Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in the Adjuvant Setting for Patients with Resected Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer: A Meta-Analysis with 11 Trials

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Keywords

Epidermal growth factor receptor tyrosine kinase inhibitors · Adjuvant setting · Non-small cell lung cancer · EGFR mutation · Meta-analysis

Abstract

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have recently become the standard first-line therapy for advanced non-small cell lung cancer (NSCLC) patients harboring EGFR mutations. This study aimed to define the role of EGFR-TKI treatment in the adjuvant setting of patients with resected EGFR-mutant NSCLC.

Methods: Three online databases (PubMed, Embase, and the Cochrane Library) were used to conduct systematic research to search for studies published before June 1, 2020. The disease-free survival (DFS) and overall survival (OS) of patients with resected EGFR-mutant NSCLC after radical surgery treated with EGFR-TKIs versus non-EGFR-TKIs in the adjuvant setting were compared. Based on rigorous self-defined inclusion and exclusion criteria, studies were selected, and a meta-analysis was performed using hazard rate (HR) and 95% CIs as effective measures. **Results:** Eleven studies, published between 2011 and 2020, with a total of 1,900 patients, were included in this meta-analysis. EGFR-TKI treatment showed a significant beneficial effect on DFS (HR 0.42; 95% CI 0.31–0.57) and OS (HR 0.62; 95% CI 0.45–0.86) for patients with resected EGFR-mutant NSCLC after radical resection in the adjuvant setting. **Conclusion:** Our meta-analysis results

suggested that EGFR-TKI treatment improved the DFS and OS of completely resected patients with EGFR-mutant NSCLC compared with non-EGFR-TKI treatment in the adjuvant setting. In the future, our conclusion should be confirmed by additional large-scale and well-designed clinical trials.

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Introduction

Lung cancer is considered as the main cause of cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung carcinoma patients [1]. Radical resection, which provides the highest probability of cure, is the most effective treatment for early and some locally advanced NSCLC [2]. However, despite optimal surgical management, the 5-year survival rate of these patients remains suboptimal, ranging between 25 and 73% for pathological stages I and IIIA [3]; therefore, adjuvant therapy after surgery is crucial. Furthermore, the results from large randomized trials and meta-analyses revealed that cisplatin-based chemotherapy as adjuvant therapy is strongly recommended for stage II–IIIA NSCLC after complete resection [4–6], which gives rise to a survival improvement of 5% at 5 years (from 40 to 45%) [7]. However, we cannot neglect the adverse effects of cytotoxic agents, which are the primary reason for refusal of or insufficient chemotherapy [5]. Therefore, although

adjuvant chemotherapy might confer a survival benefit to some patients with stage II–IIIA NSCLC, we should seek further survival improvements through the use of alternative treatments with better tolerability than adjuvant chemotherapy.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been the standard first-line therapy for patients with advanced EGFR-mutant NSCLC; these confer better disease-free survival (DFS) and overall survival (OS) than cisplatin-based chemotherapy [8, 9]. Cisplatin-based chemotherapy is the recommended standard-of-care adjuvant treatment for stage IIa–IIIB resected NSCLC, irrespective of EGFR mutation status [3, 10]. In the past 5 years, several trials that compared the efficacy and toxicity of EGFR-TKIs with those of chemotherapy or placebo among resected patients harboring EGFR mutations were published. Some trials indicated that EGFR-TKIs are superior to chemotherapy as an initial treatment for patients with EGFR-mutant NSCLC following surgical resection [11–15], whereas other trials showed no difference [16, 17]. The multicenter single-arm SELECT trial, performed by investigators from the Memorial Sloan Kettering Cancer Center, demonstrated the feasibility of adjuvant erlotinib in patients with EGFR-mutant NSCLC and revealed that EGFR-TKIs could improve the survival of EGFR-mutant patients after surgery compared with historical controls [18]. However, the previous trials BR19 [16] and RADIANT [17], without inclusion of EGFR mutation status in the patient selection criteria, yielded negative outcomes. In clinical practice, whether EGFR-TKIs in adjuvant treatment for patients with resected EGFR-mutant NSCLC improve survival compared with adjuvant chemotherapy or placebo is still controversial.

We conducted this meta-analysis of EGFR-mutant NSCLC patients after radical surgery treated with EGFR-TKIs versus non-EGFR-TKIs in the adjuvant setting to define the role of EGFR-TKI treatment in the adjuvant setting for patients with resected EGFR-mutant NSCLC.

