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ORIGINAL ARTICLE

The Effect of Next-Generation TKI in Non-Small Cell Lung Cancer after Failure of First-Line Treatment: a Meta-Analysis

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Abstract

Resistance develops against first-generation tyrosine kinase inhibitors (TKIs), which target the epidermal growth factor receptor (EGFR), after a while for non-small-cell lung cancer (NSCLC). Recently, researchers have developed specific inhibitors against them. Among those inhibitors, next-generation EGFR-TKIs have gained prominence due to the greater efficacy and more favorable tolerability. Today, the efficacy of next-generation EGFR-TKIs in patients with advanced NSCLC after failure on first-generation EGFR-TKIs still remains under investigation. The aim of this meta-analysis was to systematically assess the efficacy and safety profiles of next-generation EGFR-TKIs in advanced NSCLC after failure on first-generation EGFR-TKIs. We performed a comprehensive search of the several electronic databases to September, 2018 to identify clinical trials. The primary endpoint was overall survival (OS), progression-free survival (PFS), disease controlled rate (DCR), objective response rate (ORR), and adverse events (AEs). Severe adverse events (AEs) (grade ≥ 3) based on the EGFR-TKIs were analysed. Odds Ratio (OR) along with 95% confidence interval (95% CI) were utilized for the main outcome analysis. In total, we had 3 randomized controlled trials in this analysis. The group of next-generation EGFR-TKIs was significantly improved PFS (OR = 0.34,95%CI = 0.29–0.40, $P < 0.00001$), as well with the ORR (OR = 10.48,95%CI = 3.87–28.34, $P < 0.00001$) and DCR (OR = 6.03,95%CI = 4.41–8.25, $P < 0.00001$), respectively. However, there is no significant difference in overall survival with next-generation EGFR-TKIs (OR = 1.05,95%CI = 0.85–1.31, $P = 0.66$). While, the OR for the treatment-related AEs of grade 3 or 4 (diarrhoea, rash/acne, nausea, vomiting, anemia) between the patients who received next-generation EGFR-TKIs and chemotherapy did not show safety benefit (P>0.05). Next-generation EGFR-TKIs was shown to be the better agent to achieve higher response rate and the longer PFS in NSCLC patients as the later-line therapy for previously treated patients with first-generation EGFR-TKIs. While, the benefit of the OS and safety compared with the chemotherapy did not achieved. Further research is needed to develop a database of all *EGFR* mutations and their individual impact on the differing treatments.

Keywords NSCLC · EGFR-TKIs · Pretreated patients · Meta-analysis

Introduction

Lung cancer remains the primary cause of cancer-related death in the world [1]. Non-small-cell lung cancer (NSCLC) comprises approximately 80%–85% of all lung cancers. More than half of the NSCLC are diagnosed as advanced-stage with poor prognosis and are candidates for palliative adjuvant chemotherapy. Recent advances in genetic discoveries in NSCLC and the employment of specific inhibitors against them have played an key role in patients with disease at these stages [2].

Epidermal growth factor receptor (EGFR) mutations, such as exon 19 deletions (Ex19Del) and the exon 21point mutation, L858R, are powerful predictive markers for response to EGFR tyrosine kinase inhibitors (TKIs) in advanced-stage NSCLC, which have been accepted as the standard of care in this setting [3].

As first-generation tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib have consistently shown superior therapeutic efficacy and more favorable safety profiles than chemotherapy in patients who have a driver mutation in the EGFR gene for first-line therapy [4–6]. However, some studies have reported that the

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presence of the T790 M variant reduces binding of first-generation EGFR-TKIs to the ATP-binding pocket of EGFR, which have potentially lead to disease progression [7, 8].

Numerous genetic mutations have been identified as resistance mechanisms, and specific inhibitors are being developed against them. Next- generation TKIs, including second- generation TKIs (such as afatinib) and third- generation TKIs (osimertinib), have offered a potential alternative for patients who developed progress after first- generation EGFR-TKI treatment [2].

