Original Article

Comparing overall survival between first generation EGFR-TKIs and chemotherapy in lung cancer patients with Del19/L858R

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Abstract

Objective: Combined overall survival (OS) analysis of Lux-Lung 3 and Lux-Lung 6 demonstrated that patients with epidermal growth factor receptor (EGFR) exon 19 deletions (Del19) would benefit from first-line second generation EGFR tyrosine kinase inhibitors (TKIs) afatinib but not for those with L858R. This study was to investigate the survival difference between first-line first generation EGFR-TKIs and chemotherapy in patients with either Del19 or L858R, and to directly compare OS in these two mutation groups.

Methods: Eligibles were all prospective and retrospective studies comparing EGFR-TKIs with conventional chemotherapy or receiving single agent EGFR-TKIs and demonstrating survival analysis based on mutation types. The primary outcome was OS measured as pooled hazard ratios (HRs). All measures were pooled using random-effects models and 95% confidential interval (95% CI) was calculated.

Results: A total of 14 studies incorporating 1,706 patients with either Del19 or L858R were included. Enrolling patients with Del19 or L858R in randomized controlled trials (RCTs), first-line first generation EGFR-TKIs were associated with no OS benefit, compared with chemotherapy (pooled $HR_{TKI/Chemo}$ for Del19: 0.82, 95% CI: 0.64-1.06, P=0.14; pooled $HR_{TKI/Chemo}$ for L858R: 1.15, 95% CI: 0.85-1.56, P=0.38). Direct comparison of Del19 with L858R receiving with first-line first generation EGFR-TKIs demonstrated no significant survival difference (pooled $HR_{19/21}$: 0.88, 95% CI: 0.67-1.16, P=0.37).

Conclusions: Among patients with advanced non-small cell lung cancer (NSCLC) harboring Del19 and L858R, first-line first generation EGFR-TKIs demonstrated no survival benefit comparing with chemotherapy. Direct comparison between Del19 and L858R revealed no significant survival difference after first-line first generation EGFR-TKIs.

Keywords: NSCLC; EGFR; Del19/L858R; first generation EGFR-TKIs; OS

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Introduction

The epidermal growth factor receptor (EGFR)-dependent signaling pathway plays an indispensable role in the development and progression of non-small cell lung cancer (NSCLC) (1). Several large randomized controlled trials (RCTs) enrolling patients with EGFR mutations have demonstrated that first-line EGFR-tyrosine kinase inhibitors (TKIs) are superior to chemotherapy in terms of objective response rate (ORR) and progression-free survival (PFS) (2-8). However, *post hoc* analyses of overall survival (OS) in these trials showed that there was no statistical difference between EGFR-TKIs and chemotherapy (9-13). However, EGFR-TKIs are still recommended as the standard first-line treatment for advanced NSCLC patients harboring EGFR mutations,

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primarily exon 19 deletions (Del19) and a point mutation in exon 21 (L858R) (14).

Recently, Yang *et al*. published the combined OS analysis of Lux-Lung 3 and Lux-Lung 6. In the whole patients, afatinib (second generation EGFR-TKI) significantly delayed disease progression in EGFR mutation patients but demonstrated no remarkable impact on survival. However, when only enrolling patients with Del19, both of the two trials revealed that first-line afatinib had a significantly advantage on OS than first-line chemotherapy (Lux-Lung 3: 33.3 months *vs*. 21.2 months, P=0.0015; Lux-Lung 6: 31.4 months *vs*. 18.4 months, P=0.023). By contrast, first-line afatinib did not benefit the survival of patients with L858R comparing with first-line chemotherapy (Lux-Lung 3: 27.6 months *vs*. 40.3 months, P=0.29; Lux-Lung 6: 19.6 months *vs*. 24.3 months, P=0.34). Individual patient data (IPD)-based pooled analysis of these two trials also demonstrated that the OS improvement only existed in patients with Del19 (31.7 months *vs*. 20.7 months, P=0.0001). For those with L858R, there was no evidence of survival benefit. What's more, first-line afatinib might be inferior to first-line chemotherapy on OS (22.1 months *vs*. 26.9 months, P=0.16) (15). This was the first indication that first-line EGFR-TKIs could prolong OS and that patients harboring Del19 and L858R might be two distant populations. When translating this knowledge to clinical practice, first-line afatinib should only be recommended for patients with the Del19 mutation. However, it remains unclear whether EGFR-TKIs should be administered as the first-line treatment for patients with L858R. Given these considerations, this potential survival difference in patients receiving first generation EGFR-TKIs, such as gefitinib and erlotinib, should be investigated. Pending these results, the guidelines for EGFR-TKIs administration in advanced NSCLC patients with EGFR mutations should be revised.

