Met and subsequent receptor phosphorylation. Small molecule TKIs, on the other hand, act directly on the catalytic domains on the inner side of the cell membrane, blocking the phosphorylation process of proteins and cutting off the signalling chain. In current research and applications, small molecule TKIs have demonstrated the most promising therapeutic effects and have become a major research focus.

Currently, two major MET-targeted therapies are under clinical investigation: small-molecule MET TKIs and mAbs against MET/HGF. In 2020, the Japanese Ministry of Health, Labour and Welfare (MHLW) approved Tepotinib, an oral small-molecule MET tyrosine kinase inhibitor, and the U.S. Food and Drug Administration (FDA) approved capmatinib, both of which are MET TKIs targeting METex14 NSCLC, marking an international Major Breakthrough.

MET TKIs can be classified as type I, type II, and type III according to how and where they bind to ATP.Type I TKIs bind to the ATP pocket during the active state of the MET, and are further subdivided into two classes, Ia and Ib. For example, crizotinib belongs to class Ia and interacts with residue Y1230, the hinge region, and the solvent pre-G1163 similar to G1202 of the ALK gene and G2032 of the ROS-1 gene. Whereas, Carmatinib, Tipotinib and Sevortinib belong to the Ib category and are mainly tightly associated with the Y1230 residue and the hinge region, whereas they do not interact with G1163. These TKIs have been shown to be effective in the treatment of patients with advanced NSCLC carrying the METex14 mutation. Newer type I TKIs, such as Bozitinib (an oral small-molecule MET tyrosine kinase inhibitor) and TPX-022, are currently in clinical trials. Type II TKIs, such as cabozitinib, meritinib, and glitinib, act by expanding into the posthydrophobic pocket to bind to the ATP pocket in the inactive state. Both type I and type II TKIs are ATP Competitive inhibitors. In contrast, type III Tivantinib (an oral small molecule MET tyrosine kinase inhibitor) binds to a different variant of the ATP-binding site and is non-ATP competitive [7].

4.3. China's new policy on the development of this mechanism of action drugs

After the development of national drugs in recent years, the "Drug Registration Management Measures" set up breakthrough therapeutic drugs, conditional approval, priority review and approval, special approval of the four accelerated channel to accelerate the listing of new drugs with clinical value, with the continued deepening of the reform of the drug review and approval system, incentives for drug innovation policy dividends continue to appear, China's As the reform of drug review and approval system continues to deepen, the policy dividends to stimulate drug innovation continue to appear, China's drug R&D and innovation vitality has been continuously improved, and the industry has a new look.

In the past five years, China's pharmaceutical industry has shown a good momentum of development, the main economic indicators of the pharmaceutical industry have shown high growth, the scale of the pharmaceutical industry ranks second in the world, China's contribution to global drug research and development has increased, China's local new drugs accelerated to "go to sea", and the internationalisation of the pharmaceutical industry has stepped up to a new level.

With the support of this policy, China has listed three targeted therapeutic drugs against MET exon 14 jump mutation, namely Gumetinib, Piratinib and Triptinib, and even the world's first approved MET inhibitor, Triptinib Hydrochloride, has been approved for listing in China for the treatment of NSCLC

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patients with MET exon 14 jumps in 2023. , the arrival of these new drugs is undoubtedly not a new therapeutic option for patients with MET exon 14 skipping NSCLC [8].

5. Future research directions

The field of lung cancer treatment is undergoing a major shift from reliance on conventional chemotherapy, which can cause strong side effects, to a gradual transition to more precise targeted therapy and personalised medicine.

5.1. Exploration of new targets

In addition to targeting variants in MET exon 14, there are other drugs that are localised to different targets in the HGF/MET signalling pathway. For example, anti-HGF mAbs (e.g., Rilotumumab and Ficlatuzumab) and anti-c-Met mAbs (e.g., Onartuzumab, HLX55, SHR-A1403). However, all of these therapeutic options are currently in the clinical trial stage, and none of the drugs have been formally approved for marketing. In general, research on these drugs has focused on combinations with MET-TKIs with the aim of inhibiting or reversing resistance to MET-TKIs. In addition, MET-TKIs have been used in combination therapy with other targeted agents, again to inhibit or reverse drug resistance. Recent studies published in The Lancet Oncology have shown that combination therapy with vorlatinib and ositinib demonstrated a very high level of treatment in patients with advanced NSCLC carrying EGFR mutations and developing resistance after treatment with EGFR-TKI as well as amplification of the MET gene. Therefore, this combination therapy regimen is expected to be an important direction for future development [7].

