Research article

The efficacy and safety of erlotinib compared with chemotherapy in previously treated NSCLC: A meta-analysis

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Abstract: *Background:* An increasing number of patients with advanced non-small cell lung cancer (NSCLC) have a poor prognosis and develop progressive disease after receiving conventional treatments. In recent years, several novel therapies have been approved for later lines of therapy of previously treated NSCLC. Erlotinib, an EGFR tyrosine kinase inhibitor, was recommended as the second-line therapy for pre-treated patients. However, the use of erlotinib has been reported to represent different clinical effects and adverse effects. *Objectives:* The current study was aim to investigate the efficacy and safety of erlotinib versus chemotherapy in pre-treated patients with advanced NSCLC. *Methods:* Electronic databases were searched for eligible literatures updated on June 2018. Randomized-controlled trials assessing the efficacy and safety of erlotinib in pre-treated NSCLC were included, of which the main outcomes were ORR (objective response rate), PFS (progression-free survival), OS (overall survival) and AEs (adverse events). All the data were pooled with the corresponding 95% confidence interval using RevMan software. Sensitivity analyses and heterogeneity were quantitatively evaluated. *Results:* A total of 11 randomized controlled trials were included in this analysis. The group of erlotinib did not achieved benefit in progression-free survival (OR = 0.61, 95%CI = 0.33–1.12, P = 0.11), overall survival (OR = 0.98, 95%CI = 0.84–1.15, P = 0.81) as well with the objective response rate (OR = 0.77, 95%CI = 0.36–1.63, P = 0.49), respectively. In the results of subgroup analysis among the patients with EGFR wild-type, there is

also no significant differences in overall survival with erlotinib (OR = 0.90, 95%CI = 0.78–1.04, P = 0.15) and progression-free survival (OR = 0.33, 95%CI = 0.09–1.18, P = 0.09). The most common treatment-related adverse events in the erlotinib group is rash (OR = 5.79, 95%CI = 2.12–15.77, P = 0.0006), and neutropenia (OR = 0.02, 95%CI = 0.01–0.10, P ≤ 0.00001) is more found in the control group. In addition, fatigue (P = 0.09) and diarrhea (P = 0.52), the difference between the two groups had no statistical significance. *Conclusions*: There was no significant difference noted with regard to efficacy and safety between erlotinib vs. chemotherapy as the later-line therapy for previously treated patients with NSCLC, even with subgroup patients who have wild-type EGFR tumors. While, erlotinib might increase the risk of rash, and decrease the risk of neutropenia, compared with the chemotherapy. Further research is needed to develop a database of all EGFR mutations and their individual impact on the differing treatments.

Keywords: NSCLC; erlotinib; pretreated patients; meta-analysis

1. Introduction

Globally, lung Cancer has a high incidence and is the leading cause of cancer-related mortality [1]. Non-small cell lung cancer (NSCLC) comprises > 80% of all lung cancers, and > 7 in 10 patients are diagnosed in advanced stages [2], which reduces the standard first-line therapeutic options to platinum-based doublet chemotherapy, with modest results and disease progression [3]. Its therapeutic plateau turns this disease into an emergent area of subsequent treatment after failure of the standard first-line therapies for NSCLC.

Currently, basing on several randomized controlled trials, the established agents in the subsequent therapy setting for advanced NSCLC treatment include docetaxel, pemetrexed, erlotinib, afatinib, and S-1 [4]. Docetaxel is effective for second-line treatment of metastatic NSCLC, which is associated with improving survival and quality of life [5–7].Pemetrexed, a multi-targeted antifolate agent, has been exerts its anti-tumor efficacy comparable to docetaxel in the same setting, but with a more favorable toxicity profile [8]. In refractory patients, afatinib demonstrated a modest benefit in terms of PFS and OS, and with a well-defined safety profile [9]. Meanwhile, S-1 has been demonstrated high antitumor activity for NSCLC with low intestinal toxicity [10,11].

Since epidermal growth factor receptor (EGFR) mutation accounts 11–22% of lung cancer driver mutations [12,13], EGFR-tyrosine kinase inhibitors (TKIs) are crucial in lung cancer treatment [14,15]. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) [16,17], reportedly confers a survival benefit over placebo in the treatment of advanced-stage NSCLC after failure of previous chemotherapy [18,19]. In recently years, several trials have been conducted comparing erlotinib and other chemotherapy for NSCLC after the failure of initial therapy. But there is still conflicting results because of their toxicity or lack of therapeutic efficacy or both treatments are limited to tumors with specific genetic alterations [4].