An analysis of a single study, such as IPASS (16) or NEJ002 (11,17) has demonstrated that patients with either Del19 or L858R treated with gefitinib had no survival advantage compared with first-line chemotherapy. However, several small studies have previously demonstrated that patients with Del19 have superior OS compared to patients with L858R (18-23). Other studies demonstrated that patients with Del19 who treated with EGFR-TKIs have no survival advantage compared to patients with L858R (24-27). Therefore, under the circumstance of lacking detailed individual patient's survival data, a pooled analysis of the current available studies, including patients with Del19 and L858R, may provide clinically useful insight into first-line first generation EGFR-TKIs treatment for patients harboring common EGFR mutations (Del19 and L858R). We performed this meta-analysis by including recent studies and scattered data to explore whether patients with Del19 and L858R demonstrated survival superiority with first-line first generation EGFR-TKIs compared to chemotherapy. In addition, we validated the survival difference between patients with these two mutation types after receiving gefitinib or erlotinib.

Materials and methods

Search and selection process

Comprehensive systematic search for all relevant articles through the PubMed, EMBASE and Cochrane databases from inception to July 31, 2014 (without language limitations) was performed by two authors (Deng and Lei) independently. A combination of key words were used to search: "EGFR", "epidermal growth factor receptor", "tyrosine kinase inhibitors", "EGFR-TKI", "TKI", "gefitinib", "erlotinib", "first generation", "mutation", "mutated", "non-small-cell lung cancer", and "NSCLC". We also retrieved the meeting abstracts, including the American Society of Clinical Oncology (ASCO) annual meetings, European Society of Medical Oncology (ESMO) congresses and World Conference on Lung Cancer (WCLC), for the last 5 years by hand.

Eligibility criteria

All included prospective and retrospective studies satisfied the following eligibility criteria: 1) patients were diagnosed with local advanced (stage IIIB) or metastatic or recurrent disease (stage IV); 2) patients harbored the EGFR mutation (Del19 or L858R) and received first generation EGFR-TKIs (gefitinib or erlotinib) for monotherapy, first-line therapy or otherwise (with a detailed number of patients with each EGFR mutation type available); and 3) special hazard ratios (HRs) or survival curves of EGFR-TKIs compared to conventional chemotherapy for OS in patients harboring Del19 or L858R and definitive HRs or survival curves of Del19 compared to L858R for OS after EGFR-TKI treatment were available. All studies failing to meet the eligibility criteria were excluded, including reviews and *in vitro* and animal experiments; the number of patients harboring Del19 or L858R was not available; EGFR-TKIs were administered for maintenance treatment; or EGFR-TKIs were combined with chemotherapy. If the data were unavailable in the abstracts, we used the data in the posters and presentation slides from the ASCO, ESMO and WCLC meetings.

Data extraction and quality assessment

The data were extracted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (data

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not shown) (28). The RCTs were assessed with the Jadad scale, and the other studies were assessed with the Newcastle-Ottawa Scale (NOS). The following items were also extracted from the included studies: author, publication time, research name and type, therapeutic regimens, line of EGFR-TKI treatments, and number of patients harboring Del19 or L858R in each subgroup. The OS data were extracted as the HR and 95% confidence interval (95% CI). If the data could not be extracted directly, we soft-extracted the data from the survival curves and calculated the HR with the validated method (29). During the extraction process, we assumed that there was no significant difference in the chemotherapy efficacy for patients with Del19 and L858R and calculated the adjusted indirect comparison as previously described. Briefly, the log hazard ratio (logHR) of the adjusted indirect comparison for intervention A *vs.* B was estimated by $\log HR_{AB}=\log HR_{AC}-\log HR_{BC}$ and its standard error for the logHR was $SE(\log HR_{AB})=\sqrt{SE(\log HR_{AC})^2+SE(\log HR_{BC})^2}$ (30), where $\log HR_{AC}$ presents the logHR for the direct comparison of EGFR-TKIs *vs.* chemotherapy in patients with Del19; the $\log HR_{BC}$ indicates the logHR for the direct comparison of EGFR-TKIs *vs.* chemotherapy in patients with L858R; and $SE(\log HR_{AB})$ is the standard error of the logHR for the direct comparison between patients harboring Del19 and patients harboring L858R who received EGFR-TKIs. Two authors (Deng and Lei) conducted the assessments independently to avoid evaluation deviations. The data were discussed among the three authors (Deng, Lei and Liu) to resolve all discrepancies in the extraction.