Materials and Methods

Search Strategy

All studies comparing survival with EGFR-TKI treatment with survival with non-EGFR-TKI treatment in the adjuvant setting in completely resected patients with early-stage NSCLC were eligible for inclusion. To identify eligible studies, we searched PubMed, Embase, and the Cochrane Library without any restrictions regarding publication status, type, date, or language. The search was updated to June 1, 2020. The main search terms included “adjuvant” or “postoperative”; “epidermal growth factor receptor tyrosine kinase inhibitors,” “EGFR-TKI,” “gefitinib,” “erlotinib,” “icotinib,” “dacomitinib,” or “osimertinib”; and “non small cell lung cancer,” “NSCLC,” “lung neoplasms,” or “adenocarcinoma of lung.” We also reviewed the reference list for relevant articles.

Study Selection

Studies that met the following criteria were included: (1) adult patients with pathologically confirmed NSCLC; (2) studied patients underwent primary radical resection harboring EGFR mutations (exon 19 deletion or exon 21 Leu858Arg); (3) evaluation of the efficacy of adjuvant EGFR-TKIs versus chemotherapy, placebo; adjuvant EGFR-TKIs combined with chemotherapy versus chemotherapy alone; (4) reporting at least one relevant clinical endpoint event, for instance, DFS or OS with long-term follow-up; and (5) containing original data sufficient to calculate HR or *p* values. All the enrolled studies were published in English without any restriction on publication type.

The exclusion criteria included (1) abstracts, letters, case reports, reviews, duplicates, or nonclinical studies; (2) studied patients who had previously undergone neoadjuvant therapy (neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy) or had previously been exposed to EGFR-TKIs or immunologic therapy before surgery and those with incomplete resection; (3) single-arm studies reporting adjuvant EGFR-TKI outcomes; (4) studies with irretrievable or insufficient data for statistical analysis; and (5) original articles with unavailable full text.

Some studies analyzed the effects of EGFR inhibitors combined with conventional systematic therapy (EGFR-TKIs + chemotherapy) compared with those without EGFR inhibitors (only conventional systematic therapy), whereas others employed EGFR-TKIs instead of chemotherapy (EGFR-TKIs vs. chemotherapy) after complete resection in patients with EGFR-mutant NSCLC. Therefore, to evaluate the effects on patients who had received EGFR-TKIs in the adjuvant treatment setting compared with those who had not received these, we included all studies in our meta-analysis.

Data Extraction and Quality Assessment

We extracted all the corresponding information including the first author, publication year, region, number of participants, EGFR mutation rate, median EGFR-TKI treatment duration, median follow-up, participants’ characteristics (age, stage, and treatment strategy), and outcomes from each selected study. Two independent investigators carried out the work of study selection and data extraction. If disagreement emerged, a consensus was reached after discussion with a third author.

The methodological quality of the enrolled articles was evaluated independently by the two investigators. A rating system called the Newcastle-Ottawa Scale [19], which consists of 3 aspects, i.e., selection (0–4 points), comparability (0–2 points), and outcome (0–3 points), was used for nonrandomized cohort studies. The total score achieved from the scores of the 3 sections ranged from 0 to 9, which was positively correlated with the study’s quality. Furthermore, studies awarded with scores >5 were considered to be of acceptable quality. The Cochrane Collaboration’s tool for estimating the risk of bias (5.3.0) was used to evaluate the quality of the included randomized controlled trials (RCTs) [20] with the following methodological items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each item was classified as low risk, high risk, or unclear risk, determining the general quality when taken together. The disagreements between the two investigators were resolved by discussion with a third investigator.

Statistical Analysis

Review Manager 5.3 and STATA 12.0 software was applied to conduct all statistical analyses. Based on the methods of Tierney et al. [21] and Parmar et al. [22], we directly extracted HR and 95% CIs from each study or estimated these data. An HR <1 showed that EGFR-TKI treatment in the adjuvant setting might provide

Fig. 1. Flow diagram of study selection.

survival benefits to patients with resected EGFR-mutant NSCLC. I^2 tests were conducted to test for heterogeneity, and no heterogeneity was assumed if $p > 0.1$ or $I^2 < 50\%$ using a fixed-effects statistical model, whereas $p < 0.1$ or $I^2 > 50\%$ was suggestive of substantial journal pre-proof heterogeneity, so a random-effects model was used. Publication bias was estimated visually by funnel plots and statistically by Egger's and Begg's tests. A p value < 0.05 was deemed statistically significant.