The objective of this meta-analysis is to evaluate the efficacy and toxicity of erlotinib versus chemotherapy in pre-treated with advanced-stage non-small-cell lung cancer.

2. Materials and method

2.1. Retrieval strategy

Published studies were searched by two investigators independently up to June, 2018. The searchable databases included PubMed, Embase, and Cochrane library, and the following keywords were used: "non-small cell lung cancer" AND "erlotinib" AND "pretreated patients" and no limitation was used during the literature search. Relevant Medical Subject Heading (MeSH) terms were also utilized. The references of eligible studies were checked for additional studies.

2.2. Eligibility criteria

Studies that meet the following criteria were included in the meta-analysis should: (1) random control trials (RCTs); (2) patients were clinically diagnosed with advanced-stage NSCLC after failure of previous chemotherapy; (3) trails focused on comparing erlotinib and chemotherapy; (4) the results of interest available regarding the efficacy (survival, tumor response) and toxicity (incidence of severe adverse effects (SAEs)); (5) the full texts were only included. The studies that did not meet the above inclusion criteria would be excluded from the meta-analysis.

2.3. Quality assessment

The risk of bias was evaluated in each mentioned study based on Cochrane handbook for Systematic Reviews by Cochrane Collaboration. Study quality was justified using Jadad scale by two investigators separately [20].

2.4. Data selection and extraction

A self-designed data extraction form was used to independently extract following information by two authors including: lead author family name, year of publication, country, participant number, mean age treatment regimen, end-point of interests. We extracted the corresponding variables adjusted and risk estimates of mortality with 95%CIs.

2.5. Statistical analysis

The statistical analyses were conducted using Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom). To assess the heterogeneity of study trial and determine the model for analysis, I2 statistic and Chi-squared were conducted [21]. Random-effect model was used if the assessment of heterogeneity was moderate and high ($I2 \geq 50\%$). Otherwise, if the source of heterogeneity was low($I2 < 50\%$), we used the fixed-effect model for further analysis [22]. A $P < 0.05$ was considered as statistically significant difference.

3. Results

3.1. Overview of literature search and study characteristics

A total of 437 studies were retrieved initially for evaluation. Based on the criteria described in the methods, 16 publications were evaluated in more detail, but some did not provide enough detail of outcomes of two approaches. Therefore, a final total of 11 RCTs [9,23–32] evaluate the efficacy and toxicity of comparing erlotinib versus chemotherapy. 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.
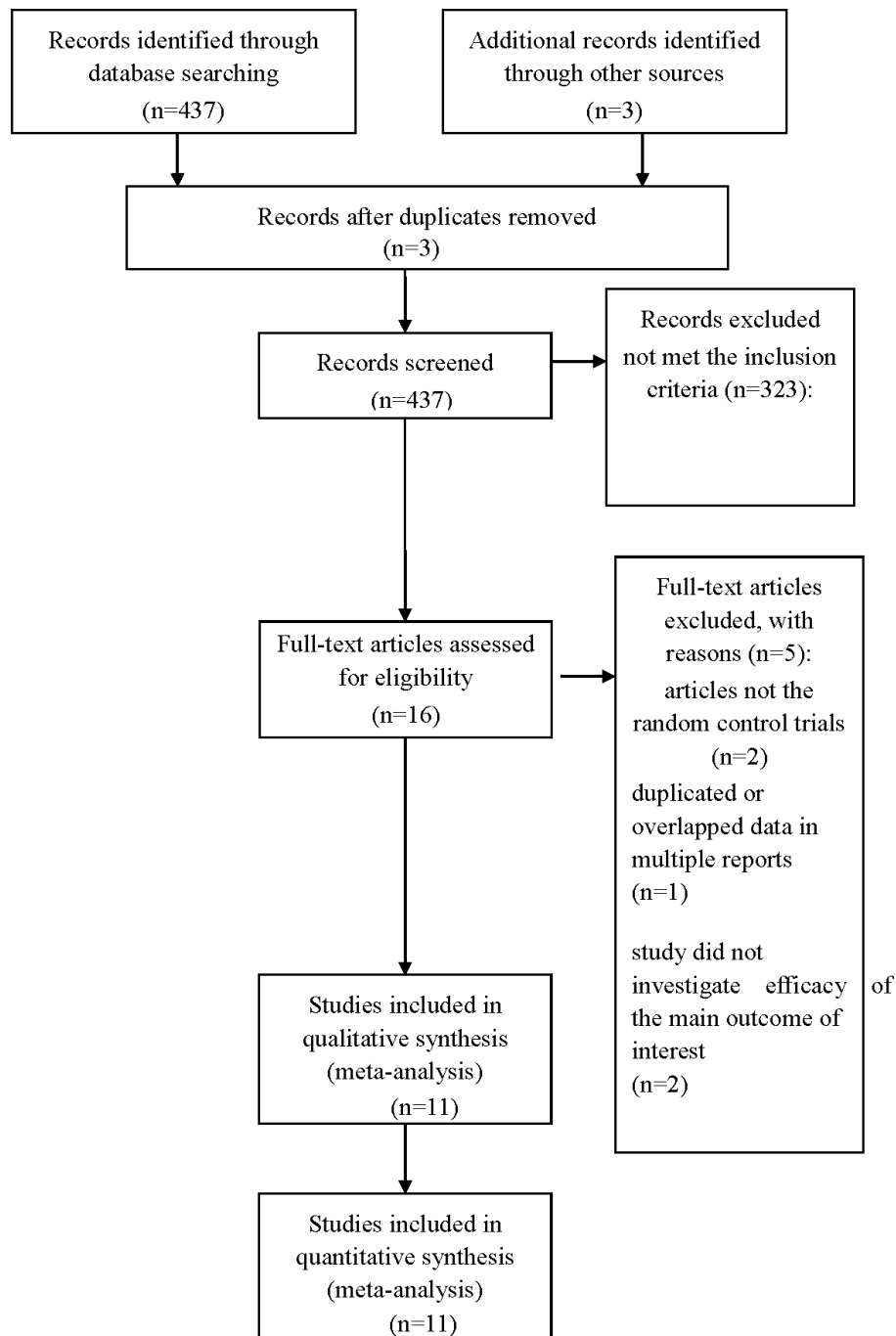
Figure 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