5.2. Immunotherapy

There are many approaches regarding immunotherapy, among which PD-1/PD-L1 inhibitors have made significant progress in the treatment of NSCLC, providing an effective therapeutic option for many patients, but there is still a subset of patients who develop resistance to these drugs either at the beginning of the treatment or after a period of time. In response to this resistance, researchers have been actively exploring the mechanisms of complex immunosuppression to explore a number of new targets to address these challenges, a key element of which is the depletion of cytotoxic immune cells (such as CD8 T cells and natural killer cells, or NK cells). This depleted state is usually confirmed by detecting increased expression of several immune checkpoint proteins (ICPs), including programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin structural domain-3 (TIM-3), T-cell immunoglobulin with immunoglobulin and ITIM structural domains of T-cell immunoreceptors (TIGIT) and B and T lymphocyte attenuators. These ICPs inhibit the tumour killing activity of T cells and NK cells by binding to ligands expressed by antigen presenting cells (APCs), tumour cells and other cells in the tumour microenvironment. These ICPs essentially act as "brakes" for T cells and NK cells [9]. Extensive research, as well as clinical indications, have shown that blocking these ICPs or their ligands can activate the anti-tumour immune response of immune cells and lead to tumour regression.

In addition to their expression on immune cells, certain ICPs are also expressed on tumour cells, and sometimes these expressions can promote tumour cell proliferation and survival. Therefore, blocking these ICPs may provide a dual benefit in tumour therapy. Since 2014, when the FDA approved the first immune checkpoint inhibitor, ipilimumab, a mAbs against CTLA-4, for the treatment of advanced melanoma, immunotherapies based on immune checkpoint blockade, have been approved for the treatment of a wide range of tumours. So far, the FDA has approved mAbs targeting PD-1, PD-L1, CTLA-4 and LAG-3 for the treatment of different types of tumours [9]. Meanwhile, inhibitors targeting TIM-3 and TIGIT are being extensively evaluated in ongoing clinical trials, providing a potential strategy for future treatment of a wide range of solid tumours and leukaemia.

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5.3. The role of big data and ai in lung cancer research

Imaging techniques often used in lung cancer screening include X-rays and CT scans, and X-ray images often tend to make doctors miss small lesions due to cascading effects and lower density resolution. If AI is given training with the help of big data, AI will achieve a very compelling and good result in the near future.

Accurate segmentation of lung nodules is essential for diagnostic confirmation and is also a critical step for nodule extraction. Compared with manual segmentation, AI's automatic segmentation technology not only saves a lot of human resources, but also greatly improves work efficiency and reduces medical errors due to human fatigue. Meanwhile, the use of AI for automatic segmentation can shorten the segmentation time to 3.15 seconds, which is much faster than the time required for manual operation.

At the same time, doctors, with AI-assisted prediction, have surpassed the prediction relying on traditional clinical features in terms of accuracy and efficiency, which is crucial for confirming the cause of the disease and adjusting the treatment plan. In the assessment of solid tumour efficacy, solid tumour efficacy evaluation criteria are commonly used, however, such criteria are mainly based on the size of the lesion and cannot differentiate between tumour tissue and inflammatory changes, thus potentially leading to false-positive results. Therefore, the importance of a fast and precise assessment of the therapeutic effect is clear at a glance, as well as having far-reaching clinical implications thereafter [10].

Conclusion

In recent years, significant progress has been made in the field of lung cancer treatment, especially in the application of targeted drugs and the development of immunotherapy. Compared with traditional chemotherapeutic drugs, targeted drugs can not only bring milder side effects, but also improve the efficacy of treatment, so it is urgent for countries to research and develop new targeted drugs. The successful development and marketing of several drugs targeting NSCLC with MET-14 exon mutation jumps have provided patients with a variety of drug choices and greatly improved the survival rate of patients. With regard to immunotherapy PD-1/PD-L1 inhibitors have made significant progress in the treatment of NSCLC, this paper also addresses the fact that inhibitors of TIM-3 and TIGIT are being extensively evaluated in ongoing clinical trials, providing a potential strategy for the future treatment of a wide range of solid tumours and leukaemias. Inhibitors of TIM-3 and TIGIT are being widely evaluated in ongoing clinical trials, providing a potential strategy for the future treatment of many solid tumours and leukaemias. However, this paper does not provide the corresponding combination therapies, such as how to combine traditional drugs with novel drugs, and it is expected that in the future there will be a wider range of combination therapies with different types of drugs for lung cancer treatment, including traditional chemotherapy, targeted therapies, and immunotherapy. The combination of traditional chemotherapy drugs, targeted drugs and immunotherapy can greatly improve the treatment effect, and with the assistance of big data and artificial intelligence, we have reason to believe that lung cancer is not so terrible.

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