Based on positive results from prospective trials in patients whose disease had progressed on the first-generation EGFR-TKI, next- generation TKIs were used to maximize its effect on delaying disease progression. Today, the efficacy of next-generation EGFR-TKIs in advanced NSCLC patients after failure on first-generation EGFR-TKIs still remains under investigation.

We performed this meta-analysis by including relevant trialswhich have been designed to determine its efficacy and toxicity with EGFR TKIs and focus primarily on whether next-generation EGFR-TKIs was superior in pre-treated NSCLC with first-line EGFR-TKI therapy.

Methods

Search Strategy

We conducted a systematic screening process using the Pubmed, Embase, and Cochrane Database of Systematic Reviews from their inception to September, 2018, based on the MeSH terms and free key words: “non small cell lung cancer” AND “EGFR-TKIs” AND “pretreated patients”. Literature was also searched using reference lists and materials.

Study Selection Criteria

Articles that were related to the following inclusion criteria ware included in this analysis: [1] the studies are designed as random control trials (RCTs); [2] trails focused on comparing next-generation EGFR-TKIs and chemotherapy; [3] patient with treatment-refractory advanced NSCLC after failure of first-generation EGFR-TKIs; [4] the outcomes were efficacy (overall survival, progression-free survival, tumor response) and toxicity (incidence of severe adverse effects (SAEs)); [5] the full texts were only included.

Quality Assessment

Two investigators separately assessed the quality of the retrieved studies. Study quality was justified using the Cochrane Collaboration’s “Risk of bias” tool.

Data Extraction

Two authors independently extracted the relevant data from each trial. Disagreement was settled through discussion. We extracted the main categories based on the following: first author family name, publication year, treatment regimen, patient number, mean age, and end-point of interests. We extracted the corresponding hazard ratios (HRs) and risk ratios (RRs) with 95% confidence interval (95%CI) to describe the endpoints of interest data.

Statistical Analysis

We performed the meta-analysis by pooling the results of reported incidence of OS、PFS、DCR、ORR and AEs data. We utilized the Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom) to perform all statistical analyses. The chi-square was used to assess the significance of heterogeneity, and the

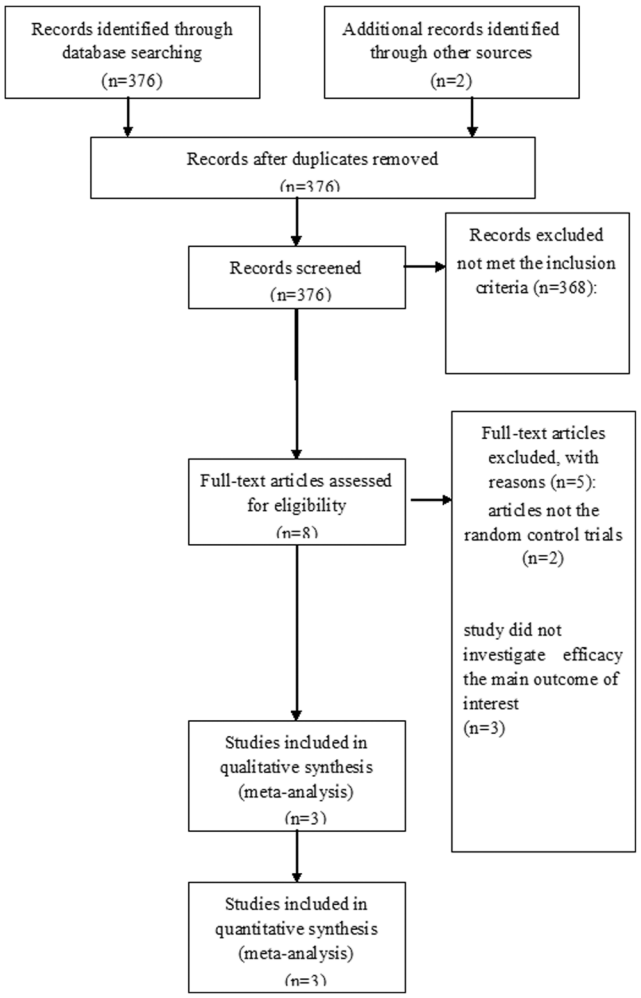

Fig. 1 PRISMA flow chart of selection process to identify studies eligible for pooling

