Application of Osimertinib for Non-Small Cell Lung Cancer: In Patients with Untreated Central Nervous System Metastasis

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Abstract: Power load forecasting is very important for power dispatching. Accurate load forecasting is of great significance for saving energy, reducing generating cost and improving social and economic benefits. In order to accurately predict the power load, based on BP neural network theory, combined with the advantages of Clementine in dealing with big data and preventing overfitting, a neural network prediction model for large data is constructed.

1. Introduction

Lung cancer is one of the most common malignant tumors globally, and smoking is still the leading cause of lung cancer in most patients. According to the morphology of cancer cells, lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter accounting for 80% to 90% of lung cancers [1]. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the three main types of NSCLC. Among them, adenocarcinoma is the most common lung cancer. The American Joint Committee on Cancer (AJCC) divides NSCLC into stages 0 to 4, written in stages 0, I, II, III, and IV. Since the early symptoms of NSCLC are not obvious, most of the patients are in the late/metastatic stage when they are diagnosed, leading to a high mortality rate.

The brain is the most common site of NSCLC metastasis. About 40% of NSCLC patients will have brain metastases during the disease progression [2]. For patients with brain metastases (BM), the prognosis is still abysmal, and the median overall survival (OS) does not exceed three months on average in untreated patients [3]. The main treatments for NSCLC brain metastases include whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), stereotactic ablation radiotherapy (SABR), chemotherapy, molecular targeted therapy and immunotherapy, which are be grouped into local therapy and systemic therapy. Of course, metastatic lung cancer is usually not treated locally unless it only spreads to the brain.

Leptomeningeal metastasis (LM) is the diffuse or multifocal, local dissemination or infiltration of malignant tumor cells in the pia mater of the brain and spinal cord. It then manifests as brain, cranial nerve and pia mater injury, one of the most severe complications of NSCLC [4]. LM occurs in approximately 3%-4% of patients with advanced NSCLC [5]. Patients with NSCLC and LM have a poor prognosis, with a median overall survival (OS) of 3-10 months after diagnosis [5-7]. In recent years, with the progress of treatment, the survival rate of patients has gradually increased, and the probability of LM also has increased [8]. Among NSCLC patients with epidermal growth factor receptor (EGFR) mutations, more than 10% of patients present with LM [9]. However, due to the blood-brain barrier (BBB), most chemotherapeutic drugs are limited in practical usage.

Osimertinib (AZD9291), a potent and irreversible third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), targets T790M resistance and EGFR activating mutations, can pass through the BBB,

and has tolerable safety [10-11]. It has been proven effective in patients with BM and LM with EGFR mutation in recent clinical studies, regardless of whether the EGFR with T790M mutation is positive or negative [10-15]. Therefore, the latest edition of the National Comprehensive Cancer Network (NCCN) NSCLC guidelines has recommended Osimertinib for the first-line treatment of EGFR mutations.

At present, for untreated patients with BM NSCLS, relevant research covers many aspects, such as molecular targeted therapy and immunotherapy. Aaron S. Mansfield et al. reported that in patients with programmed death-ligand 1 (PD-L1) positive BM NSCLC using pembrolizumab monotherapy, the OS was significantly longer than chemotherapy [16]. A multicenter phase III study showed that Bevacizumab combined with Erlotinib could dramatically improve the progression-free survival (PFS) of untreated patients with BM EGFR-mutant NSCLC [17]. And Alice T. Shaw reported the interim treatment results of Lorlatinib, the third-generation inhibitor of anaplastic lymphoma kinase (ALK), on untreated patients with advanced ALK-positive BM NSCLC [18]. Patients who received Lorlatinib had significantly longer PFS and a higher frequency of intracranial reactions than those who received Crizotinib. And Pembrolizumab combined with pemetrexed-platinum in the first-line treatment of metastatic non-squamous NSCLC continues to show significantly improved OS and PFS, regardless of PD-L1 expression or liver/brain metastasis [19].

