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A Review of Research and Development on Lung Cancer Drugs

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Abstract: With an incidence of 1.2 million new cases reported annually worldwide, 80% of which are non-small cell lung cancer, the majority of which are advanced at the time of diagnosis and have a poor prognosis, lung cancer continues to be the leading cause of cancer-related mortality in many countries. The effectiveness of chemotherapy for advanced lung cancer is still lacking, despite notable advancements in this area. The most prevalent histologic form of lung cancer is non-small cell lung cancer (NSCLC). Platinum-based chemotherapy is the conventional treatment for individuals with advanced non-small cell lung cancer (NSCLC), although it has a high rate of side effects and is not very effective. In recent years, molecular targeted therapy has become an important therapeutic tool for patients with advanced NSCLC with the continuous development of lung cancer targets and molecular targeted drugs. At present, these drugs have been successfully applied in the clinic and achieved remarkable efficacy, creating a new era of molecularly targeted therapy for NSCLC. The paper summarizes the progress of molecularly targeted therapy for advanced NSCLC. Targeted therapeutic drugs are now widely used in clinical practice and play an important role in tumor treatment, but most of them are resistant after a period of time. In addition, the high price limits their uses in general patients. Therefore, new drugs with lower efficacy, smaller side effects, a longer effective time, and a reasonable price are expected to come out as soon as possible.

Keywords: Non-small cell lung cancer, Targeted drugs, Predictors, Clinical trials

1. Introduction

Lung cancer is a malignant tumor originating from the bronchial epithelium or glands of the lungs, with its incidence and mortality rates remaining high for a long period of time, making it one of the most common malignant tumors with the worst prognosis in the world. Lung cancer accounts for more than 20% of new malignant tumor cases and cancer-related deaths in China, which is the largest cancer in China. In recent years, targeted drug therapy (TDT) has gradually emerged, which is highly favored by non-small cell cancer (NSCLC) patients because of its safety, efficacy, and ease of use. Meanwhile, drug resistance and adverse effects of TDT have brought new challenges to clinical treatment. The introduction of targeted drugs has changed the treatment pattern of NSCLC with sensitive gene mutations. With the discovery of new targets and the development of new targeted drugs, more adverse reactions specific to new targeted drugs need to be further explored and summarized in the clinic. Active prevention, correct education, scientific assessment and

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standardized diagnosis and treatment are the key points of the whole management of adverse reactions associated with targeted drugs, which means only the combination of good drug efficacy and effective adverse reaction management mode can bring better survival benefits for patients [1].

The little clinical evidence indicates that combination therapy is an unavoidable trend that will increase the likelihood of recovery, and the development of targeted molecular treatments has opened up new avenues for the perioperative management of non-small cell lung cancer. Nevertheless, the investigation into the effectiveness of both monotherapy and combination therapy is currently in its exploratory phase and faces numerous challenges. However, the present evidence still holds potential for therapeutic use. More people with early-stage NSCLC may survive and be cured if efforts are made to "precisely" choose the right patients and investigate safer and more effective treatment options in the future.

2. Predictors Affecting the Efficacy of Targeted Agents in Non-small Cell Lung Cancer

2.1. Clinical Predictors

Effective predictors of gefitinib and erlotinib in early clinical trials included female, Asian origin, no smoking history, adenocarcinoma phenotype, and the type accompanied by bronchioloalveolar carcinoma (BAC) component. The BR.21 randomized trial and the proto-termal transeferase labling technique (ISEL) further demonstrated that these clinical features are indicative of the effectiveness of tyrosine kinase inhibitors. For nonsmoking patients in the ISEL study, the gefitinib group had a higher survival rate than the placebo group (Hazard Ratio (HR), 0.67; 95% Confidence Interval (CI), 0.49-0.91), while for smoking patients, there was no discernible difference between the two groups [2]. The BR.21 trial's multivariate analysis revealed that adenocarcinoma phenotypes (HR, 0.8; 95% CI, 0.6-0.9), Asian (HR, 0.7; 95% CI, 0.5-0.9), and nonsmoking (HR, 0.8; 95% CI, 0.6-1.0) were independent predictors of longer survival [3].