Table 1 Detailed description of included trails

Study	Year	Treatment regimen		Patients number		Age(years)	
		Study arm	Comparative arm	Study arm	Comparative arm	Study arm	Comparative arm
V.A. Miller	2012	afatinib plus best supportive care	Placebo plus best supportive care	390	195	58	59
T.S. Mok	2016	osimertinib	intravenous pemetrexed plus either carboplatin or cisplatin	279	140	62	63
Keke Nie	2018	osimertinib	docetaxel plus bevacizumab	74	73	49.4	48.6

degree of heterogeneity was then examined through the I^2 statistic. [9]. Fixed-effect model was used if the assessment of heterogeneity was insignificant ($I^2 \leq 50\%$). If the source of heterogeneity was not insignificant (I^2>50%)uncertain, we used the random-effect model for further analysis [9]. A *P* value less than 0.05 was considered statistically significant.

Results

Overview of Literature Search and Study Characteristics

Totally, 376 articles were identified initially. During the preliminary screening of the abstracts and titles, 8 publications were further included because of the exclusion criteria. At last, a final total of three RCTs [10–12] were assessed for eligibility in the meta-analysis (Fig. 1). Table 1 describes a brief description of these 3 studies.

Clinical and Methodological Heterogeneity

Pooled Analysis of PFS Comparing Next-Generation EGFR-TKIs Versus Chemotherapy

In the analysis of the rate of PFS, all studies were included, and the data are shown in Fig. 2. Results showed that benefit was found between next-generation EGFR-TKIs and chemotherapy (OR = 0.34,95%CI = 0.29–0.40, *P* < 0.00001).

Pooled Analysis of OS Comparing Next-Generation EGFR-TKIs Versus Chemotherapy

Only two trials reported the OS data. As displayed in Fig. 3, pooled estimates of effect sizes showed no significant statistical difference of OS when comparing the two groups (OR = 1.05,95%CI = 0.85–1.31, *P* = 0.66).

Pooled Analysis of ORR Comparing Next-Generation EGFR-TKIs Versus Chemotherapy

A random- effects model was used to pool the ORR data, since the heterogeneity across the all studies was significant high. The pooled data showed that there is advantage between two groups (OR = 10.48,95%CI = 3.87–28.34, *P* < 0.00001). In other words, next-generation EGFR-TKIs increased the rate of ORR (Fig. 4).

Pooled Analysis of AEs Comparing Next-Generation EGFR-TKIs Versus Chemotherapy

We define the grade 3/4 toxicities as sever AE. In the analysis of diarrhoea, rash/acne, nausea, vomiting, and anemia were included, and the data are shown in Fig. 5. While, all above data did not reach a statistically significant level (P>0.05).

Pooled Analysis of DCR Comparing Next-Generation EGFR-TKIs Versus Chemotherapy

The pooling DCR data did show advantage in the next-generation EGFR-TKIs groups (OR = 6.03,95%CI = 4.41–8.25, *P* < 0.00001) (Fig. 6).

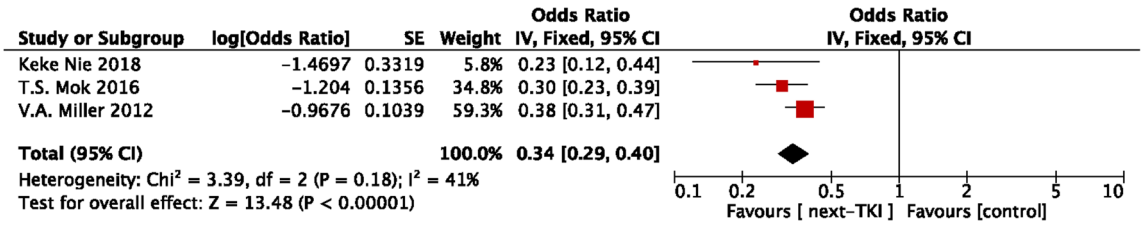

Fig. 2 Pooled analysis of PFS comparing next-generation EGFR-TKIs versus chemotherapy