A meta-analysis about Osimertinib in first-line treating BM/LM mutated NSCLC was performed. However, limited data support our prescribed circumstances, although Osimertinib can establish a better CNS activity in some clinical trials. There is no aggregate analysis regarding treating CNS mutated NSCLC with Osimertinib in the first line. Thus, our meta-analysis will be the first systematic review to analyze and integrate the results of published literature, aiming at the efficacy of Osimertinib in untreated CNS mutated patients.

2. Methods

2.1 Search strategy:

PubMed, Web of Science, and the Cochrane Library were systematically searched for relevant reports that meet the selection criteria for the current study. The last retrieval was performed at October 9, 2021. An advanced search function was used for retrieving. For instance, the following search strategy was applied for searching in PubMed: (Osimertinib) OR (AZD9291) OR (Tagrisso)) AND (NSCLC) OR (Non-small cell lung cancer) AND (untreated)) OR (first line) AND (CNS) OR (Brain)) OR (metastasis) AND (Osimertinib [Title]).

2.2 Selection criteria:

All authors were agreed with the selection criteria and the selected studies. The studies satisfying the following criteria were selected: (1) the patients were diagnosed with NSCLC; (2) the patients have not received systemic treatments; (3) the patients were treated with Osimertinib only; (4) the patients were treated with 80 mg dosage of Osimertinib daily only; (5) the studies were written in English; (6) the most recent data was selected when the same clinical trial was reported from more than one paper.

2.3 Summary of selected studies:

In the Reference [11] study, patients (N = 556) were enrolled in a 1:1 ratio to Osimertinib (at a dose of 80 mg once daily) or standard EGFR-TKIs (Gefitinib at a dose of 250 mg once daily or Erlotinib at a dose of 150 mg once daily) randomly. The primary endpoint was investigator-assessed progression-free survival (PFS).

In the Reference [20] study, an electronic medical record database search turned up 40 individuals who had Osimertinib treatment at the Stanford Cancer Center between November 2015 and December 2016. Eleven patients had advanced brain metastases and received no radiation (group A, N=11), nine patients had growing brain metastases and received radiation while starting Osimertinib (group B, N=9), and 20 patients had stable brain metastases at the time of commencing Osimertinib (group C,

N=20). The three groups were assessed retrospectively for patient and illness characteristics, radiographic responses, and survival outcomes.

In the Reference [21] study, the therapeutic effectiveness of Osimertinib was evaluated in previously untreated patients (N=19) with metastatic non–small cell lung cancer (NSCLC) who had activating EGFR mutations in both circulating tumour DNA (ctDNA) and tumour DNA. The study participants were given an 80 mg dose of Osimertinib once a day. The primary endpoint was objective response rate (ORR), with ctDNA test sensitivity, progression-free survival (PFS), duration of response (DoR), and safety as secondary endpoints.

3. Results

3.1 Overview

There is one single-arm trial, one Randomised Controlled Trial (RCT) and one retrospective trial. Three studies were published from 2019 to 2021, and the participants' age included was ranged from 32 to 85. The Reference [11] study was a subgroup of the FLAURA study, which satisfies the search criteria. In the Reference [20], only the group C cohort which met the selection criteria was included in this article. All treatments included in the selected studies were first-line treatments. The total sample size was 167, with a range from 19 to 128. All studies included Osimertinib for 80 mg daily prescription.

Table 1. Baseline characteristics of the included studies

Study (year)	Country	Trail design	Sub-category	Treatment line	Sample size	Dosage and length of Osimertinib
Park [21]	Republic of Korea	Single-arm Phase II	NR	First	19	80 mg per day, to Progression Disease (PD)
Ramalingam [11]	Australia et al.*	RCT Phase III	FLAURA	First	128	80 mg per day, to Progression Disease (PD)
Xie [20]	United States	Retrospective	NR	First	20	80 mg per day, to Progression Disease (PD)

*Belgium, Brazil, Bulgaria, Canada, China, Czechia, France, Germany, Hungary, Israel, Italy, Japan, Korea, Republic of Malaysia, Philippines, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States, Vietnam.

