RESEARCH ARTICLE

Comparison of the Efficacy and Safety of EFGR Tyrosine Kinase Inhibitor Monotherapy with Standard Second-line Chemotherapy in Previously Treated Advanced Non-small-cell Lung Cancer: a Systematic Review and Meta-analysis

Wei-Xiang Qi, Zan Shen, Feng Lin, Yuan-Jue Sun, Da-Liu Min, Li-Na Tang, Ai-Na He, Yang Yao*

Abstract

Purpose: To compare the efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitormonotherapy (EFGR-TKIs: gefitinib or erlotinib) with standard second-line chemotherapy (single agent docetaxel or pemetrexed) in previously treated advanced non-small-cell lung cancer (NSCLC). Methods: We systematically searched for randomized clinical trials that compared EGFR-TKI monotherapy with standard second-line chemotherapy in previously treated advanced NSCLC. The end points were overall survival (OS), progression-free survival (PFS), overall response rate (ORR), 1-year survival rate (1-year SR) and grade 3 or 4 toxicities. The pooled hazard ratio (HR) or risk ratio (RR), with their corresponding 95% confidence intervals (CI) were calculated employing fixed- or random-effects models depending on the heterogeneity of the included trials. Results: Eight randomized controlled trials (totally 3218 patients) were eligible. Our meta-analysis results showed that EGFR-TKIs were comparable to standard second-line chemotherapy for advanced NSCLC in terms of overall survival (HR 1.00, 95%CI 0.92-1.10; p=0.943), progression-free survival (HR 0.90, 95%CI 0.75-1.08, P=0.258) and 1-year-survival rate (RR 0.97, 95%CI 0.87-1.08, P=0.619), and the overall response rate was higher in patients who receiving EGFR-TKIs(RR 1.50, 95%CI 1.22-1.83, P=0.000). Sub-group analysis demonstrated that EGFR-TKI monotherapy significantly improved PFS (HR 0.73, 95%CI: 0.55-0.97, p=0.03) and ORR (RR 1.96, 95%CI: 1.46-2.63, p=0.000) in East Asian patients, but it did not translate into increase in OS and 1-year SR. Furthermore, there were fewer incidences of grade 3 or 4 neutropenia, febrile neutropenia and neutrotoxicity in EGFR-TKI monotherapy group, excluding grade 3 or 4 rash. Conclusion: Both interventions had comparable efficacy as second-line treatments for patients with advanced NSCLC, and EGFR-TKI monotherapy was associated with less toxicity and better tolerability. Moreover, our data also demonstrated that EGFR-TKImonotherapy tended to be more effective in East Asian patients in terms of PFS and ORR compared with standard second-line chemotherapy. These results should help inform decisions about patient management and design of future trials.

Keywords: Non-small-cell lung cancer - second-line - erlotinib - gefitinib - docetaxel - pemetrexed - meta-analysis

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Introduction

Lung cancer is still a leading cause of cancer-related deaths worldwide with a 5-year survival of less than 15% (Parkin et al., 2002; Schiller et al., 2002; Kim et al., 2012). Because the majority of people diagnosed with non-small cell lung cancer (NSCLC) are unsuitable for surgery, chemotherapy remains the cornerstone of treatment and prolongs survival with a positive impact on quality of life. However, the majority of patients with advanced NSCLC experience cancer progression after 3-6 months of first-line chemotherapy, and approximately 40% of them have progressive disease during the treatment (Passaro et al., 2011). Of note is that approximately 50% of patients progressing to first-line treatment still have a good performance status, which would make them suitable for second-line therapy (Stinchcombe et al., 2009). At present, although docetaxel and pemetrexed are still considered as standard second-line therapy in patients with good performance status (Fossella et al., 2000; Shepherd et al., 2000; Rossi et al., 2009), there is still much room for improvement in terms of efficacy as well as toxicity.