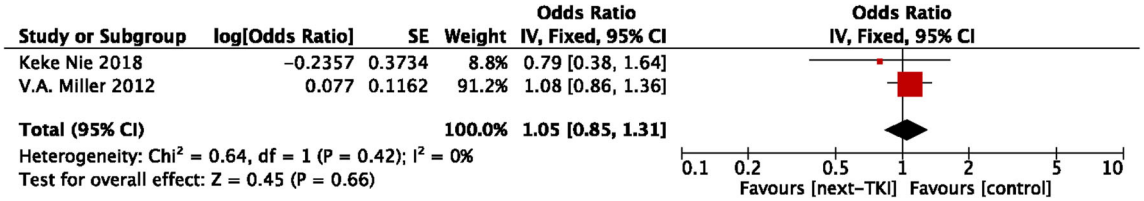

Fig. 3 Pooled analysis of OS comparing next-generation EGFR-TKIs versus chemotherapy

Discussion

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the accepted as the first-line therapy in NSCLC harboring mutations in EGFR. Nonetheless, the majority of patients eventually develop disease progresses [13, 14]. To our knowledge, acquiring resistance refers to disease progression after response to EGFR-TKI treatment [15, 16]. Nowadays, lacking effective treatment for NSCLC patients with an activating EGFR mutation after the development of acquired resistance to first-generation EGFR TKIs is a major clinical problem [17, 18].

Researches have been focused on the multiple resistance mechanisms for patients who acquired resistance to first-generation EGFR TKIs [19]. These mechanisms include the secondary mutations of the driver oncogene, and the activation of new signaling pathways other than the EGFR pathway [15, 20].

With resistance developed in patients who received previous first-generation EGFR TKIs, next-generation TKIs have drawn all the attention basing on positive results from previous trials in patients who have disease progressed after first-generation EGFR-TKI. Unlike the reversible first-generation EGFR TKIs, second- generation TKIs (afatinib) is an irreversible ErbB-family blocker [21]. Moreover, osimertinib, a third generation, irreversible EGFR TKI inhibits primary EGFR-TKI sensitizing and secondary EGFR T790 M resistance mutations [8, 22, 23].

The primary results of our study further supported the conclusion. Our analysis did not show difference between groups in terms of the overall survival, although results of the progression-free survival and response rate were promising. In Miller's study, since 39% patients were still alive, as the trial was post-hoc analyzed in February, 2012, there is still no benefit was found in overall survival between groups. Consistent with the similar results, statistical significance was not achieved in Nie's study.

The effect on survival efficacy seemed to be associated with specific EGFR mutations, which might potentially separate patients into different biological entities. Patients treated by afatinib and osimertinib have different predictive and prognostic impacts with Del19 and L858R mutations in EGFR [7, 22, 24, 25]. A retrospective study reported that compared with the L858R-positive disease with osimertinib, the prevalence of the secondary T790 M mutation was associated with better response in del19-positive disease [26]. While, in vitro and in vivo study with afatinib, the activating EGFR mutations models, including L858R and deletion-19, and the exon 20 gatekeeper T790 M mutations, with less benefit [7, 22]. In future, the study to compare the next-generation EGFR-TKIs between patients with EGFR 19 del + T790 M mutation and EGFR L858R + T790 M mutation is needed.

The improved anti-tumor activity with second/third-generation TKIs noted in this study might reflect its more potent and irreversible inhibition of EGFR signalling [24, 27]. In addition, patients treated with second/third-generation TKIs had statistically significant and clinically achieved response rate improvements in this study, which were consistent with previous trials [10–12].