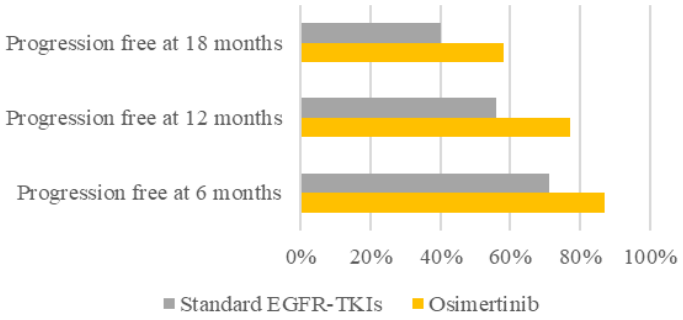

Fig 1. The percentage of Standard EGFR-TKIs treated patients versus Osimertinib treated patients with progression-free in 18 months, 12 months and six months.

3.2 Original and pooled results:

In the Reference [11] study, the proportion of progression-free patients treated by Osimertinib at six months, 12 months and 18 months was 88%, 77%, 58%, respectively, while 71%, 56%, 40% for the patients treated by standard EGFR-TKIs. The pooled percentage of progression-free at six months was 81%, progression-free at 12 months was 58.5%, progression-free at 18 months was 41.5%. The pooled median PFS was 9.7275 (95% CI, 5.570-14.8). Fig 1. provides the percentage of Standard EGFR-TKIs treated patients versus Osimertinib treated patients with progression-free in 18 months, 12months and six months.

Fig 2. shows the rate of Progression Disease (PD), Stable Disease (SD), Partial Response (PR) and Complete Response (CR) in Standard EGFR-TKIs treated patients versus Osimertinib treated patients. According to the pooled results from Reference [8], no patients with Osimertinib progressed their diseases while 9% of Standard EGFR-TKIs treated patients have PD. 15% patients with Osimertinib and 30.5% patients with Standard EGFR-TKIs had SD. 46.5% of patients with Osimertinib and 43.5% patients with Standard EGFR-TKIs had PR. 32% of patients with Osimertinib and 12% patients with Standard EGFR-TKIs had CR.

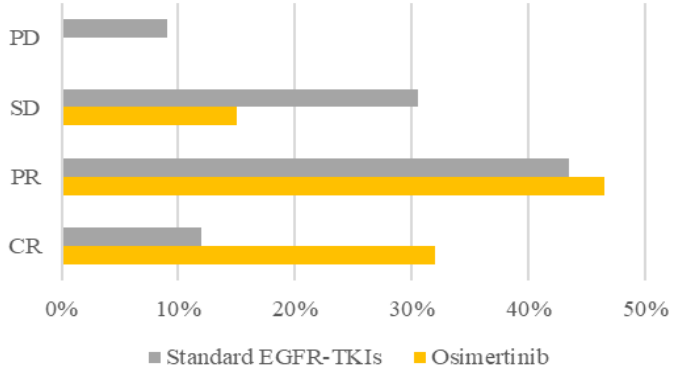

Fig 2. The pooled rate of Progression Disease (PD), Stable Disease (SD), Partial Response (PR) and Complete Response (CR) in Standard EGFR-TKIs treated patients versus Osimertinib treated patients.

The median best percentage change in Reference [11] was -64% ranged from -100% to +20% with Osimertinib, and -45% ranged from -100% to +20% with Standard EGFR-TKIs. The Reference [21] shows -40% as the median with a range of -68.4% to 51.7%. Fig 3. shows the percentage change from the baseline of Reference [11].

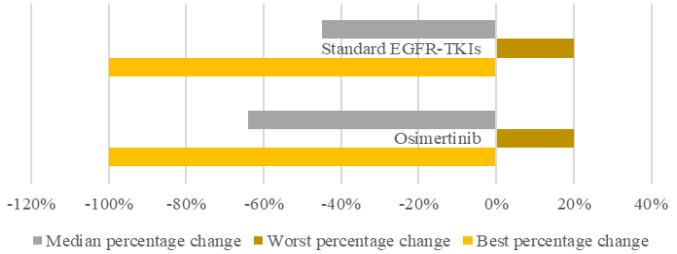

Fig 3. The percentage change from the baseline of the study Reference [11] in CNS target lesion size with Osimertinib and Standard EGFR-TKIs.

