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Research article

A meta-analysis of the comparing of the first-generation and next-generation TKIs in the treatment of NSCLC

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Abstract: *Background:* The current standard approach to the treatment of patients with non–small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI)—sensitizing mutations has been the treatment with a first-generation EGFR-TKIs. While, with resistance developed against first-generation EGFR-TKIs, second/third-generation TKIs have attracted all the attention, and replaced first-generation EGFR- TKIs upon disease progression due to the greater efficacy and more favorable tolerability. In the past few years, this strategy has been challenged by clinical evidence when next-generation EGFR-TKIs are used in patients with advanced NSCLC. *Objective:* In this study, we performed a meta- analysis to investigate the efficacy of next-generation TKIs comparison with first-generation TKIs in the treatment of NSCLC. *Methods:* The multiple databases including Pubmed, Embase, Cochrane library databases were adopted to search for the relevant studies, and full-text articles involving to comparison of next-generation TKIs and first-generation TKIs were reviewed. After rigorous reviewing on quality, the data was extracted from eligible randomized controlled trial (RCT). Meta-analysis Revman 5.3 software was used to analyze the combined pooled ORs with the

corresponding 95% confidence interval using fixed- or random-effects models according to the heterogeneity. Results: A total of 5 randomized controlled trials were included in this analysis. The group of next-generation TKIs did achieved benefit in progression-free survival (PFS) (OR = 0.58, 95%CI = 0.45–0.75, P＜0.0001), overall survival (OS) (OR = 0.76, 95%CI = 0.65–0.90, P = 0.001) as well with the objective response rate (ORR) (OR = 1.27, 95%CI = 1.01–1.61, P = 0.04), respectively. In the results of subgroup analysis of PFS with EGFR mutations, there is also significant differences with exon 19 deletion (OR = 0.56, 95%CI = 0.41–0.77, P = 0.0003) and exon 21 (L858R) mutation (OR = 0.60, 95%CI = 0.49–0.75, P＜＝0.00001). While, the treatment-related severe adverse event (SAE) between the next-generation TKIs and first-generation TKIs did not have statistical significance (OR = 1.48, 95%CI = 0.62–3.55, P = 0.38). Conclusion: The next-generation TKIs significantly improved efficacy outcomes in the treatment of EGFR mutation–positive advanced NSCLC compared with the first-generation TKIs, with a manageable safety profile. These results are potentially important for clinical decision making for these patients.

Keywords: NSCLC; first-generation EGFR-TKIs; second/third-generation EGFR-TKIs; meta-analysis

1. Introduction

Systemic chemotherapy has long been employed as the basic treatment approach for advanced-stage NSCLC. Recently, positive results achieved with somatic mutations in NSCLC have led to a growing number of treatment options on the employment of specific inhibitors. Epidermal growth factor receptor (EGFR) mutations are well known oncogenic driver mutations that comprise approximately 10–44% of lung cancer [1,2].

The first-generation, reversible, EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib have improvement in response and progression-free survival relative to chemotherapy as initial therapy among patients with EGFR-mutant NSCLC [3–5]. However, resistance develops against all these agents after a while. Numerous genetic mutations have been identified as resistance mechanisms against EGFR-TKIs, and researchers are developing specific inhibitors against them. Among those inhibitors, second/third-generation EGFR-TKIs have gained prominence due to their improvement in effectiveness and manageable toxicity profile [6].

Distinct from the first-generation EGFR TKIs (gefitinib and erlotinib), which are reversible inhibitors that selectively target EGFR, the next-generation EGFR TKIs are irreversible binding with broad spectrum of activity. The advantages of next-generation EGFR-TKIs as first-line treatment option for NSCLC harbors activating mutations in EGFR have been already reported when compared with chemotherapy; however, until recently, when studied head-to-head comparisons with first-generation TKI, the benefits were still under debate [7,8].