During the last decades, the second-line treatments for advanced NSCLC have evolved substantially, many trials have been conducted to evaluate the efficacy and safety of docetaxel-based or pemetrexed-based doublets

*Department of Oncology, the Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China *For correspondence: qwxzlk@163.com*

therapies in previously treated advanced NSCLC. Though the combined meta-analyses results show that both doublet combination therapy significantly improved progression free survival (PFS) and overall response rate (ORR) compared with single agent chemotherapy, it do not translate into increase in overall survival (OS) (Qi et al., 2012; Qi et al., 2012). Recently, selective targeting of EGFR signaling pathways that contribute to the development and progression of NSCLC has the potential to provide antitumor efficacy with reduced toxicity compared with the conventional cytotoxic agents. Two EGFR TKIs, erlotinib (Tarceva; Genentech, San Francisco, CA) and gefitinib (Iressa; Astra-Zeneca, Wilmington, DE), have received approval for the treatment of advanced NSCLC in the second- or third-line setting worldwide (Shepherd et al., 2005; Thatcher et al., 2005). As both interventions share a common indication, we consider it particularly important to investigate the comparative effectiveness and safety of EGFR-TKIs and standard second-line chemotherapy.

Materials and Methods

Search strategy

We searched PubMed (up to March 2012), Embase (1980 to March 2012), the Cochrane Register of Controlled Trials and China National Knowledge Infrastructure (CNKI: up to March 2012) using various combinations of different terms "advanced NSCLC'', ''docetaxel'', ''pemetrexed", "gefitinib", "erlotinib", "EGFR-TKIs", "randomized" and "second-line". We looked at posters from the annual meetings of the European Society of Medical Oncology (ESMO) and the American Society of Medical Oncology (ASCO) in the past 10 years. We did not set any language restrictions, and reference listed from relevant primary studies and review articles were also examined to find additional publications.

Study selection

The relevant clinical trials were manually selected carefully based on the following criteria: (1) trails comparing EGFR-TKIs monotherapy with standard second-line chemotherapy (single agent docetaxel or pemetrexed); (2) patients were pathologically confirmed of NSCLC and previously treated; (3) prospective phase II and III randomized controlled trials (RCTs); (4) The included study has sufficient data for extraction. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

Data extraction and Quality assessment

Two independent investigators reviewed the publications and extracted the data. The following information was extracted from each article: (1). Basic information from papers such as, year of publication, phase of trials and author name etc. (2).Characteristics of patients such as: median age, nonsmoker, EGFR mutation and female patients. (3). Information of study designation such as: sample size per-group, study design, randomization scheme, inclusion criteria, and type of end point used. (4). Information of treatment such as: treatment regimen, dose of chemotherapy, withdrawals, median overall survival (OS), progression-free survival (PFS), overall response rate (ORR), 1-year survival rate (1-year SR), and adverse events (AEs) and so on. Available information was extracted and recorded to a data collection form and entered into electronic database. The quantitative 5-point jadad scale was used to assess the quality of included trials based on the reporting of the studies' methods and results (Moher et al., 1998).

Data analysis

The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. Statistical analysis of the overall hazard ratio (HR) for OS, and PFS, the risk ratio (RR) for overall response rate, 1-year SR, and grade 3 or 4 AEs was calculated using Stata version 12.0 software (Stata Corporation, College Station, Texas, USA).When OS and PFS could not be extracted from the original reports directly in several RCTs, we deciphered them from the survival curve as reported by Parmar et al. (1998). Between-study heterogeneity was estimated using the χ^2-based Q statistic (Zintzaras et al., 2005). Heterogeneity was considered statistically significant when P heterogeneity < 0.05 or $I^2 > 50\%$. If heterogeneity existed, data was analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. A statistical test with a p-value less than 0.05 was considered significant. HR>1 reflected more deaths or progression in EGFR-TKIs monotherapy, and RR>1 indicated more toxicities and overall response rate in EGFR-TKIs monotherapy; and vice versa. The presence of publication bias was evaluated by using the Begg and Egger tests (Begg et al., 1994; Egger et al., 1997; Vandenbroucke et al., 1998). All p-values were two-sided. All CIs had a two-sided probability coverage of 95%.