The AE profiles of both treatments were reflected no statistics distinct, which will be useful in the consideration of second/third-generation TKIs for patients with EGFR mutation–positive NSCLC after first-line EGFR-TKI therapy. This finding suggests that the systematically established safety used in this trial worked well to keep patients on treatment, achieving the maximum benefit from next-generation TKIs. All AEs were manageable and predictable, and with low discontinuation rates, indicating that proactive supportive therapy and dose modification were an adequate strategy to select the EGFR inhibition.

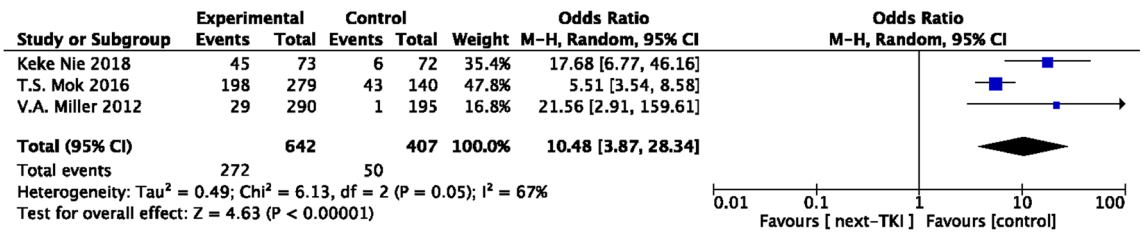

Fig. 4 Pooled analysis of ORR comparing next-generation EGFR-TKIs versus chemotherapy