Our meta-analyses were done to address this question, and identify the most efficacious drug, by assessing the efficacy and safety of first-generation EGFR TKIs and next-generation EGFR-TKIs in patients with EGFR-mutant NSCLC.

2. Materials and method

2.1. Search strategy

PubMed and Embase databases were searched to identify studies. Two investigators independently performed the literature search up to September 2018.

The process was established to find all articles with the keywords: "non-small cell lung cancer" AND "first -generation EGFR-TKIs", AND "second/third -generation EGFR-TKIs", and relevant Medical Subject Heading (MeSH) terms were utilized. The reference lists of all articles that dealt with the topic of interest were also manually checked for additional relevant publications.

2.2. Eligibility criteria

The eligible studies in the meta-analysis should meet the following criteria : (1) the studies are designed as random control trials (RCTs); (2) articles that enrolled NSCLC patients harboring activating mutations in EGFR; (3) articles that comparing second/third -generation EGFR-TKIs and first -generation EGFR-TKIs; (4) the outcomes of interest were efficacy (survival, tumor response) and toxicity (incidence of severe adverse effects (SAEs)), and HRs with corresponding 95% CIs were provided; If we found duplicated or overlapped data in multiple reports, we just include the one with most complete information.

2.3. Quality assessment

Two investigators separately rated the quality of the retrieved studies. Study quality was justified using Jadad scale [9].

2.4. Data extraction

Two authors (Yongxing Li and Xiaodong Lv) independently extracted the following information from included studies: first author family name, year of publication, clinical trials' name, total number of cases, mean age, treatment regimen, end-point of interests. We extracted the corresponding hazard ratios (HRs) and risk ratios (RRs) to describe the strength of the association for survival (overall (OS) and progression-free survival (PFS)) and dichotomous (overall response rate (ORR) and serve adverse effect (SAE) rate) data, respectively, with corresponding 95 % confidence intervals (CIs). Disagreement was revolved by consensus.

2.5. Statistical analysis

The result is basing on the data from random control trials. The endpoints of interest in the pooled analysis were OS, PFS, ORR and SAE data, and the endpoint outcome were considered as a weighted average of individual estimate of the HR in every included study, using the inverse variance method. The statistical analyses were conducted using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). A sensitivity analysis to be determined depending on the degree of heterogeneity across the included studies. The heterogeneity across studies was examined the I2 statistic [10]. Studies with an I2 $\geqslant$ 50% was considered to indicate moderate and high heterogeneity, I2$<$50% was considered to have low heterogeneity, respectively [11]. When there was low heterogeneity among studies, the fixed-effects model was used. Otherwise, the random effects model was used. A P value less than 0.05 was

considered as statistically significant difference. The Beg test and the Egger test were conducted to evaluate publication bias.

3. Results

3.1. Overview of literature search and study characteristics

A total of 535 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 10 publications were evaluated in more detail, but some did not provide enough detail of outcomes of two approaches. Therefore, a final total of 5 RCTs including 3 clinical trials [7,8,12–14] evaluated the efficacy and toxicity of comparing next-generation EGFR-TKIs versus first -generation EGFR-TKIs. The search process is described in Figure 1.

All included studies in this study were based on moderate to high quality evidence. Table 1 describes the primary characteristics of the eligible studies in more detail.