Results

Study identification and eligibility

After the selection procedure (Figure 1), eight trials were considered eligible. The characteristics of these studies were listed in Table 1. Of these eight trials, two

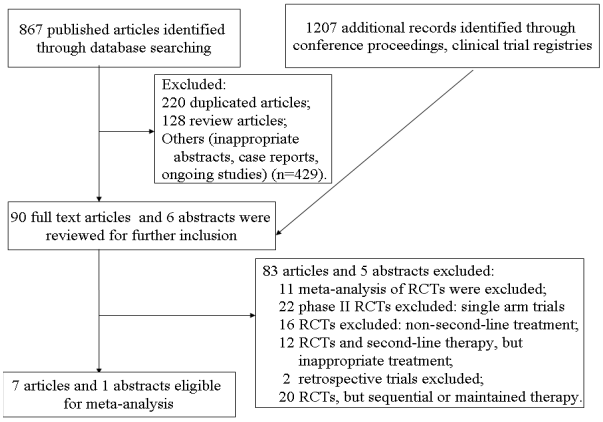

Figure 1. Flow Chart of Trial Selection Process

Table 1. Overview of Studies in the Pooled Analysis

Year	Phase	Country	Patients analyzed	Patient per arm	Regimen	Age, median (years)	female, %	EGFR mutation, %	Nonsmoker, %	Adeno/BAC, %	MS (mo)	PFS/TTP (mo)	1-year SR, %	Jadad score
2006	II	International	141	68	Gefitinib: 250mg/d	68	31	NA	26.5	NA	7.5	3	NA	3
				73	TXT:75mg/m2 iv.q.3.w.	73	27	NA	24.7	NA	7.1	3.4	NA	
2008	III	International	1466	733	Gefitinib: 250mg/d	61	36.4	11.8	20.2	56.2	7.6	2.2	32	3
				733	TXT:75mg/m2 iv.q.3.w.	60	33.4	12.5	20.5	57	8	2.7	34	
2008	III	Japan	490	245	Gefitinib: 250mg/d	NA	38.4	NA	29	78.4	11.5	2	47.8	3
				244	TXT:60mg/m2 iv.q.3.w.	NA	38.1	NA	35.7	77	14	2	53.7	
2010	III	Korea	161	82	Gefitinib: 250mg/d. Po.	57	32.9	NA	36.6	67.1	14.1	3.3	NA	3
				79	TXT:75mg/m2 iv.q.3.w..	58	43	NA	45.6	69.6	12.2	3.4	NA	
2010	III	Greece	297	150	Erlotinib 150mg/d. po.	NA	NA	NA	NA	NA	8.9	2.9	NA	2
				147	Pemetrexed 500mg/m2. iv. q.3.w.	NA	NA	NA	NA	NA	7.7	3.6	NA	
2010	II	China	98	50	Gefitinib: 250mg/d. Po.	50.7	40	NA	NA	NA	7.1	4.1	35.9	3
				48	TXT: 75mg/m2 iv. q.3.w	48.2	39.6	NA	NA	NA	6.9	3.6	31.5	
2012	III	International	424	203	Erlotinib 150mg/d. po.	59	21	3	15	47	5.3	6.3 weeks	26	3
				221	TXT 75mg/m2 iv.q.3.w. or pemetrexed 500mg/m2 iv. q.3.w.	59	28	2	14	52	5.5	8.6 weeks	24	
2012	III	Korea	141	71	Gefitinib: 250mg/d. Po.	58	85.3	23.5	NA	100	22.2	9	73.6	3
				70	Pemetrexed 500mg/m2. iv. q.3.w.	64	85.1	25.4	NA	100	18.9	3	70.5	

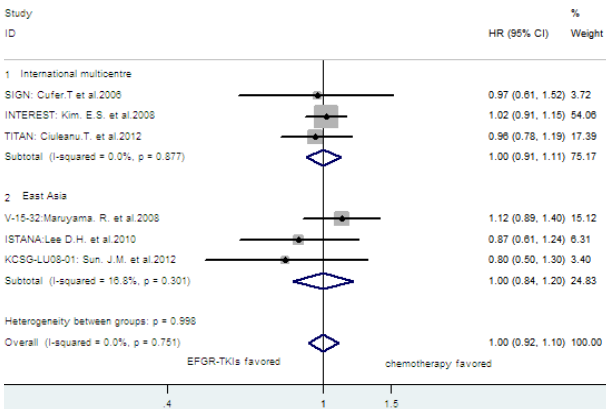

Figure 2. Fixed-effects Model of Hazard Ratio (95% confidence interval) of OS Associated with EGFR-TKIs Monotherapy Versus Standard Second-line Chemotherapy