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

Author	Year	Country	Control group	No. of patients Erlotinib	control	Median age Erlotinib	control
Fiala Onderj	2016	Czech	Pemetrexed	88	49	65	61
Li Ning	2014	China	Pemetrexed	61	62	54.3	55.1
Athanasios Karampeazis	2013	Greece	Pemetrexed	166	166	65	66
Dae Ho Lee	2013	China	Pemetrexed	82	80	53.9	55.9
Kawaguchi	2014	Japan	Docetaxel	150	151	68	67
Garassino	2013	Italy	Docetaxel	109	110	66	67
Solange Peters	2017	Switzerland	Docetaxel	38	42	66.3	69.7
Gregorc	2014	Italy	Pemetrexed + Docetaxel	134	129	65	65
Ciuleanu	2012	Romania	Pemetrexed + Docetaxel	203	221	59	59
Soria J-C	2015	USA	Afatinib	397	398	64	65
Yasuyuki Ikezawa	2017	Japan	S-1	19	18	65	64

3.2. Clinical and methodological heterogeneity

3.2.1. Pooled analysis of PFS comparing erlotinib versus chemotherapy

The pooling PFS data did not achieve advantage between two groups (OR = 0.61, 95%CI = 0.33–1.12, P = 0.11). In other words, neither erlotinib nor chemotherapy leads a PFS advantage (Figure 2). While, subgroup analyses also indicated that the comparison of two groups did not show PFS benefit (OR = 0.33, 95%CI = 0.09–1.18, P = 0.09) (Figure 3) among EGFR wild-type patients.
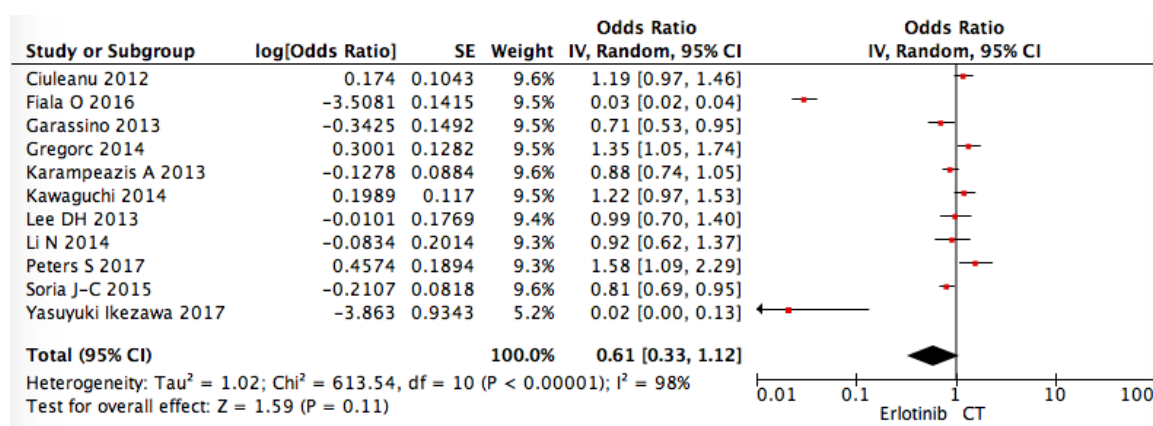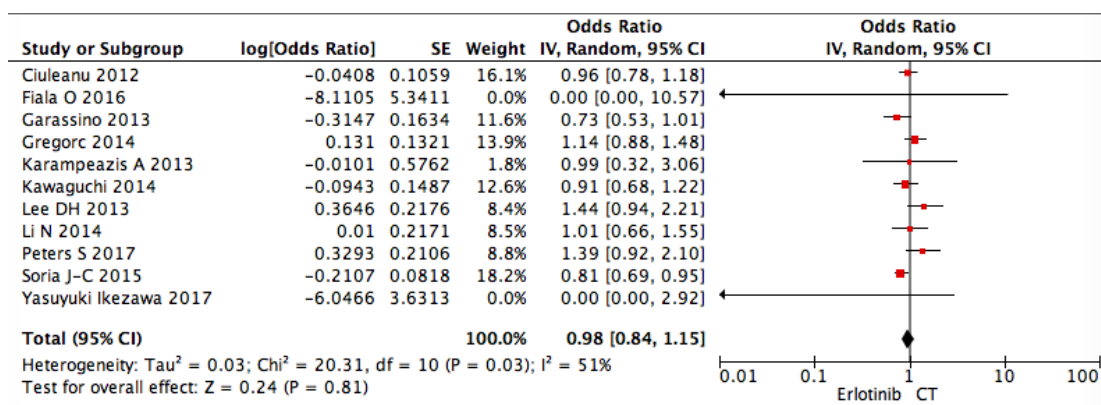

Figure 2. Pooled analysis of PFS comparing erlotinib versus chemotherapy.
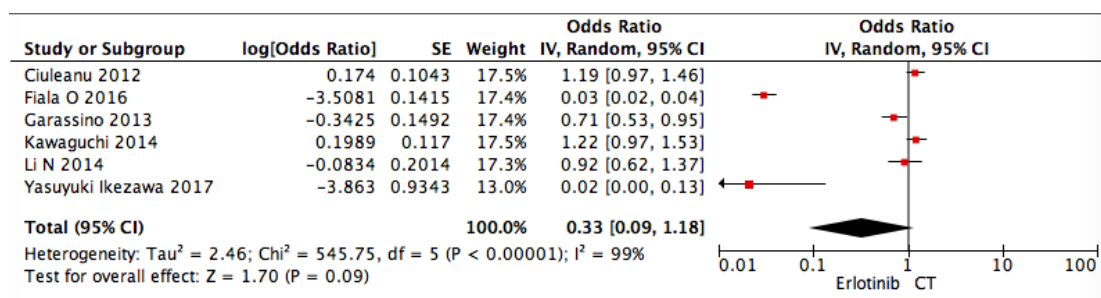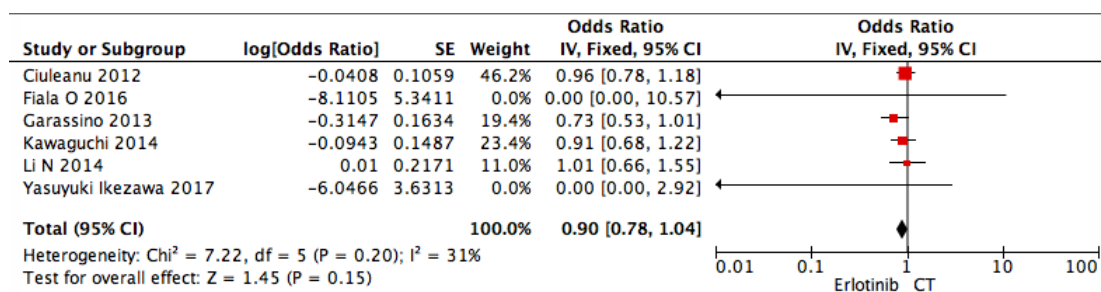
Figure 3. Pooled analysis of PFS comparing erlotinib versus chemotherapy among EGFR wild-type patients.