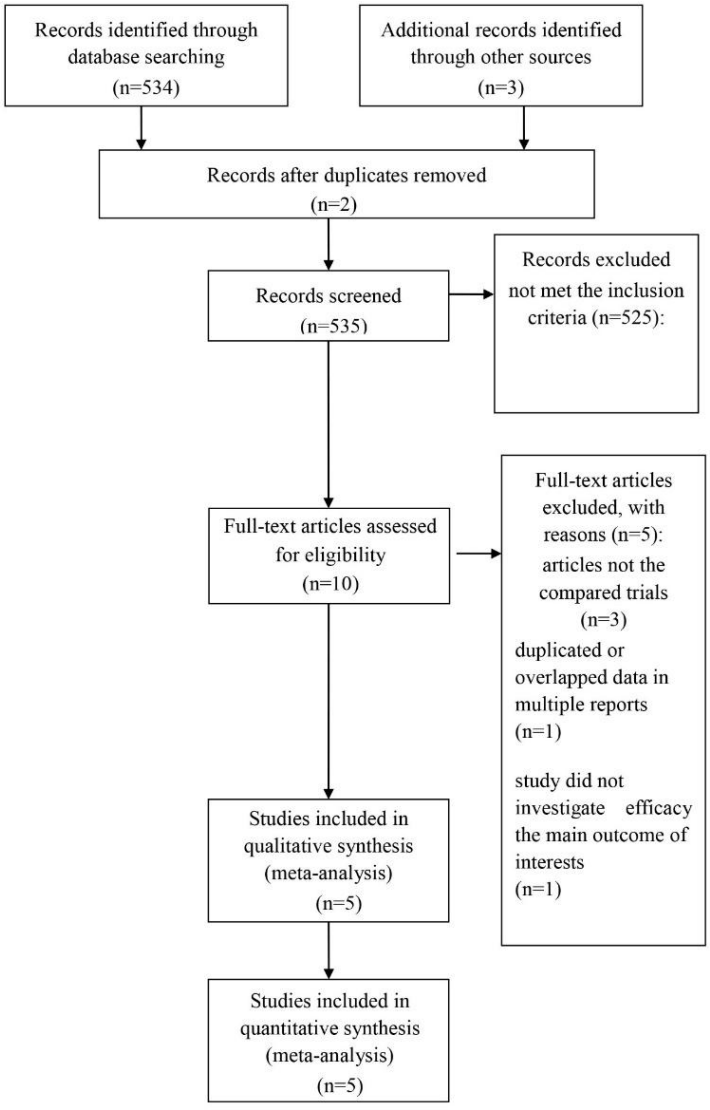

Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

Table 1. The primary characteristics of the eligible studies in more detail.

Study	Year	Clinical Trials	Treatment regimen		Patients number		Age(years)	
			Study arm	Comparative arm	Study arm	Comparative arm	Study arm	Comparative arm
J.-C. Soria	2017	FLAURA	osimertinib	gefitinib/erlotinib	279	277	64	64
Keunchil Park	2016	LUX-Lung 7	afatinib	gefitinib	160	159	63	63
L. Paz-Ares	2017	LUX-Lung 7	afatinib	gefitinib	146	151	/	/
Yi-Long Wu	2017	ARCHER 1050	dacomitinib	gefitinib	227	225	62	61
Tony S. Mok	2018	ARCHER 1050	dacomitinib	gefitinib	227	225	62	61

3.2. Clinical and methodological heterogeneity

Pooling the PFS data from three trials showed that next-generation EGFR-TKIs did prolong the PFS (OR = 0.58, 95%CI = 0.45–0.75, P＜＝0.0001 compared with the first-generation EGFR-TKIs (Figure 2). While, subgroup analyses with EGFR mutations, there are also significant differences with exon 19 deletion (OR = 0.56, 95%CI = 0.41–0.77, P = 0.0003) (Figure 3) and exon 21 (L858R) mutation (OR = 0.60, 95%CI = 0.49–0.75, P＜0.00001) (Figure 4).