Statistical analysis

As there are no two identical studies, each of them is different. For this reason, we recommend random effects model in general for calculating the pooled HRs for OS with 95% CIs. The statistical heterogeneity between studies was tested with the Cochran Q test and was quantified using I^2 and the respective 95% CIs (31). All analyses were performed in R3.1.2. All P values are two-sided, and $P<0.05$ was considered statistically significant. The publication bias was tested with the Egger funnel plot.

Results

Flow of studies screening

The study screening process is illustrated in *Figure 1*. A total of 6,645 potential records were identified in our initial search. After duplication and eligibility screening of all the titles and relevant abstracts, 276 promising articles were remained. After screening these articles by reading the full articles and abstracts in detail, 15 studies were included. In the *post hoc* analysis, one retrospective study used survival curve fitting to determine the HR value, but we excluded this study due to inaccuracy. Finally, 14 studies were included into this meta-analysis.

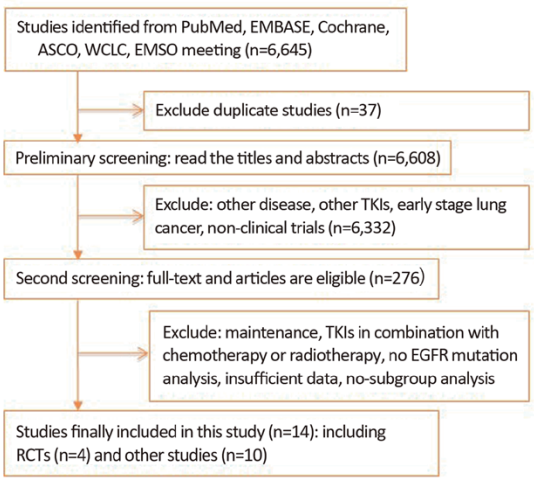

Figure 1 Flow of study screening. RCTs, randomized controlled trials; other studies included retrospective and prospective without randomized controlled.

Baseline characteristics of eligible studies

A total of 14 studies with 1,706 patients harboring the EGFR exon 19 deletion and L858R mutations were included. The baseline characteristics of all RCTs and non-RCTs included in this meta-analysis are summarized in *Table 1* and *Table 2*, respectively. Three RCTs (EURTAC, IPASS, and NEJ002) with 639 patients provided the HR for OS comparing first-line EGFR-TKIs with chemotherapy based on Del19 and L858R, respectively. Four RCTs (EURTAC, IPASS, NEJ002, and WJTOG3405) with 409 NSCLC patients were treated with first-line gefitinib or erlotinib. From the data provided, we performed a direct survival comparison between patients with Del19 and L858R receiving first-line EGFR-TKIs. Ten non-RCT studies enrolled 895 patients. Among them 4 studies with 422 patients received first-line gefitinib or erlotinib. The remaining 6 studies included 473 patients did not describe the treatment line of EGFR-TKIs.

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Table 1 Characteristics of included studies of RCTs