3.2.2. Pooled analysis of OS comparing erlotinib versus chemotherapy

A random- effects model was used to pool the OS data, since the heterogeneity across the eight studies was high. The pooled data showed that there was no benefit comparing erlotinib versus chemotherapy for pretreated advanced NSCLC (OR = 0.98, 95%CI = 0.84–1.15, P = 0.81) (Figure 4), as well as in the EGFR wild-type subgroup (OR = 0.90, 95%CI = 0.78–1.04, P = 0.15) (Figure 5).
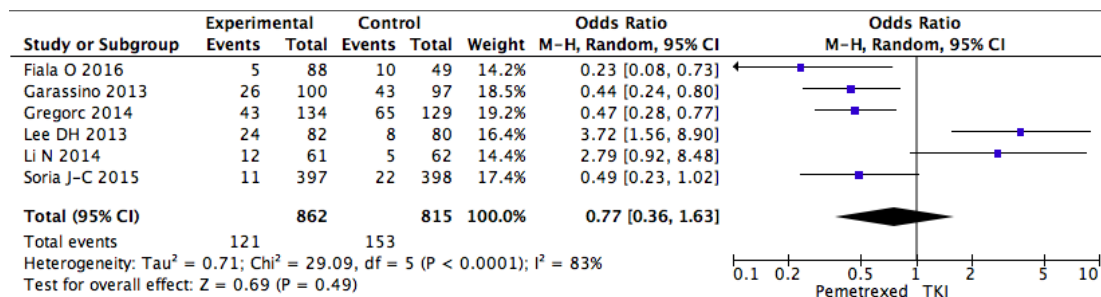

Figure 4. Pooled analysis of OS comparing erlotinib versus chemotherapy.

Figure 5. Pooled analysis of OS comparing erlotinib versus chemotherapy among EGFR wild-type patients.

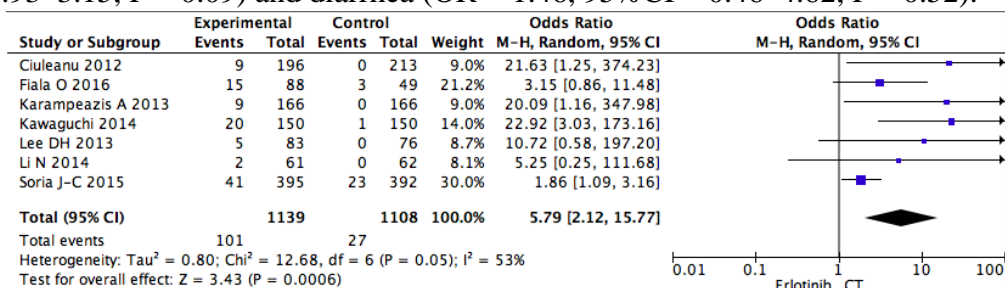### 3.2.3. Pooled analysis of ORR comparing erlotinib versus chemotherapy

Pooling the ORR data from six studies showed that erlotinib did not increased the rate of the ORR (OR = 0.77, 95%CI = 0.36–1.63, P = 0.49) compared with the chemotherapy group (Figure 6).

Figure 6. Pooled analysis of ORR comparing erlotinib versus chemotherapy.

3.2.4. Pooled analysis of SAE comparing erlotinib versus chemotherapy

We define the grade 3/4 toxicities as SAE. The rate of the rash, neutropenia, fatigue and diarrhea were included, and the data are shown in Figure 7–10. Statistically significant level was reached in rate of rash (OR = 5.79, 95%CI = 2.12–15.77, P = 0.0006), and neutropenia (OR = 0.02, 95%CI = 0.01–0.10, P < 0.00001). While, no difference was found in the incidence rate of fatigue (OR = 1.71, 95%CI = 0.93–3.15, P = 0.09) and diarrhea (OR = 1.46, 95%CI = 0.46–4.62, P = 0.52).