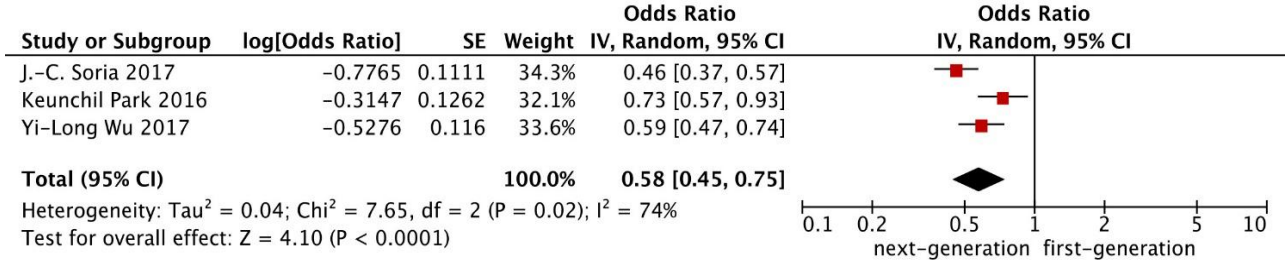

Figure 2. Pooled analysis of PFS comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs.

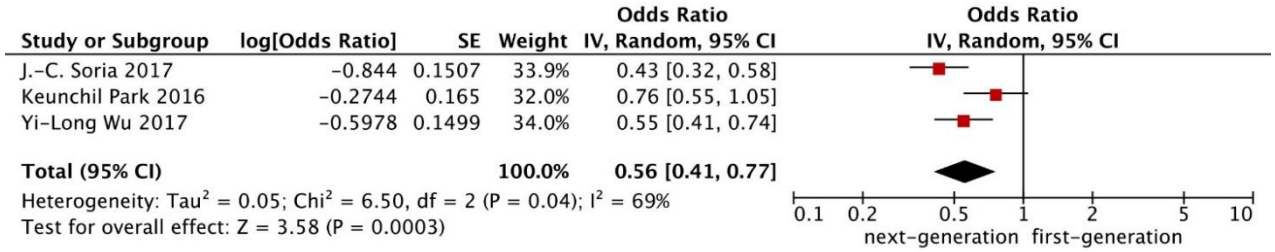

Figure 3. Subgroup analysis of PFS comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs with exon 19 deletion.

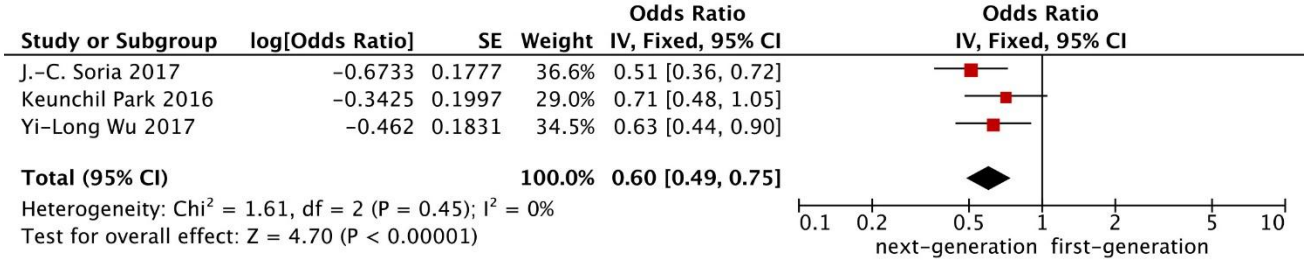

Figure 4. Pooled analysis of PFS comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs with exon 21 (L858R) mutation.

Pooled data showed that the next-generation EGFR-TKIs had significantly better OS rate than first-generation group, with the pooled OR being 0.76 (95 % CI 0.65–0.90, P = 0.001) (Figure 5).