Author	Year	Study (phase)	Line of TKI	Therapeutic regimens (TKI/Chemo)	Exon of EGFR mutation*	Sample size (TKI/ Chemo)	$HR_{TKI/chemo}$ for OS (95% CI)	$HR_{19/21}$ for OS (95% CI)	Jadad
Rosell R (4)	2012	EURTAC (III)	First	Erlotinib *vs*. Docetaxel/Gemcitabine + Cisplatin/Carboplatin	19	57/58	0.94 (0.58-1.54)	0.95 (0.45-2.00)	3
Khozin S (10)	2014				21	29/30	0.99 (0.56-1.75)		
Mok TS (6)	2009	IPASS (III)	First	Gefitinib *vs*. Paclitaxel + Carboplatin	19	66/74	0.79 (0.54-1.14)	0.55 (0.30-1.01)	3
Fukuoka M (9)	2011				21	64/47	1.43 (0.90-2.30)		
Yang J (16)	2011								
Maemondo M (7)	2010	NEJ002 (III)	First	Gefitinib *vs*. Paclitaxel + Carboplatin	19	58/59	0.78 (0.47-1.30)	1.04 (0.61-1.77)	3
Inoue A (11)	2013				21	49/48	0.96 (0.54-1.70)		
Mitsudomi T (8)	2010	WJTOG3405 (III)	First	Gefitinib *vs*. Docetaxel + Cisplatin	19	50/37	NA	0.98 (0.64-1.51)	3
Yoshioka H (12)	2014				21	36/49	NA		

*, exon of EGFR mutation means either exon 19 deletion (Del19) or point mutation in exon 21 (L858R); TKI, tyrosine kinase inhibitor; Chemo, chemotherapy; HR, hazard ratio; OS, overall Survival; 95% CI, 95% confidence interval; $HR_{19/21}$, hazard ratio for comparison between patients with Del19 and patients with L858R who received EGFR-TKIs therapy; NA, not available.

Table 2 Characteristics of included studies of non-RCTs (prospective and retrospective)

Author, year	Research type	Line of TKI	Therapeutic regimens (TKI)	Exon of EGFR mutation*	Sample size	$HR_{19/21}$ for OS (95% CI)	Nos
Rosell R (18), 2009	Prospective	No-special	Erlotinib	19	135	0.34 (0.17-0.68)	8
				21	82		
Kim DW (19), 2011	Prospective	First	Gefitinib	19	29	0.48 (0.13-1.71)	7
				21	15		
Jackman DM (20), 2006	Retrospective	No-special	Erlotinib/Gefitinib	19	22	0.30 (0.12-0.76)	7
				21	10		
Riely GJ (21), 2006	Retrospective	No-special	Erlotinib/Gefitinib	19	23	0.33 (0.09-1.19)	6
				21	11		
Zhu JQ (22), 2008	Retrospective	No-special	Gefitinib	19	13	0.36 (0.13-0.97)	5
				21	13		
Sun JM (24), 2011	Retrospective	No-special	Erlotinib/Gefitinib	19	58	0.96 (0.49-1.87)	6
				21	19		
Won YW (25), 2011	Retrospective	No-special	Erlotinib/Gefitinib	19	61	0.83 (0.50-1.38)	7
				21	26		
Lee VH (26), 2013	Retrospective	First	Erlotinib/Gefitinib	19	64	0.73 (0.45-1.20)	7
				21	80		
Hsiao SH (27), 2013	Retrospective	First	Erlotinib/Gefitinib	19	48	0.82 (0.45-1.47)	7
				21	66		
Choi CM (38), 2014	Retrospective	First	Erlotinib/Gefitinib	19	77	0.87 (0.26-2.93)	6
				21	43		

*, exon of EGFR mutation means either exon 19 deletions (Del19) or point mutation in exon 21(L858R); TKI, tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival; 95% CI, 95% confidence interval; $HR_{19/21}$, hazard ratio for comparison between patients with Del19 and patients with L858R who received EGFR-TKIs therapy; no-special means patients received TKIs with unknown special lines; Nos, Newcastle-Ottawa scale.

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Association of first generation EGFR-TKIs vs. chemotherapy in the first-line setting in NSCLC patients with Del19 or L858R in terms of OS

Among the four randomized clinical trials we could obtain the data of hazard ratio from only three trials (EURTAC, IPASS, and NEJ002) for the direct comparison of EGFR-TKIs *vs.* chemotherapy in patients with Del19 or L858R. From the WJTOG3405, we could only acquire the data of HR for the direct comparison of patients with Del19 *vs.* patients with L858R under EGFR-TKIs therapy. So, three trials (EURTAC, IPASS, and NEJ002) were included into pooled analysis in this part. The pooled $HR_{TKI/Chemo}$ of EGFR-TKIs *vs.* chemotherapy for NSCLC patients with Del19 was 0.82 (95% CI: 0.64-1.06, P=0.14). The pooled $HR_{TKI/Chemo}$ of EGFR-TKIs *vs.* chemotherapy for patients with L858R was 1.15 (95% CI: 0.85-1.56, P=0.38). *Figure 2* presents association of first generation EGFR-TKIs *vs.* chemotherapy in the first-line setting in NSCLC patients with Del19 (*Figure 2A*) or L858R (*Figure 2B*) in terms of OS. No significant heterogeneity existed in this part analysis. As the results indicate, there was no difference in first-line EGFR-TKIs *vs.* conventional platinum-based doublet chemotherapy regarding OS for patients with Del19 or L858R.

