Research On Befortinib: Characteristics, Role, And Development of Fourth-Generation EGFR-Tkis

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Abstract. Lung cancer is one of the most common cancers in terms of morbidity and mortality. Among them, non-small cell lung cancer (NSCLC) accounts for 90% of lung cancer patients. Epidermal Growth Factor Receptor (EGFR) mutations are also the most common type of driver gene mutation in advanced NSCLC. In Chinese NSCLC patients, the proportion of EGFR mutations was 28.2%, and this proportion increased to 50.2% in lung adenocarcinoma. All three generations of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKI) are effective therapeutics for lung cancer patients carrying EGFR-sensitive mutations or T790M mutations, each of which has its own advantages and characteristics, as well as its own limitations and adverse reactions. Befortinib, which is new to the market in 2023, has better Median progression-free survival (mPFS). However, three generations of EGFR-TKI cannot completely overcome the resistance mechanism of lung cancer. In addition to the T790M mutation, there are other mutations or mechanisms that cause lung cancer to become resistant to third-generation EGFR-TKI, such as C797S mutation, MET amplification, HER2 amplification, etc. At present, the fourth-generation of EGFR-TKI is still under continuous research and development.

Keywords: Lung cancer; NSCLC; Befortinib; the fourth-generation EGFR-TKI.

1. Introduction

In many cancers, EGFR is overexpressed or mutated, contributing to continuous activation of downstream signaling pathways, irrespective of ligand binding. This aberrant activation promotes tumor growth, survival, angiogenesis and metastasis. EGFR-TKI (Beta-cysteinone deaminase) represents a new anticancer medication that directly targets the EGER (beta-cysteinone deaminase receptor), inhibiting the proliferation and division of cancer cells. EGFR is a common malignant tumor antigen and is expressed in many cancers [1, 2]. EGPR-TKI can delay the development of cancer by inhibiting EGFR receptor activity, resulting in a short-term extension of survival for patients [3].

When EGFR-TKI binds to the EGFR receptor, it inhibits the activity of the receptor, thus inhibiting the growth and division of cancer cells. It can bind to various types of kinases of the EGFR receptor, which can inhibit the activity of the receptor, thereby inhibiting the growth and division of cancer cells. In addition, EGFR-TKI can directly target EGFR active sites and block EGFR receptor signaling in cancer cells, thereby reducing cancer cell growth and metastasis [4].

First-generation EGFR-TKI include Gefitinib, Erlotinib, Ectinib and so on. They primarily treat patients with metastatic or recurrent NSCLC with EGFR-activating mutations. They attach reversibly to the ATP-binding site within the tyrosine kinase domain. Nonetheless, the first generation of EGFR inhibitors can manifest significant resistance after a period of 10 to 12 months [5], primarily due to the secondary T790M mutation.

Second-generation EGFR-TKIs include Afatinib, Dacotinibs and so on. They are primarily used in the treatment of NSCLC, especially in patients with specific EGFR mutations. In certain instances, they have demonstrated enhanced effectiveness in comparison to first-generation EGFR-TKIs, possessing the capability to surmount specific resistance mechanisms [6].

Third-generation EGFR-TKIs include Osimertinib, Amitinib, Befortinib and so on. The third generation TKIs overcome the resistance caused by the T790M mutation and were well tolerated.BPI-16350, a novel molecular entity compound, has been independently developed by Beida

Pharmaceutical, possessing comprehensive independent intellectual property rights. It is intended to be used in conjunction with fluvestrant, as opposed to a placebo combined with fluvestrant, for treating locally advanced, recurrent, or metastatic HR+/HER2- breast cancer that has progressed following previous endocrine therapy, targeting cyclin-dependent kinase 4/6 (CDK4/6). Preclinical data reveal that BPI-16350 exhibits consistent biological activity both in vivo and in vitro in animal models, effectively curtailing the proliferation of numerous solid tumor cells. It has demonstrated commendable anti-tumor effects as both a standalone and combination drug in various solid tumor models, along with possessing excellent physicochemical and pharmacokinetic properties.

Up to the present, five CDK4/6 inhibitors have achieved global approval, namely Pfizer's Pipercilil, Novartis' Rebocilil, Eli Lilly's Abesilil, G1 and Cimcere's Treacilil, and Hengri Pharmaceuticals' Darcilil. Of these, Pibesili, Abesili, and Dalsilili have received approval for marketing in China. BPI-16350 is classified as 'innovative drugs that are not listed either domestically or internationally' and is registered as a Class 1 chemical drug. This article discusses the characteristics, functions of the Befortinib and the development of the Fourth-Generation EGFR-TKIs.