Results

Study Characteristics

In the initial search, a total of 2,246 articles were identified by combining the results from PubMed (708), Embase (1,802), and the Cochrane Library (116) and removing duplicates (Fig. 1). After reviewing the titles and abstracts of these articles, the full texts of 28 studies were retrieved and examined for eligibility, 6 of which were excluded because they were not completed, 4 trials were excluded because of unavailable survival data, 3 studies were excluded due to a single-arm design, and 4 studies were excluded because they were reviews and meta-analyses. The remaining 11 studies of acceptable quality were finally included in our meta-analysis according to the inclusion and exclusion criteria, 8 of which were RCTs and 3 were retrospective comparative studies. Figure 1 presents the detailed study selection procedure in the

form of a flow diagram. In 9 studies, all of the patients were diagnosed with EGFR-mutant NSCLC [11–14, 23–26]. Moreover, the other 2 studies (BR19 and RADIANT) [16, 17] reported detailed data for EGFR-mutant subgroups, though the proportions were relatively low (4 and 16.5%, respectively). We enrolled only a portion of patients with EGFR mutations in the BR19 and RADIANT trials into the meta-analysis to compare OS and DFS because some of those patients did not harbor EGFR mutations in the study. A total of 1,900 patients were enrolled in the pooled analysis, including 887 in the EGFR-TKI treatment group and 1,013 in the non-EGFR-TKI treatment group in the adjuvant setting. All patients enrolled in this meta-analysis harbored EGFR-sensitive mutations. Table 1 shows the characteristics of all the 11 included studies.

Effect of EGFR-TKI Treatment in the Adjuvant Setting on the DFS of Patients with EGFR-Mutant NSCLC

Eleven studies (1,900 patients) were included in the analysis of DFS for the comparison between the EGFR-TKI group (TKIs only/TKIs plus chemotherapy) and the non-EGFR-TKI group (placebo/chemotherapy) in the adjuvant setting for patients with resected EGFR-mutant NSCLC, considering the heterogeneity ($I^2 = 62.2\%$, $p = 0.003$). Therefore, a random-effects model was applied.

Table 1. Basic characteristics of the enrolled studies

Study	Study region	Patients, <i>n</i>	Median age, years	Pathologic stage	EGFR mutant (exon 19 del and exon 21 L858R), %	Adjuvant therapy setting	Usage of drugs	Asian, %	Median TKI treatment duration, months	Median follow-up, months	Design	Outcome	HR and 95% CI
Janjigian et al. [26], 2011	USA	167	68.7	I–III	100	56	111	G/E	NA	20	RCT	DFS, OS	DFS 0.53 (0.28–1.03) OS 0.62 (0.18–1.40)
D’Angelo et al. [25], 2012	USA	286	68	I–IIIA	100	84	202	G/E	NA	18.6	RCS	DFS, OS	DFS 0.43 (0.26–0.72) OS 0.50 (0.23–1.08)
Goss et al. [16], 2013 (BR19)	USA	15	66.5	IB–IIIA	4	7	8	G	0	4.8	RCT	DFS, OS	DFS 1.84 (0.44–7.73) OS 3.16 (0.61–16.45)
Li et al. [24], 2014	China	60	57	IIIA (N2)	100	30	30	G	100	6	RCT	DFS, OS	DFS 0.37 (0.16–0.85) OS 0.37 (0.12–1.13)
Lv et al. [11], 2015	China	138	60.8	I–IIIA	100	31	107	G/E/I	100	18	RCS	DFS, OS	DFS 0.34 (0.18–0.73) OS 0.62 (0.29–1.34)
Kelly et al. [17], 2015 (RADIANT)	USA	161	62	IB–IIIA	16.5	102	59	E	NA	11.9	RCT	DFS, OS	DFS 0.61 (0.38–0.98) OS 1.09 (0.55–2.16)
Feng et al. [23], 2015	China	41	56	IB–IIIA	100	21	20	I	100	NA (range 4–8)	RCT	DFS	DFS 0.29 (0.07–1.17)
Zhong et al. [13], 2018 (ADJUVANT)	China	222	59	II–IIIA (N1–N2)	100	111	111	G	100	21.9	RCT	DFS	DFS 0.60 (0.42–0.87)
Xie et al. [12], 2018	China	116	57.5	II–IIIA	100	55	61	G	100	20.7	RCS	DFS, OS	DFS 0.36 (0.19–0.68) OS 0.50 (0.18–1.40)
Yue et al. [14], 2018 (EVAN)	China	102	58	IIIA	100	51	51	E	100	23.9	RCT	DFS, OS	DFS 0.327 (0.160–0.669) OS 0.165 (0.047–0.579)
Wu et al. [31], 2018 (ADAURA)	China	682	63	IB–IIIA	100	339	343	O	64	22.5	RCT	DFS	DFS 0.20 (0.14–0.30)

AC, adjuvant chemotherapy; E, erlotinib; G, gefitinib; I, icotinib; O, osimertinib; RCS, retrospective comparative study; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval. NA, not available.