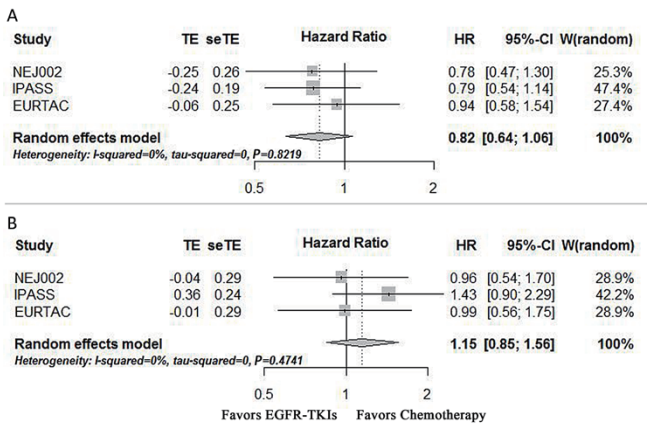

Figure 2 Forest plot of $HR_{TKI/Chemo}$ for EGFR-TKIs *vs.* chemotherapy in NSCLC patients with EGFR Del19 or L858R in terms of OS. TE, lnHR; SeTE, SelnHR; CI, confidence interval; W, weight; HR, (A) $HR_{TKI/Chemo}$ means hazard ratio for the direct comparison of EGFR-TKIs *vs.* chemotherapy in patients with Del19; (B) $HR_{TKI/Chemo}$ means hazard ratio for the direct comparison of EGFR-TKIs *vs.* chemotherapy in patients with L858R.

Association of NSCLC patients with Del19 or L858R receiving first generation EGFR-TKIs in terms of OS

All studies were divided into RCT and non-RCT studies. The pooled $HR_{19/21}$ of patients with Del19 *vs.* L858R after first-line gefitinib or erlotinib was 0.88 (95% CI: 0.67-1.16, P=0.37) in the four RCTs (*Figure 3*). For other studies, the pooled $HR_{19/21}$ of patients with Del19 *vs.* L858R after EGFR-TKIs was 0.62 (95% CI: 0.47-0.81, P=0.006) (*Figure 4*). No significant heterogeneity was noted in this analysis (I^2=24.4%, P=0.22). We performed an influential analysis reflecting consistent results. It means that if we eliminate any of the studies, the pooled analysis results of the rest studies had no obvious change in all non-RCTs. Moreover, we conducted subgroup analyses according to the type of EGFR-TKIs. The pooled $HR_{19/21}$ of Del19 *vs.* L858R for patients receiving first-line EGFR-TKIs therapy was 0.75 (95% CI: 0.53-1.06) with no significance. The pooled $HR_{19/21}$ of Del19 *vs.* L858R for patients with non-special lines (no-special line of EGFR-TKIs means the treatment line of patients with Del19 or L858R received EGFR-TKIs did not describe specifically in the studies, maybe first-line or second-line or third-line and so on) of EGFR-TKIs was 0.51 (95% CI: 0.33-0.81) and was significant. There was no significant survival difference between patients with Del19 and L858R receiving first-line EGFR-TKIs. However, when non-special lines of EGFR-TKIs were used, patients with Del19 had superior OS compared to patients with L858R.