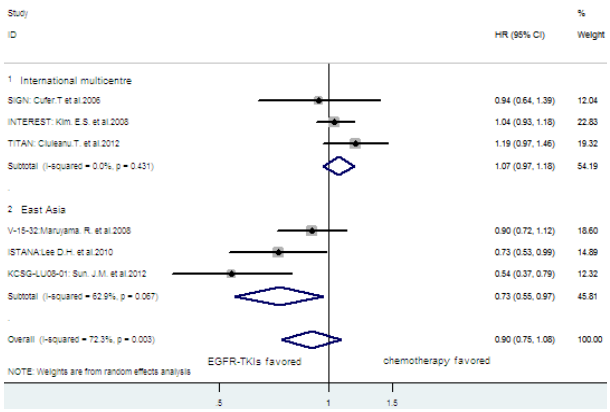

Figure 3. Random-effects Model of Hazard Ratio (95% confidence interval) of PFS Associated with EGFR-TKIs Monotherapy Versus Standard Second-line Chemotherapy

were phase II trials (Cufer et al., 2006; Li et al., 2010) and six were large, phase III trials (Kim et al., 2008; Maruyama et al., 2008; Lee et al., 2010; Vamvakas et al., 2010; Ciuleanu et al., 2012; Sun et al., 2012), there was no placebo-controlled double-blinded trial. One trial did by Garassino M.C. et al was excluded due to limited survival data (Garassino et al., 2012). Finally, a total of 3218 patients from eight clinical studies were available for analysis, with 1602 in the EGFR-TKI monotherapy arm and 1616 in the standard second-line chemotherapy arm. The total number of each trial varied from 98 to 1466; The quality of each included study was roughly assessed according to Jadad scale, and seven trials had Jadad scores of 3 and one trial had Jadad scores of 2 (Table 1).

Efficacy

Overall survival: Six of the eight trials reported OS data. Taken together, the pooled hazard ratio for OS did not show significant difference between EGFR-TKIs monotherapy and standard second-line chemotherapy (HR 1.00, 95%CI 0.92-1.10; p=0.943, Figure 2) without evidence of heterogeneity between studies (p=0.52). The pooled HR for OS was performed using fixed-effort model. Then, we did sub-group analysis according to geographical origin and found that EGFR-TKIs monotherapy was also comparable to standard second-line chemotherapy in Eastern Asian patients (HR 1.00, 95%CI: 0.84-1.20, p=0.973).

Progression-free survival: Six of the eight trials reported PFS data. The pooled hazard ratio for PFS did not show significant difference between EGFR-TKI monotherapy and standard second-line chemotherapy (HR 0.90, 95%CI 0.75-1.08, P=0.258, Figure 3).There was significant heterogeneity between trials (p=0.003), and the pooled HR for PFS was performed using random-effort model. Sub-group analysis based on geographical origin demonstrated that EFGR-TKI was superior to standard second-line chemotherapy in Eastern Asian patients (HR 0.73, 95%CI: 0.55-0.97, p=0.03) without significant evidence of heterogeneity between studies (p=0.067).

Figure 3 Random-effects model of hazard ratio (95% confidence interval) of progression free survival associated with EGFR-TKI monotherapy versus standard second-line chemotherapy.

Overall response rate: All eight trials reported ORR data, the pooled RR for overall response rate showed EGFR-TKI monotherapy significantly improved overall response rate (RR 1.50, 95%CI 1.22-1.83, P=0.000, Figure 4).There was no significant heterogeneity between the trials (p=0.336), and the pooled RR for overall response was performed using random-effort model. Sub-group analysis based on geographical origin also demonstrated that EFGR-TKI was superior to standard second-line chemotherapy in Eastern Asian patients (RR 1.96, 95%CI: 1.46-2.63, p=0.000) without significant evidence of heterogeneity between studies (p=0.642).