2. Methods

2.1. Data Source and Description

The Data use in this paper come from Befotertinib: First Approval writed by Blair [7] and Beda Pharmaceutical website about befortinib bottle instructions (Table 1) [8].

Table 1. Basic data on Befotinib

Alternative names	Surmana®
Appearance	White powder
Indications and usage	Treatment of adults with locally advanced or NSCLC who have previously experienced disease progression during or after treatment with EGFR-TKI and have been tested positive for EGFR T790M mutations
Route of administration	Oral
Adverse events	thrombocytopenia, headache, leukopenia, anemia and rash
Gauge lattice	(1)25mg (2) 50mg
Dosage and administration method	Once daily, starting at a starting dose of 75mg for 21 days; If there are no serious side effects or grade ≥2 thrombocytopenia or grade ≥2 headache, the dose is adjusted to 100mg once daily after 21 days.

2.2. Description of Relevant Indicators

In the Phase II [6] clinical study, eligible the patients were evenly distributed GroupA and GroupB. They were given different doses of befortinib orally. Group A took befortinib 50mg orally once a day, and 176 people were actually evaluated. Group B participants took oral befortinib 75-100mg once daily, and 290 participants were actually evaluated. The objective response rates of patients were evaluated by an independent review committee, and the results are in the table2.We can see that the second group has better data.

The associated adverse effects of treatment include thrombocytopenia, leukopenia, asymptomatic pulmonary embolism, other venous embolism and thrombosis, electrolyte disturbance, rash, and hyperuricemia. Among them, grade 3 and above treatment-related adverse reactions and serious adverse reactions were 20.5% and 11.4% in group A and 29.3% and 10.0% in group B (Table 2).

Table 2. The results of the phaseII

-	GroupA	GroupB
Objective remission rate	54%	56.90%
Disease control rate	93.20%	94.80%
Median progression-free survival	11.0 months	12.5 months
Intracranial objective response rate	26.70%	57.10%
Intracranial median progression-free survival	16.5 months	Impossible to evaluate
Brain metastases(patients with brain metastases)	56	84

3. Results and Discussion

3.1. The Results of Befotertinib

This study evaluated its efficacy and minimal toxicity by oral administration of 75-100 mg befortinib (D-0316). This suggests that Befortinib is mainly targeted at NSCLC patients with T790M resistance mutations and resistance to first or second-generation EGFR-targeting drugs [8].

In patients with secondary T790M mutations, the Independent Review Committee evaluated the Objective Response Rate (ORR) of Befortinib at 67.6%, and the median Progression-Free Survival (PFS) was 16.6 months. This is the longest mPFS data for all three generations of second-line EGFR-TKI therapy. Chinese scholars further studied the efficacy and safety of this drug as the primary treatment for patients with advanced NSCLC with EGFR-sensitive mutations.

This multicenter, open-label, randomized controlled clinical trial included participants aged 18 and above, diagnosed with either locally advanced or metastatic NSCLC,a PS score of 0 to 1, 19del or 21L858R mutation, and asymptomatic BMS. Eligible patients were randomly assigned 1:1 to Befortinib or Ectinib, with studies stratified based on EGFR mutation type, presence or absence of central nervous system metastasis, and sex [6].

The study hypothesized that Befortinib could increase the median PFS from 10 months to 16 months in the Ectinib group, i.e., HR=0.625. A sample size of 144 patients was required in each group, with a total of 360 subjects considering a 20% shedding rate. An interim analysis was performed, and the primary endpoint PFS reached the preset α level in the first interim analysis, ensuring the final analysis was not affected by multiple adjustments.

A total of 568 patients were screened at 39 medical centers in China within a year, with 362 patients enrolled and assigned to either the Befortinib group (n=182) or the Ectinib group (n=180) on a 1:1 randomized basis. The baseline characteristics were comparable between the two groups. At the time of data analysis on July 30, 2022, 36% and 16% of patients in both groups continued to receive the study drug therapy. The median PFS of the two groups, assessed by the Independent Trial Committee, were 22.1 months and 13.8 months, respectively, with an HR=0.49.When HR < 1,the event (in this case, disease progression or death) is less likely to occur in the group treated with Befortinib compared to the Ectinib group.When HR = 0.49,it can reflect that patients in the Befortinib group have a 49% chance of experiencing the event (progression or death) at any point in time compared to those in the Ectinib group. In other words, the risk of disease progression or death is 51% lower in the Befortinib group compared to the Ectinib group.