Figure 7. Pooled analysis of rash comparing comparing erlotinib versus chemotherapy.
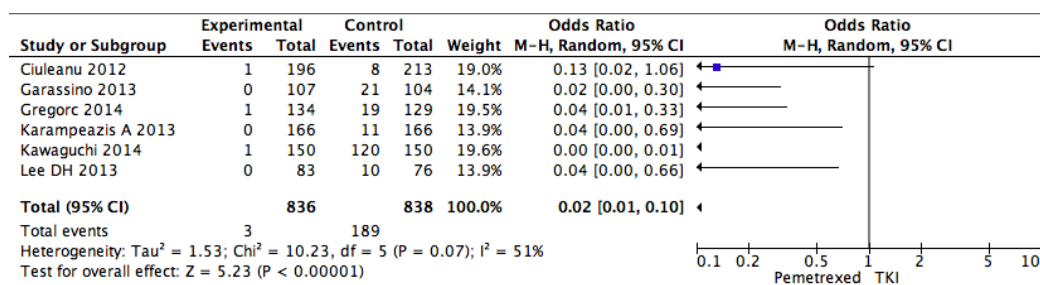
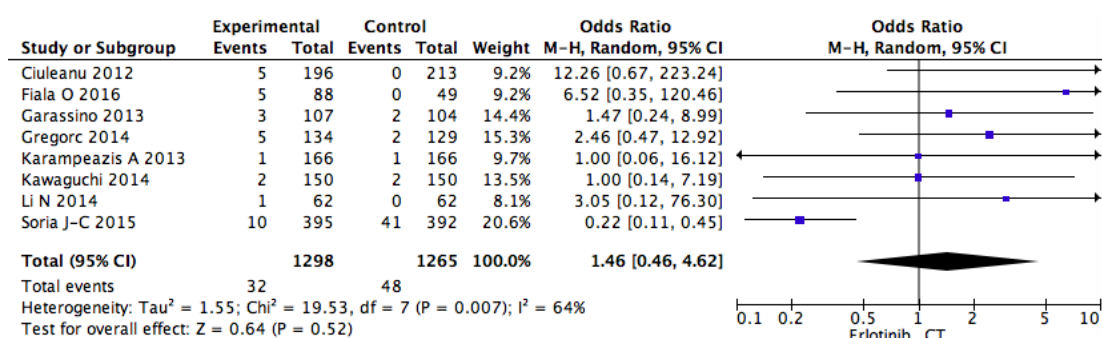**Figure 8.** Pooled analysis of neutropenia comparing erlotinib versus chemotherapy.

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M–H, Fixed, 95% CI
	Events	Total	Events	Total		
Ciuleanu 2012	0	196	1	213	8.9%	0.36 [0.01, 8.90]
Fiala O 2016	1	88	1	49	7.9%	0.55 [0.03, 9.02]
Karampeazis A 2013	12	166	1	166	5.7%	12.86 [1.65, 100.05]
Kawaguchi 2014	8	150	7	150	41.0%	1.15 [0.41, 3.26]
Soria J–C 2015	7	395	6	392	36.6%	1.16 [0.39, 3.49]
Total (95% CI)		**995**		**970**	**100.0%**	**1.71 [0.93, 3.15]**
Total events	28		16			

Heterogeneity: Chi² = 6.28, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 1.71 (P = 0.09)

Figure 9. Pooled analysis of fatigue comparing erlotinib versus chemotherapy.

Study or Subgroup	Experimental		Control		Weight	Odds Ratio M–H, Random, 95% CI
	Events	Total	Events	Total		
Ciuleanu 2012	5	196	0	213	9.2%	12.26 [0.67, 223.24]
Fiala O 2016	5	88	0	49	9.2%	6.52 [0.35, 120.46]
Garassino 2013	3	107	2	104	14.4%	1.47 [0.24, 8.99]
Gregorc 2014	5	134	2	129	15.3%	2.46 [0.47, 12.92]
Karampeazis A 2013	1	166	1	166	9.7%	1.00 [0.06, 16.12]
Kawaguchi 2014	2	150	2	150	13.5%	1.00 [0.14, 7.19]
Li N 2014	1	62	0	62	8.1%	3.05 [0.12, 76.30]
Soria J–C 2015	10	395	41	392	20.6%	0.22 [0.11, 0.45]
Total (95% CI)		**1298**		**1265**	**100.0%**	**1.46 [0.46, 4.62]**
Total events	32		48			

Heterogeneity: Tau² = 1.55; Chi² = 19.53, df = 7 (P = 0.007); I² = 64%
Test for overall effect: Z = 0.64 (P = 0.52)

Figure 10. Pooled analysis of diarrhea comparing erlotinib versus chemotherapy.