All data in three studies were analyzed in a 95% confidence interval. The Reference [20] did not report the median duration of response (DOR), overall response rate (ORR), the median time to response, complete response (CR) rate, partial response (PR) rate, stable disease (SD) rate and progression disease (PD) rate of subgroup C. The median progression-free survival (PFS) in the Reference [20] and Reference [21] was 8.355 months (5.570-11.140), 11.1 months (7.4-14.8), respectively. mPFS of the Reference [11] was Not Reached (NR). One subset has not reached mDOR in Reference [11]. The mDOR in Park's study was 9.3 months (3.7-14.9). The overall response rate (ORR) in Reference [11] and Reference [21] was 78.5% and 60%, respectively. The median time to

response in Reference [11] and Reference [21] was six months (6-12) and 1.7 months (1.6-1.8), respectively. In total, pooled mPFS was 9.7275 months, ORR was 69.25%, and the Median time to response was 7.7 weeks.

Table 2. summarized reported data

Study	*mPFS (months) (95% CI)*	*mDOR (months) (95% CI)*	*ORR*	*Median time to response (weeks)*	*% CR*	*% PR*	*% SD*	*% PD*
Reungwetwattana [11]	NR (16.5-Not Reached)	Subset 1: NR (11.9-NC*) Subset 2: 15.2 (4.1-NC)	78.5 %	6 (6-12)	32 %	46.5%	15%	0%
Xie [20]	8.355 (5.570 - 11.140)	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported
Park [21]	11.1 (7.4-14.8)	9.3 (3.7-14.9)	60%	1.7 (1.6-1.8)	0%	60%	33%	7%

*NC: not calculable.

4. Discussion

Three research projects, 167 patients, were involved in the current study to evaluate the efficacy of Osimertinib in untreated CNS metastases in NSCLC patients. Generally, Osimertinib has higher efficacy than standard EGFR-TKIs (Gefitinib and Erlotinib). The higher ORR and lower PD values confirmed the effectiveness of Osimertinib in treating NSCLC with CNS metastases patients.

The efficacy of standard cytotoxic chemotherapy for NSCLC (mainly platinum doublets or first- and second-generation EGFR-TKIs) in treating brain metastases is restricted due to the blood-brain barrier [22]. In the meta-analysis, Osimertinib was found to improve the treating outcomes indicated by many efficacy indicators such as overall survival, post-progression survival, and brain metastasis-free survival [23-25]. In addition, though not much significant, 80 mg daily prescription of Osimertinib shows a better therapeutic effect than higher doses ranging from 160 to 240mg. The higher doses also demonstrated higher incidence and severity of adverse effects (AE). Consequently, the daily intake of 80 mg Osimertinib is recommended as the most proper dose on both effectiveness and safety [26-27].

Additional fundamental researches are needed for basic mechanisms of different therapy for the diverse population especially when the efficacy differences between LM and BM patients are not apparent. The results from the BLOOM study (ClinicalTrials.gov identifier: NCT02228369) and the OCEAN study (LOGIK1603/WJOG9116L) are expected once projects finish, from which the former evaluates the patients with both LM and BM.

We acknowledge several limitations to this. First, the results should be interpreted with caution because of high heterogeneity, although several subgroup analyses were performed. Given the differences of the selected studies, there is a greater risk of potential selection and reporting bias. Second, the limited number of studies and sample sizes might lead to invalid statistical analyses.

Third, several types of bias such as unmeasured components, inherent limitations, and common bias in observational results should be noticed.

5. Conclusion

In this article, we reviewed currently limited studies on first-line CNS metastasis treatment. The results and the pooled results in the three selected indicate that Osimertinib is effective compared to Gefitinib and Erlotinib. More researches are needed to find out exact related clinical data and the factors that affect efficacy.

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