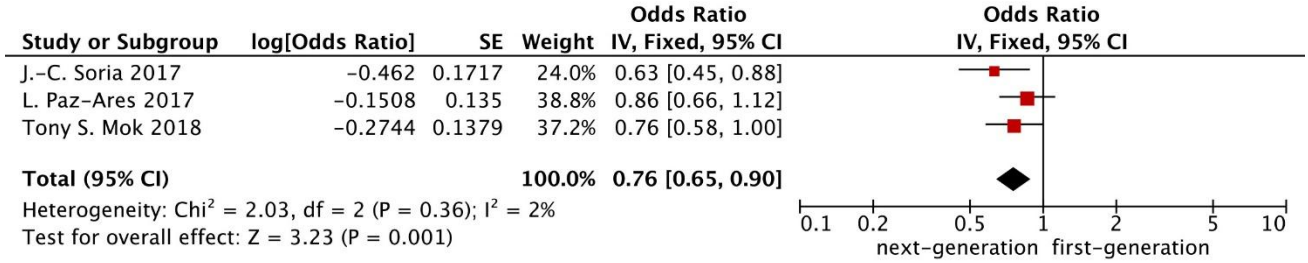

Figure 5. Pooled analysis of OS comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs.

The pooling ORR data achieved advantage in the next-generation EGFR-TKIs agents (OR = 1.27, 95%CI = 1.01–1.61, P = 0.04). In other words, the next-generation EGFR-TKIs agents did increase the rate of ORR (Figure 6).

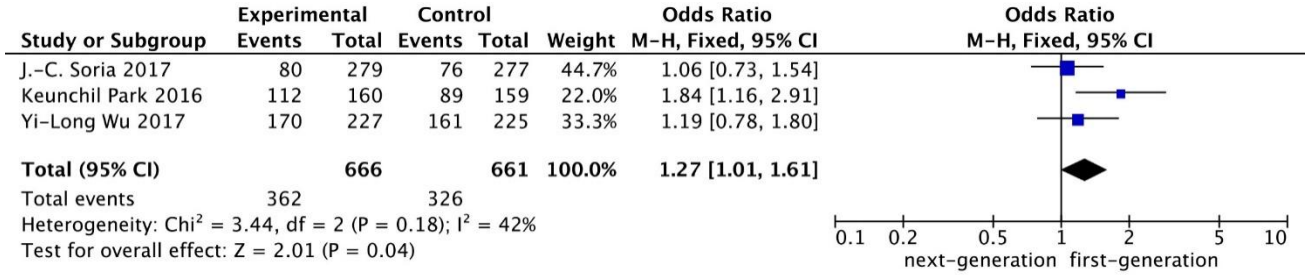

Figure 6. Pooled analysis of ORR comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs.

We define the grade 3–5 toxicities as SAE. Pooling the SAE data show that there is no statistical difference between the two groups (OR = 1.48, 95%CI = 0.62–3.55, P = 0.38) (Figure 7).

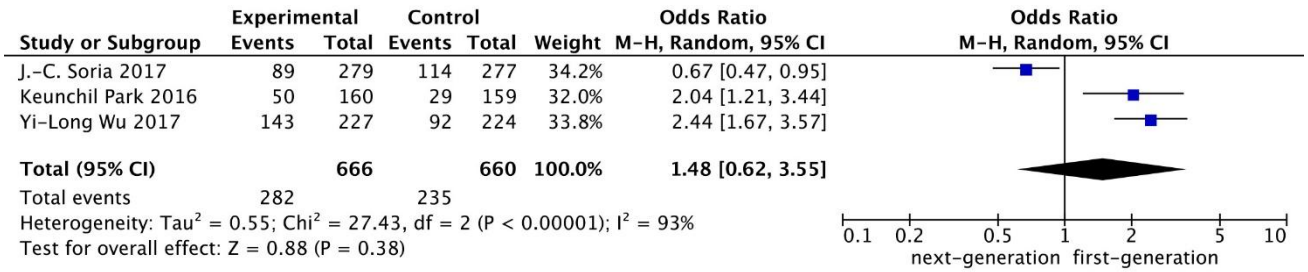

Figure 7. Pooled analysis of SAE comparing next-generation EGFR-TKIs versus first-generation EGFR-TKIs.