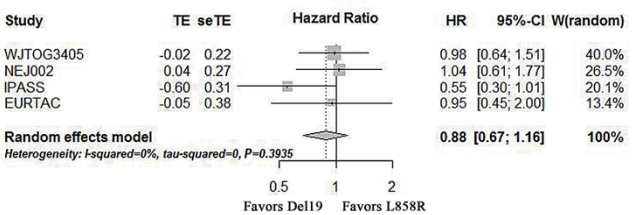

Figure 3 Forest plot of $HR_{19/21}$ for patients with Del19 *vs.* patients with L858R under EGFR-TKIs therapy in the four RCTs. TE, lnHR; SeTE, SelnHR; CI, confidence interval; W, weight; HR, $HR_{19/21}$ means hazard ratio for the direct comparison of for patients with Del19 *vs.* patients with L858R under EGFR-TKIs therapy in the RCTs; RCTs, randomized controlled trials.

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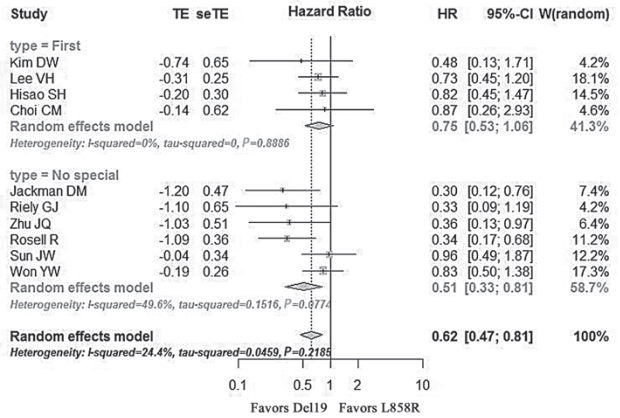

Figure 4 Forest plot of $HR_{19/21}$ for patients with Del19 *vs.* patients with L858R under EGFR-TKIs therapy in non-RCTs. TE, lnHR; SeTE, SelnHR; CI, confidence interval; W, weight; HR, $HR_{19/21}$ means hazard ratio for the direct comparison of for patients with Del19 *vs.* patients with L858R under first-line EGFR-TKIs; first-line means patients received EGFR-TKIs in the first-line setting; no-special means patients received EGFR-TKIs in any line; other studies included retrospective and prospective without randomized controlled.

Publication bias

The publication bias was analyzed for non-RCTs. When P values were greater than 0.05, it means that there was no publication bias for the outcome measures. The Egger funnel plot analysis presented a symmetrical appearance, and the P value was 0.08 (*Figure 5*).

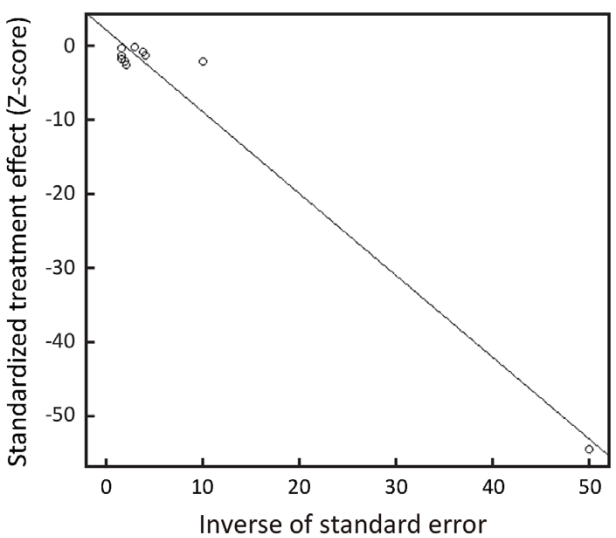

Figure 5 Funnel plot by Egger's test.

Discussion

This study focuses on the survival difference between first-line first generation EGFR-TKIs and chemotherapy based on EGFR mutation types. A newly published meta-analysis revealed that patients with Del19 demonstrated superior PFS after receiving first-line EGFR-TKIs compared to patients with L858R (32). Furthermore, the findings from the two Lux-Lung trials also indicate that only patients with Del19 can benefit from first-line afatinib. If Del19 and L858R are two distinct mutation types, we should reconsider the treatment strategy for patients with L858R. It is very important to understand whether first generation EGFR-TKIs, such as erlotinib and gefitinib, have different efficacies on patients with Del19 or L858R.

Our results indicate that neither patients with Del19 nor L858R have significant overall survival benefits from first-line, first generation EGFR-TKIs compared to chemotherapy. Our results agreed with the primary results from the individual first-line, first generation RCT analyses, such as EURTAC (10) and IPASS (16). Based on this analysis, we anticipate that patients with common EGFR mutations (Del19/L858R) share the same OS benefit when receiving first-line, first generation EGFR-TKIs.