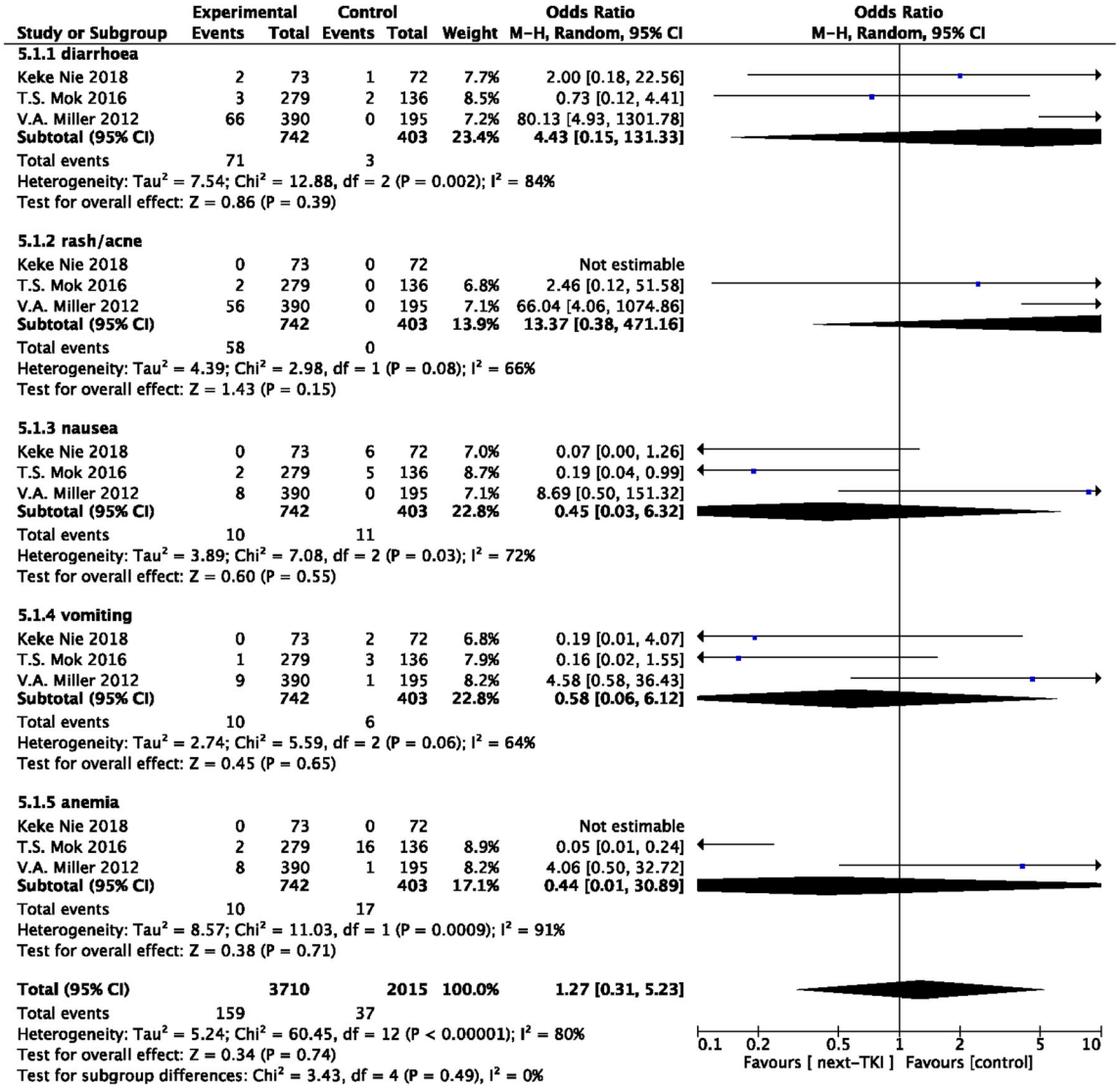

Fig. 5 Pooled analysis of AEs comparing next-generation EGFR-TKIs versus chemotherapy

In this systematic analysis assessing effect of next-generation TKIs in patients with advanced NSCLC after failure on first-generation EGFR-TKIs, there are some limitations should not be ignored. First, the current study on the rate of OS provided insufficient data. Thus, there was no strong statistical evidence to analyzed; Secondly, as this study was a study-level meta-analysis, the imbalance existed between the two groups due to different quality and the different using of EGFR-TKIs of the included studies, and findings of the current study might be affected by the clinical heterogeneity among trials; Thirdly, subgroup analysis of EGFR-TKIs mutations in the two cohorts did not provide enough data on subtype, so we could not extract relative subgroup data from literature.

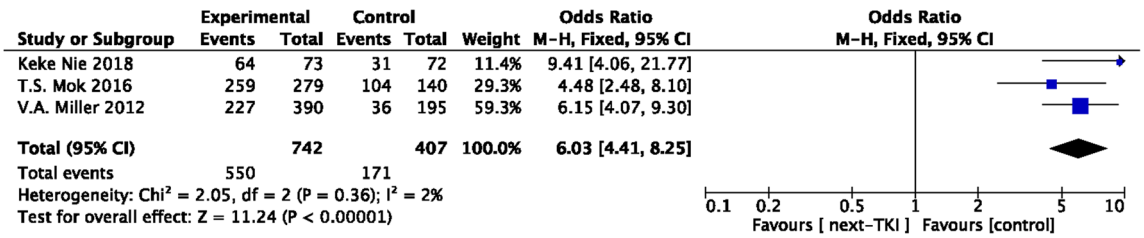

Fig. 6 Pooled analysis of DCR comparing next-generation EGFR-TKIs versus chemotherapy

Conclusion

Acquired resistance refers to disease progression after response to first-generation EGFR-TKI is complicated; and the survival result is gloomy if resistance occurs. Our data showed that, next-generation EGFR-TKI could prolong PFS and better response rate in NSCLC patients after failed to first-generation EGFR-TKI.

Relevant clinical studies have been developed to study the paradigm of "personalized" medicine in the treatment of NSCLC, at least in a subset of patients with oncogenic-driven; examples include mutations in the EGFR gene. From an efficacy standpoint, further trials into bio- markers that will benefit patients by subtype, which can be instructive in driving treatment decisions, while conferring with manageable adverse events. It is important to consider the risk of AEs when choosing treatment, particularly in patients with underlying immune disfunction.

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