4. Discussion

In the past decade, the first-generation EGFR tyrosine-kinase inhibitors (TKIs) gefitinib, erlotinib, and icotinib, have been accepted as standard-of-care first-line treatments for EGFR-mutant NSCLC patients [15]. Although remarkable results have been achieved with these TKIs, the therapeutic plateau eventually experience disease progression owing to the resistance of therapeutics [16].

The broader and more durable inhibitory profile of second/third-generation EGFR-TKIs has been postulated to be associated with improved inhibition of EGFR-dependent tumor growth compared with first-generation EGFR-TKIs [17]. While, the role of next-generation EGFR-TKIs still remains controversial. We aim to evaluate potential approaches of next-generation EGFR-TKIs agents against first-generation EGFR-TKIs.

In the current meta-analysis, there was significant benefit in survival efficacy and objective response with next-generation EGFR-TKIs than the first-generation EGFR-TKIs. The 'gatekeeper' mutation may have contributed to this improvement.

It is known that 50%–60% of patients treated with first-generation TKI acquired resistance, which was mediated by the acquisition of the 'gatekeeper' mutation T790M [18–21]. To the best of our knowledge, the second–generation EGFR-TKI, afatinib or dacomitinib, as an irreversible ErbB family blocker, is active against EGFR harboring the T790M gatekeeper mutation [22,23]. Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI–sensitizing and EGFR T790M resistance mutations, with lower activity against wild-type EGFR [24,25]. These mechanisms include the secondary mutations of the driver oncogene, and the activation of new signaling pathways other than the EGFR pathway [26,27]. Deletion at exon 19 and point mutation at exon 21 (L858R) are the most common EGFR mutations [28].

Previous studies have shown that EGFR TKIs have been particularly active in patients with the exon 19 deletion than they do with the Leu858Arg mutation [29]. However, the result is based on trials that comparing TKI versus chemotherapy rather than used TKI as a comparator. In our study, there are no differences with exon 19 deletion and exon 21 (L858R) mutation. Therefore, as the efficacy benefit with next-generation EGFR-TKIs over first-generation EGFR-TKIs would not be restricted to patients harboring exon 19 deletions only, our data support that the using of a TKI as a treatment option for an individual patient might not be based on specific EGFR mutation.

Moreover, the safety profile of both generation TKIs therapy was also evaluated in this article. We concluded that next-generation EGFR-TKIs was comparable with that of first-generation

EGFR-TKIs. This result suggests that the systematically established management of adverse events used worked well to keep patients on treatment neither the next-generation EGFR-TKIs nor first -generation EGFR-TKIs. Despite higher frequencies of next-generation EGFR-TKIs, all those AEs were manageable and predictable in all included trials, indicating that proactive supportive treatment and dose modification were an adequate strategy to properly manage the expected class effects associated with EGFR inhibition.

Our results contribute to the growing evidence that supports next-generation EGFR-TKIs in EGFR mutation–positive advanced NSCLC. However, there are limitations to our study. Firstly, although the experimental methods of the included studies were similar, they were not identical, and some clinical parameters, which may have an effect on the prognosis of NSCLC patients. Therefore, heterogeneity due to varying experimental methods cannot be discounted entirely. Furthermore, though our study including the studies are all designed as random control trials (RCTs). Nevertheless, due to all included studies' retrospective nature, bias still exist, and this may impact the comparison of interested outcomes. So, it indicated that the large-scale study with greater statistical power would be imperative to compare the efficacy and safety outcomes of next-generation EGFR-TKIs and first-generation EGFR-TKIs.

5. Conclusion

In summary, our meta-analysis indicates that next-generation EGFR-TKIs are superior to the first-generation EGFR-TKIs with respect to survival and objective response in the treatment of NSCLC patients with EGFR activating mutations. And the efficacy benefits are found both in exon 19 deletion and exon 21 (L858R) mutation when comparing the next-generation EGFR-TKIs over first -generation EGFR-TKIs. We believe that these results provide additional evidence to help to inform decision-making when choosing the standard treatment option for patients with EGFR mutation- positive NSCLC.

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Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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