The Objective Response Rate (ORR) and Disease Control Rate (DCR) of the two groups were 67.0% and 64.4%, and 93.4% and 97.2%, respectively. The median DOR assessed by the investigators was 18.1 months and 9.7 months, respectively. Intracranial PFS assessed by the investigators were not reached and 15.2 months, respectively, with HR=0.69, and intracranial ORR were 70% and 50%, respectively. At the time of data analysis, 78% of patients in the Ectinib group had disease progression, with only 14% of patients ending up cross-receiving Befortinib. Additionally, 19% and 51% of patients in the Befortinib and Ectinib groups, respectively, continued to receive third-generation TKI therapy not limited to Befortinib after disease progression.In this study, a total

of 104 patients passed away, with the overall OS maturity reaching 29%. The median OS for both groups was not mature, with the 30-month OS rates being 67.3% and 60.3%, respectively [7].

3.2. Comparison with Other Thrid-Generation EGFR-TKIs

According to research, in late-stage NSCLC patients with t790m positivity who have failed first-line EGFR TKI treatment, Osimertinib has more advantages than chemotherapy. Among patients with sensitive EGFR mutations, Osimertinib is superior to first-generation EGFR TKIs such as Gefitinib or Erlotinib [9]. However, it has serious adverse events and higher medical costs. Aumolertinib in studies has an ORR of 68.9%, and an intracranial ORR (iORR) of 60.9%. Furmonertinib has an ORR of 74%, and its safety is acceptable for patients with EGFR T790M mutations. Befotertinib, at 75 - 100mg, has satisfactory efficacy and controllable toxicity for locally advanced or metastatic NSCLC patients carrying the T790M mutation and resistant to first or second-generation EGFR TKIs. The efficacy of Befotertinib is competitive with other third-generation EGFR TKIs (such as Osimertinib, Omolertinib, Furmonertinib, and Lazertinib) while maintaining commendable safety. In first-line treatment of EGFR mutation-positive NSCLC patients, Befotertinib has significantly superior efficacy in terms of PFS compared to active drugs (Table 3).

Table 3. Comparison with Other Thrid-Generation EGFR-TKIs

	first-line treatment mPFS(months)	second-line treatment mPFS(months)	first-line treatment ORR(%)	second-line treatment ORR(%)
Osimertinib	18.9	10.1	80	71
Almonertinib	19.3	12.4	74	68.9
Vometinib	20.8	11.1	89	76.7
Befortinib	22.1	12.5	75.8	68.5

Note: Dates from FLAURA study, AURA3 study, AENEAS Study, APOLLO study, FURLONG study, NCT3127449, D-0316 studyand, IBIO-102 study. See References [10, 11] for details.

3.3. Development of Fourth-Generation EGFR-TKIs

The superior developmental benefit of fourth-generation EGFR-TKI lies in its elevated inhibitory activity against the triple-mutant EGFR featuring the C797S mutation. Various fourth-generation EGFR-TKIs have been documented, encompassing natural product derivatives and heterogeneous inhibitors. Among these, natural product derivatives like compound 75 and compound 76 have demonstrated inhibition of the EGFR del19/T790M/C797S and EGFR L858R/T790M/C797S cell lines. Furthermore, isomerized inhibitors, such as compound 77 and compound 78, have also exhibited potent inhibitory activity against EGFR L858R/T790M/C797S.These fourth-generation EGFR-TKI are more selective and are able to avoid inhibition of wild-type EGFR, thus reducing the occurrence of side effects. However, there are still some challenges, such as improving the selectivity of drugs, improving cell activity and anti-tumor activity in vivo. the future outlook is to further optimize the structure of fourth-generation EGFR-TKI to improve its selectivity and anti-tumor activity, and to conduct more clinical studies to verify its efficacy and safety [12].

4. Conclusion

As a Class I third-generation EGFR-TKI produced in China, Befortinib has superior overall efficacy, good safety and strong accessibility. It has achieved significant systemic and intracranial outcomes in both first line and second-line EGFR-positive NSCLC, with transverse non-head-to-head comparisons showing the longest PFS at all lines. In addition, its first line and second-line treatment studies were conducted in Chinese patients, and its data are more consistent with the actual situation of Chinese patients. At the same time, it is safe and well tolerated, and common adverse events include thrombocytopenia, headache, leukopenia, anemia and rash. Befortinib is expected to make up for the

existing clinical treatment system and bring hope to more patients with EGFR-mutated NSCLC. Three generations of EGFR-TKI have not been able to completely overcome the resistance mechanism of lung cancer. In addition to the T790M mutation, there are other mutations or mechanisms that cause lung cancer to become resistant to third-generation EGFR-TKI, such as C797S mutation, MET amplification, HER2 amplification, etc. These resistance mechanisms may diminish or disappear the effect of third-generation EGFR-TKI, leading to tumor reprogression or recurrence. However, the future outlook is to further optimize the structure of fourth-generation EGFR-TKI to improve its selectivity and anti-tumor activity, and to conduct more clinical studies to verify its efficacy and safety.

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