4. Discussion

Lung cancer is the most common diagnosed cancer and the frequent cause of cancer death [4]. More than 80% of all newly diagnosed lung cancers are non-small-cell lung cancers (NSCLCs) [33]. Despite NSCLC patients have received standard first-line treatment, most patients would experience disease progression ultimately and need subsequent treatment [34].

Later-line treatment options available to previously treated patients who fail from first-line treatment include additional chemotherapy or targeted therapy [6–8,35]. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have been investigated in several trials in the second-line setting. Erlotinib is an orally administered small molecule tyrosine kinase inhibitor (TKI) targeting epidermal growth factor receptor (EGFR), which was reported to improve overall survival, progression-free survival, and quality of life, compared with placebo as second- line or third-line therapy in previously treated NSCLC [36,37]. However, the role of erlotinib still remains controversial.

The objective of this study was to assess the efficacy and toxicity of erlotinib versus chemotherapy in pre-treated with advanced-stage non-small-cell lung cancer. While, our data failed to demonstrate the superiority of erlotinib over chemotherapy, and the differences with regard to PFS, OS, and the ORR were not statistically significant between two arms for NSCLC after the failure of initial therapy, even with subgroup patients harboring EGFR wild-type (wt- EGFR).

The exploratory analysis could be that patients who may have a distinct clinical behavior according to different EGFR status. Overall, the EGFR mutated (mut-EGFR) patients experienced a trend toward improvement in the ORR and TTP, but not OS, compared with EGFR wild type patients,

as previously reported [38,39]. A preliminary report from the TAILOR study indicated that chemotherapy has an improvement in patients with wt- EGFR tumors [27]. The observed higher ORR and the improvement in OS in patients with mut-EGFR tumors in the erlotinib arm, which is consistent with the predictive value of EGFR mutations for response to EGFR-TKIs [14,40–42]. In addition, association between EGFR mutation status and survival is difficult to estimate, particularly outside of a clinical trial setting. The obstacle to this association could be associated with the different lines of treatment and the crossover of treatments [41–43].

The toxicity observed in our study showed that the crash occurred more frequently in the erlotinib arm compared with the chemotherapy arm, and resulted in decreasing the risk of neutropenia. Consistent with our findings, a recently meta-analysis suggests that the anemia, neutropenia and alopecia occurred less with erlotinib treatment compared with the chemotherapy, whereas rash and diarrhea occurred more often among the patients treated with erlotinib [44]. This result suggests that the systematically established management of adverse events used in this therapy worked well to keep patients on treatment, enabling the maximum benefit from drugs. Given the different safety profiles of erlotinib or chemotherapy, a key factor in selecting treatment should be patients' comorbidities and tolerance of expected toxicity.

This is the first pooled analysis focused on the efficacy and toxicity comparing the efficacy and toxicity of erlotinib versus chemotherapy in pre-treated with advanced-stage non-small-cell lung cancer. However, there are limitations to our study. First, as this study was a study-level meta-analysis, due to the lack of patient-level data, clinical heterogeneity among trials should be taken into consideration in the interpretation of our findings, even though all the included studies are randomized clinical trials. Second, subgroup analysis of EGFR TKI mutation status did not provide enough data on subtype. It has been reported that the presence of KRAS mutation is a possible negative predictive factor for response to EGFR TKIs [38,45,46], so we could not extract relative subgroup data from literature. Therefore, analyses from individual patient data on subtype are need debated in the future.

5. Conclusion

In summary, the current study indicates that erlotinib and chemotherapy are comparable efficacy with well-manageable tolerability for previously treated NSCLC. Recent advances in the treatment of NSCLC have disease progression after the failure of initial therapy have developed to a part of a paradigm of "personalized" medicine in oncology, at least in a subset of patients with oncogenic-driven; examples include mutations in the EGFR gene and other gene. From an efficacy standpoint, further trials into biomarkers that will benefit patients by subtype, which can be instructive in driving treatment decisions, while conferring with manageable adverse events.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical statement

This article does not contain any studies with human participants or animals performed by any of

the authors.

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