Our findings regarding first generation EGFR-TKIs are inconsistent with the afatinib trials. As we know, patients with EGFR common mutations could achieve survival benefits from first-line afatinib. However, in our meta-analysis, in patients with Del19 or L858R, first-line first generation EGFR-TKIs demonstrated no superiority over first-line chemotherapy in terms of OS, but, there was a trend that patients with Del19 received EGFR-TKIs therapy had longer OS. The obvious discrepancy between first and second generation EGFR-TKIs encouraged us to explore the potential factors that lead to the survival benefit of afatinib.

First, in our article, the sample was limited. Three RCTs (EURTAC, IPASS, and NEJ002) with 639 patients provided the HR for OS comparing first-line EGFR-TKIs with chemotherapy based on Del19 and L858R, respectively. But, in afatinib trials, 709 cases were included. Second, this prolonged OS could be attributed to the low crossover rate to EGFR-TKIs after the chemotherapy arm in Lux-Lung 3 and Lux-Lung 6. Compared to RCTs investigating first-line, first generation EGFR-TKIs, the pooled crossover rate was only 62% in the two afatinib trials (15). In contrast, the crossover rate of IPASS (9), NEJ002 (11) and WJTOG3405 (12) were 64.3%, 98.0%, and 91.0%, respectively. The improved OS in patients receiving first-line afatinib may be partly related to the

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relatively lower frequency of patients receiving EGFR-TKIs in the chemotherapy arm. According to the OPTIMAL (13) trial for EGFR mutations in NSCLC patients, patients will benefit more from the sequential combination of TKIs and chemotherapy than either treatment alone. Third, the survival benefit resulting from first-line afatinib may correlate with the different mechanisms of afatinib and gefitnib or erlotinib. Afatinib, an irreversible tyrosine kinase inhibitor, blocks the entire ErbB family, which includes the kinase domains of EGFR, human epidermal growth factor receptor 2 (HER2) and HER4. Afatinib also inhibits transphosphorylation of HER3 (33, 34). However, gefitinib and erlotinib only inhibit the tyrosine kinase activity of EGFR (35,36). Moreover, afatinib combined with various agents has been investigated as a strategy to overcome EGFR-TKI acquired resistance mediated by the EGFR T790M mutation after gefitnib or erlotinib exposure (37). The relative blocking advantage of afatinib can partially explain the superior OS after receiving first-line afatinib.

This study had several limitations. First, until now, seven large RCTs have performed head-to-head comparisons between first generation EGFR-TKIs and chemotherapy. This analysis only enrolled three RCTs comparing first-line EGFR-TKIs with conventional chemotherapy based on EGFR mutation types. For the direct comparison of Del19 and L858R, we acquired data from only four trials. The results would be stronger if we could include all seven trials. Therefore, we strongly recommend that investigators collaborate to include individual patient's survival data in those seven trials for analysis. Second, during the direct survival comparison of Del19 and L858R receiving first line EGFR-TKIs, we assumed that patients with Del19 and L858R had no difference in the efficacy of first-line chemotherapy. Few studies focused on the prognostic value of different EGFR mutation in patients with advanced NSCLC with chemotherapy, and as a consequence, our hypothesis is in need of confirmation by more convincing evidence (39). In addition, there may be a deviation from the actual results because the survival data of NEJ002 was extracted from the survival curves.

Conclusions

For patients with Del19 or L858R, first-line, first generation EGFR-TKIs demonstrated no survival benefit compared with platinum-based chemotherapy. Additionally, no significant survival differences were found between Del19 and L858R after receiving gefitinib or erlotinib. We have no evidence to support the differential treatment of patients with Del19 and L858R. The NEJ002 trial reported that the response rate of EGFR-TKIs in the second-line setting was 58.5%, which was lower than it used in first-line (73.3%) (7). Besides, EGFR mutated patients had a risk of losing their EGFR mutation after chemotherapy (40). Considering the assurance of EGFR-TKIs, better tolerance, improved quality of life and prolonged PFS, first-line EGFR-TKIs are still the optimal choices for patients with these two common mutations.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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