Gefitinib (500 mg/d) was given to this clinically verified patient cohort as part of a prospective phase II research by the Southwest Oncology Collaborative Group (SWOG) to assess the effectiveness of TKIs in the BAC subtype of adenocarcinoma [3]. The findings indicated that patients who were female had a significantly longer survival time (19 months) compared to those who were male (8 months) (P=0.02), patients who had a rash had a longer survival time (16 months) compared to those who did not have a rash (5 months) (P=0.003), and non-smokers had a longer survival time (26 months) compared to those who were smokers (10 months) (P=0.049).

The incidence and severity of rash induced by Epidermal Growth Factor (EGFR-TKIs) remained consistent with efficacy in non-small cell lung cancer, with skin toxic reactions associated with EGFR inhibitors related to the important role of EGFR in skin physiology.

2.2. Molecular Biology Predictors

Two independent studies in 2004 showed that EGFR TK region mutations were strongly associated with the gefitinib efficacy in NSCLC [4,5]. The potential association of significant drug efficacy with target mutation variation in the study was analyzed to find that 8 of 9 remission patients had EGFR mutations, but none of the 7 non-remission patients had mutations (P<0.001) [4]. Paez et al. [5] found that EGFR mutations were predominantly seen in Asian patients after screening for kinase mutations in untreated NSCLC patients, and that all 5 gefitinib-treated remission patients had mutations. EGFR kinase mutation, which can result in enhanced ligand-dependent activation of EGFR and increased sensitivity to TKIs, is more common in nonsmokers, women, Asians, and adenocarcinomas, which may be the reason why the efficacy of TKIs is significant in treating these patients. About 90% of the mutations affect some specific amino acid sequence, in which 45%-50% are in-frame deletions in the

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codon 746-750 region in exon 19, and the remaining 35%-45% are missense mutations from leucine to arginine at codon 858 in exon 21 (L858R).

The above mutations have a recurrent nature, which means that the organism will thus acquire specific functional properties. Many retrospective studies have confirmed the association between clinical characteristics and TKI's efficacy and EGFR mutations, with the mutation rate being higher in Asian patients (25%-50%) than in North America and Western Europe (10%). Patients with mutations receiving TKI had a Respiratory Rate (RR) of 77% (range 30%-100%, most reports >60%), while patients without mutations had an RR of 10% (range 0-33%). Exon 19-deficient patients treated with TKIs appear to have a higher remission rate and longer survival time than those treated with L858R, according to some evidence [6]. It is interesting to note that the receptors expressed by the different types of mutations seem to have distinct signaling biochemical capabilities, even though the biological reason for the aforementioned therapeutic distinctions is yet unknown. In comparison to the wild type, several studies have also shown that patients with EGFR mutations treated with TKIs have a longer survival time—up to 30 months in the case of multiple sclerosis (MS).

Many conceptual and technical issues may interfere with the analysis of the relationship between EGFR mutations and efficacy. First, most retrospective studies collect tumor specimens at the time of initial diagnosis, but treatment with TKIs may begin after failure of multiple cycles of chemotherapy. In other words, additional mutations resistant to TKIs that occurred during this period may lead to ineffective treatment. In contrast, the limited sensitivity of nucleotide sequencing technology may be one reason why treatment is effective in mutation-free cases. Second, rare EGFR mutations are found in unselected NSCLC participants, but the specimens obtained by commonly used fine-needle aspiration methods are insufficient for molecular testing, resulting in a relatively small number of mutated cases in most studies. Therefore, the statistical efficacy of most European and American studies is not strong, but the conclusions of studies from Asian countries with higher rates of EGFR mutations are more reliable. Finally, technical difficulties in assessing EGFR mutation status in formalin-soaked and paraffin-embedded tissues by polymerase chain reaction (PCR) may lead to differences in the mutation rates reported in various studies [7].

3. Current Status of Translational Medicine Research on Targeted Drugs in Non-small Cell Cancer (NSCLC)

3.1. Combination Application of Targeted Drugs

Monotherapy of EGFR-TKIs can improve the survival period of some patients, but the effect is still not very satisfactory. Therefore, researchers have tried to combine EGFR-TKIs with chemotherapy, radiotherapy and other molecularly targeted drugs to further explore their potential value in improving efficacy and prolonging survival.

Two phase I clinical trials, INTACT1 and INTACT2, compare gefitinib plus chemotherapy to a placebo as the first-line treatment for advanced non-small cell lung cancer. According to the outcomes of both trials, the combination group did not significantly outperform the control group in terms of efficiency, median survival, or disease progression. The effectiveness of carboplatin + paclitaxel with or without sorafenib in treating patients with primary advanced non-small cell lung cancer (NSCLC) was examined in another phase III clinical trial called Esophageal Cancer (ESCA PE). The results indicated that there were no statistically significant differences between the two groups in terms of overall survival (OS), progression free survival (PFS), or RR. It is evident that first-line chemotherapy and EGFR-TKI did not work more effectively together than chemotherapy alone [8].