Fig. 2. Forest plots of the HR of disease-free survival (DFS) with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) versus non-EGFR-TKIs in the adjuvant setting in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after radical resection.

Our results clearly demonstrated that EGFR-TKIs showed a significant beneficial effect on DFS in patients with EGFR-mutant NSCLC (HR 0.42; 95% CI 0.31–0.57; Fig. 2).

Effect of EGFR-TKI Treatment in the Adjuvant Setting on the OS of Patients with EGFR-Mutant NSCLC

A meta-analysis of 8 studies (955 patients) showed effects of EGFR-TKIs versus non-EGFR-TKIs in the adjuvant setting on the OS of patients with EGFR-mutant NSCLC after radical resection. EGFR-TKI treatment exhibited superiority over non-EGFR-TKI therapy in the adjuvant setting (HR 0.62; 95% CI 0.45–0.86; heterogeneity $I^2 = 41.3\%$, $p = 0.103$; Fig. 3).

Publication Bias

Based on the data for DFS and OS, publication bias was evaluated by Begg's funnel plot and Egger's linear regres-

sion test. In our meta-analysis, no publication bias was found in the DFS group ($p = 0.325$ [>0.05] for Begg's test) and in the OS group ($p = 0.262$ [>0.05] for Begg's test) (Fig. 4).

Discussion

According to the previous clinical trials and meta-analyses, cisplatin-based chemotherapy as the previous standard adjuvant treatment does improve the OS time for NSCLC patients, regardless of the EGFR mutation status, after radical operation [4–6]. However, its benefits have reached a plateau, and a high risk of recurrence and adverse events also limits its application. In recent years, EGFR-TKIs have been the standard first-line therapy for patients with EGFR-mutant advanced NSCLC. However, whether they can be employed as adjuvant therapy for

Fig. 3. Forest plots of the HR of overall survival (OS) with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) versus non-EGFR-TKIs in the adjuvant setting in patients with EGFR-mutant non-small cell lung cancer (NSCLC) after radical resection.

those patients with resected EGFR-mutant NSCLC is still controversial. Hence, our research came about to investigate these factors.

Our meta-analysis showed that EGFR-TKI treatment for EGFR-mutant NSCLC patients improved the DFS and OS compared with non-EGFR-TKI treatment in the adjuvant setting after radical resection. Two previous meta-analyses showed that EGFR-mutant NSCLC patients benefited from adjuvant TKI treatment after radical resection [27, 28]. However, our updated meta-analysis included 2 large clinical trials (EVAN and ADJUVANT research). These studies therefore strengthened the evidence for the efficacy of adjuvant EGFR-TKI treatment in terms of DFS and OS in patients with EGFR-mutant NSCLC. Furthermore, our meta-analysis results notably suggested that patients with EGFR-mutant NSCLC may benefit from EGFR-TKI treatment in the adjuvant setting in terms of DFS and OS after complete surgical resection.

The single-arm phase II SELECT study revealed that patients with EGFR-mutant stage IB–IIIA resected NSCLC might benefit from adjuvant EGFR-TKIs [18]. Pa-

tients ($n = 100$) with resected stage IA–IIIA (the 7th edition of the American Joint Committee on Cancer Staging System) EGFR-mutant NSCLC were treated with erlotinib (150 mg/day for 2 years) after standard adjuvant chemotherapy, with or without radiotherapy. The median follow-up was 5.2 years, and the 2-year DFS rate was 88% (96% with stage I, 78% with stage II, and 91% with stage III). The median DFS and OS have not been reached, and the 5-year DFS and OS rates were 56% (95% CI 45–66) and 86% (95% CI 77–92). A retrospective study reported a trend toward an improvement in DFS among individuals with resected stage I–III lung adenocarcinomas harboring EGFR mutations compared with a historical comparator [26]. These 2 studies presented a low rate of recurrence and an encouraging OS with adjuvant TKIs. The limitation of these studies was that they were not RCTs.