Table 2. Outcome of Grade 3 or 4 Toxicity Meta-analysis Comparing EGFR-TKIs with Standard Second-line Chemotherapy

Toxicities	Trials	EGFR-TKIs Monotherapy, n (events/total)	Standard second-line chemotherapy, n (events/total)	Heterogeneity P value	Heterogeneity I^2	RR (95%CI)	P value
Grade 3–4 Neutropenia	4	36/1117	612/1121	0.003	78.20%	0.1 (0.038-0.261)	<0.001
Grade 3-4 Febrile neutropenia	3	11/1046	91/1051	0.946	0	0.136 (0.074-0.249)	<0.001
Grade 3-4 Diarrhea	6	31/1402	27/1421	0.281	21%	1.158 (0.702-1.912)	0.566
Grade 3-4 Rash	5	30/1331	7/1351	0.402	0.70%	3.894 (1.795-8.449)	0.001
Grade 3-4 Mucositis	5	1/1331	6/1351	0.803	0	0.344 (0.083–1.426)	0.141
Grade 3-4 Vomiting	5	9/1331	12/1351	0.588	0	0.756 (0.32-1.787)	0.524
Grade 3–4 Nausea	6	10/1402	20/1421	0.802	0	0.511 (0.241-1.084)	0.08
Grade 3–4 Neurotoxicity	5	2/1157	19/1176	0.149	52%	0.11 (0.026-0.465)	0.003

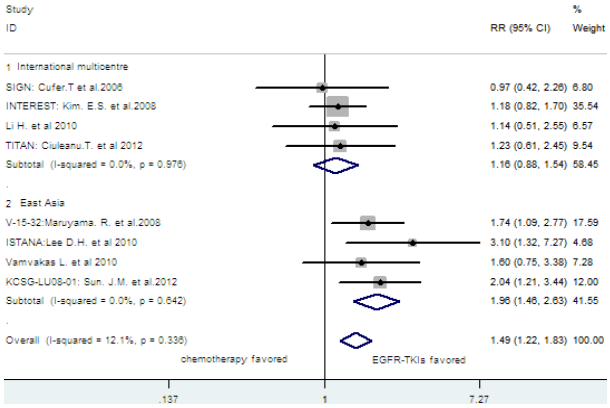

Figure 4. Fixed-effects Model of risk ratio (95% confidence interval) of ORR Associated with EGFR-TKIs Monotherapy Versus Standard Second-line Chemotherapy

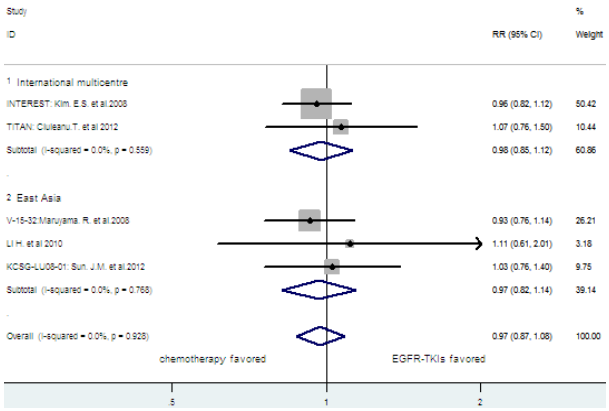

Figure 5. Fixed-effects Model of Risk Ratio (95% confidence interval) of 1-year SRe Associated with EGFR-TKIs Monotherapy Versus Standard Second-line Chemotherapy

1-year survival rate: Five trials reported 1-year survival data, the pooled RR for 1-year SR showed that EGFR-TKI monotherapy was comparable to standard second-line chemotherapy in terms of 1-year survival rate (RR 0.97, 95%CI 0.87-1.08, P=0.619, Figure 5). There was no significant heterogeneity (p=0.928), and the pooled RR for 1-year survival rate was performed using fixed-effort model.

There were fewer incidences of grade 3 or 4 neutropenia, febrile neutropenia and neurotoxicity in EGFR-TKI monotherapy group, but more incidences of grade 3 or 4 rash were observed in EGFR-TKI monotherapy group. With regard to the risk of grade 3 or 4 diarrhea, mucositis, nausea and vomiting, equivalent frequencies were found between the two groups (Table 2).