There is evidence that radiotherapy itself can activate EGFR, leading to increased cell proliferation and increased clonal repopulation of tumor cells during radiotherapy, resulting in radiotherapy

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resistance. Therefore, EGFR inhibitors appear to prevent the development of radiotherapy resistance. Nevertheless, the outcomes of multiple clinical trials involving radiation and TKIs have been unsatisfactory. In their investigation on the effectiveness of gefitinib in conjunction with radiation therapy for advanced non-small cell lung cancer, Stinchcomb [9] et al. found that the overall survival was just nine months. Gefitinib's contribution to increasing the OS and PFS of patients treated with radiation therapy was assessed retrospectively in the SWOG phase III research [10], which discovered that the PFS of the gefitinib group was shorter than that of the placebo group. The results of the CALGB30106 trial demonstrated that gefitinib with radiation therapy still did not significantly improve side effects or toxicities. The combination of targeted agents with radiotherapy did not seem to provide significant benefit to patients, which may be related to the molecular heterogeneity of tumor patients. In addition, TKI treatment may have poor efficacy in patients with K-RAS mutations who previously received radiotherapy [8]. Therefore, the exact efficacy of the combination of the two remains to be verified in more clinical trials.

3.2. Research and Development of New-generation Targeted Drugs

Tumorigenesis is a multigene, multistep, long-term evolutionary process, with the EGFR mutation being only one of the NSCLC cancerous processes that have been clearly confirmed, which means targeted therapy for EGFR alone cannot cure all NSCLC patients. Therefore, the discovery of new therapeutic targets and the development of new targeted drugs are the top priorities in the current research on lung cancer diagnosis and treatment.

It has been found that 60% to 80% of NSCLC patients have overexpression of Cellular-mesenchymal epithelial transition factor (c-met), whose amplification can activate the erbB-3-dependent signaling pathway to achieve non-EGFR-dependent activation through the Phosphatidy 3 Kinase (PI3K)/Protien Kinase B (AKT) pathway, promoting tumor development, with this function being independent of whether EGFR is mutated or not. Therefore, c-met is expected to be an effective therapeutic target for patients with acquired resistance to TKI [11]. The monoclonal antibody Monoclonal Antibody (MET-MAb), PF-299804, and ARQ-197 are the primary c-met antagonists that are presently being studied. In 167 patients with advanced non-small cell lung cancer (NSCLC) who had undergone chemotherapy (but not EGFR-TKI), a randomized phase I clinical trial comparing ARQ-197 in conjunction with erlotinib or placebo revealed a tendency toward longer PFS and longer OS [12].

4. Conclusion

Research on molecular diagnosis or molecular prediction of lung cancer has made great progress in recent years. The development of high-throughput technologies such as gene chips, tissue chips and protein chips has discovered many new molecular markers or combinations of molecular markers for lung cancer. As lung cancer treatment is increasingly moving toward targeting and specificity, the detection of molecular markers may play a major role in lung cancer diagnosis and treatment.

In the past twenty years, translational medicine research on NSCLC-targeted drugs has developed rapidly and achieved world-renowned results. More and more NSCLC-targeted drugs have been approved by drug regulatory authorities for clinical use, with the individualized therapy based on which having brought new opportunities for the NSCLC treatment, which is the result of translational medicine research and the future direction of international medical research.

Although traditional radiotherapy has become mature in the treatment of NSCLC patients, it also has many limitations, such as many side effects, poor patient tolerance, and generally shorter survival. The exploration of the efficacy of combination therapy and monotherapy is still in the exploratory stage and faces many difficulties. Nonetheless, the therapeutic prospect revealed by the current data is

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still promising, and it is worthwhile to further explore how to further "accurately" select patients who are suitable for and explore more efficient and safer treatment modes, bringing hope for the survival and cure of more NSCLC patients. Molecularly targeted antitumor drugs are playing an increasingly important role in the NSCLC treatment because of their unique targeting, efficacy and safety. With the research of new targets and the continuous development of targeted drugs, the application of molecularly targeted antitumor drugs will have a broader prospect and will lead the NSCLC treatment into a new period.

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