Moreover, EGFR-TKIs have no effect on patients with wild-type EGFR. In unselected patients with advanced NSCLC, EGFR-TKIs did not improve survival compared with a placebo [29]. For unselected patients with resected lung cancer, the treatment with adjuvant EGFR-TKIs did

Fig. 4. **a** Publication bias for disease-free survival between epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and non-EGFR-TKIs in the adjuvant setting. **b** Publication bias for overall survival between EGFR-TKIs and non-EGFR-TKIs in the adjuvant setting.

not prolong survival. The BR19 [16] and RADIANT trials [17] were two large RCTs that compared adjuvant EGFR-TKIs with placebo in unselected and resected NSCLC patients. The BR19 trial was a negative trial. It recruited unselected patients; only 15 (4%) of them had EGFR mutations. Most of these patients had wild-type EGFR. Therefore, the BR19 study was underpowered because it was terminated prematurely. The RADIANT trial also included unselected patients. Among the 973 enrolled patients, 161 (16.5%) were in the EGFR mutation subgroup, wherein erlotinib prolonged the DFS of the patients. The patients with EGFR mutations in the BR19 and RADIANT trials were recruited and included in our meta-analysis.

Osimertinib is a third-generation EGFR-TKI that effectively and selectively inhibits EGFR-sensitive mutations and EGFR-resistant mutations (T790M). In a phase III trial of patients with EGFR-mutant advanced NSCLC, the first-line osimertinib treatment compared with gefitinib or erlotinib resulted in clinically and significantly improved progression-free survival (median 18.9 vs. 10.2

months; HR 0.46; 95% CI 0.37–0.57; $p < 0.001$). Osimertinib is superior to the standard first-generation EGFR-TKIs such as gefitinib and erlotinib as the first-line treatment strategy for EGFR-mutant advanced NSCLC [30]. The ADAURA trial was a phase III, double-blind, randomized study of osimertinib versus placebo in early-stage NSCLC patients who harbored EGFR-sensitive mutations after complete surgical resection. This study also confirmed that adjuvant osimertinib improved the DFS for EGFR-mutant early-stage NSCLC after radical resection. However, the data on OS from the ADAURA trial were premature [31].

The safety and tolerability have to be taken into account when comparing EGFR-TKI treatment with non-EGFR-TKI treatment in the adjuvant setting for resected NSCLC patients with EGFR mutations. For the EGFR-TKI group, the most frequent adverse events were rash, liver dysfunction, and diarrhea [32], and the most common adverse events associated with adjuvant chemotherapy treatment were hematologic toxic effects and appetite

loss [33]. The patients who were treated with adjuvant EGFR-TKIs experienced fewer grade 3–4 adverse events than those treated with adjuvant chemotherapy, and EGFR-TKIs have also been shown to cause no increase in toxicity even when combined with chemotherapy or radiotherapy [34]. All of the results clearly support the idea that EGFR-TKIs do not increase grade 3–4 adverse events and may be a promising treatment option for patients with resected EGFR-mutant NSCLC compared with non-EGFR-TKIs in the adjuvant setting.

Although our meta-analysis showed that EGFR-TKI treatment improved the DFS and OS compared with non-EGFR-TKI treatment in the adjuvant setting for patients with resected EGFR-mutant NSCLC, there are still many questions that need to be addressed regarding EGFR-TKI treatment for patients with EGFR-mutant NSCLC after radical resection, for example, which stage of lung cancer benefits most from adjuvant EGFR-TKIs? What is the optimal duration of adjuvant EGFR-TKI treatment? Which is the most optimal treatment regimen, adjuvant EGFR-TKI alone or in combination with adjuvant chemotherapy, radiotherapy, or VEGF inhibitors? We need more well-designed clinical trials to answer this question.

There are some limitations to our meta-analysis which should be addressed. First, we included several retrospective studies, increasing the heterogeneity of this meta-analysis. Second, the median duration of EGFR-TKI treatment differed in each study, which could cause some selection bias. Besides, the BR19 trial might contribute to some publication bias due to its limited sample size.

Conclusions

Adjuvant therapies are required to prevent disease recurrence and improve patient survival after surgery. Our meta-analysis results suggest that EGFR-TKI treatment

improved the DFS and OS of patients with completely resected EGFR-mutant NSCLC compared with non-EGFR-TKI treatment in the adjuvant setting. In the future, our conclusions should be confirmed by additional large-scale and well-designed clinical trials.

Statement of Ethics

This study conforms to the ethical guidelines in a priori approval by the local Ethics Committee of Hebei General Hospital. Our research was approved on May 20, 2020, by the Ethics Committee of Hebei General Hospital. All enrolled patients signed informed consent.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

H.L. conceived the study. G.Y. collected the data. X.X. analyzed the data and performed the statistical analyses. Q.Y. drafted the manuscript. H.C. provided important intellectual contributions and critically revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

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