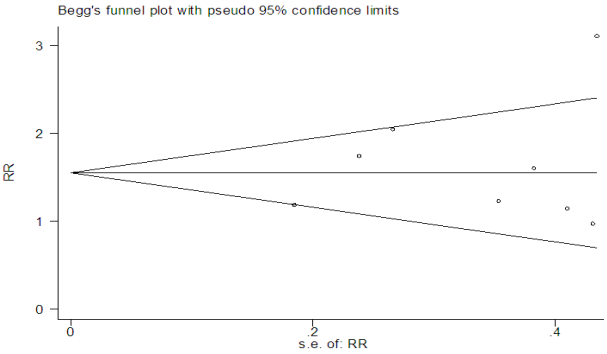

Figure 6. Funnel Plot of Publication bias in the Meta-analysis

Table 2 Outcome of grade 3 or 4 toxicity meta-analysis comparing EGFR-TKI monotherapy versus standard second-line chemotherapy.

Publication bias: Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (p=0.902 for ORR, Figure 6). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias (p=0.239 for OS, p=0.140 for PFS, P= 0.069 for 1-year SR, p=0.538 for ORR, respectively).

Discussion

Our meta-analysis, with inclusion of all available randomized trials data regarding EGFR-TKIs versus standard second-line chemotherapy for advanced NSCLC, failed to demonstrate any efficacy differences in terms of OS, PFS and 1-year SR, though EGFR-TKIs monotherapy significantly improved ORR. In addition, EGFR-TKIs monotherapy was clearly more favorable than that of chemotherapy, though both treatments were well-tolerated. The results of our meta-analysis were consistent with those of a previous meta-analysis comparing gefitinib with docetaxel as second-line treatment for advanced NSCLC (Jiang et al., 2011). This former meta-analysis showed a statistically significant improvement in overall response rate with gefitinib whereas the trend for an improved overall survival and progression free survival were not significant. In addition, more grade 3

or 4 neutropenia and fatigue were observed in docetaxel group. But this previous meta-analysis included only 4 studies (Cufer et al., 2006; Kim et al., 2008; Maruyama et al 2008; Lee et al., 2010) instead of 8 studies in our meta-analysis, representing 4 additional papers (Li et al ., 2010; Vamvakas et al., 2010; Ciuleanu et al., 2012; Sun et al., 2012). With the present sample size, we therefore had greater statistical power to evaluate the treatment effect, which made our results more convincing.

Previous researches had demonstrated that geographic origin was an important factor influencing survival benefit from EGFR-TKIs monotherapy (Yang et al., 2008; Jiang et al., 2011). Therefore, we performed subgroup-analysis according to geographic origin and found that EGFR-TKIs monotherapy significantly improved PFS and ORR in East Asian patients, but it did not translate into increase in OS and 1-year SR. In addition, we also found that the characters that well known to affect the efficacy and survival to EGFR-TKIs therapy, such as high proportions of female patients, never-smokers, and patients with adenocarcinoma histology (Shepherd et al., 2005; Thatcher et al., 2005; Uhm et al., 2009), were not substantially different between unselected patients receiving EGFR-TKIs and receiving single-agent therapy in this study except for the most recent trial conducted by Sun et al. (2012). The KCSG-LU08-01 study aimed to compare the efficacy of gefitinib with pemetrexed as second-line treatment in patients with advanced NSCLC. Results clearly favored gefitinib monotherapy therapy, the median OS (22.2 mo versus 18.9 mo) and PFS (9.0 mo versus 3.0 mo) was significantly prolonged in gefitinib monotherapy. Moreover, a significant improvement in PFS was observed in 33 patients with activating EGFR mutation (HR0.30; 95%CI 0.13-0.72). Several reasons might partially explain these differences: Firstly, 85.2% of included patients in this trial were female, which was higher than other included trials; secondly, only patients with adenocarcinoma histology were included in the trial; finally, all included patients were Asian patients.

The Iressa NSCLC Trial Evaluating REsponseand Survival versus Taxotere (INTEREST) was the largest trial evaluating second-line treatment for patients with advanced NSCLC (Kim et al., 2008). Nearly 1466 patients were randomly assigned to single-agent docetaxel or single-agent gefitinib. More frequencies of neutropenia, asthenia disorders and alopecia were observed in single docetaxel group, but both treatments were generally well tolerated. Response rates were similar between gefitinib and docetaxel (9.1% versus 7.6%, respectively). Progression-free survival (HR 1.04; 95%CI: 0.93-1.18) and Overall Survival (HR 1.02; 95%CI: 0.905-1.15) did not significantly differ between the two arms, which led the authors to recommend gefitinib monotherapy. In contrast, a recent trial did by Garassino et al. (2012) found that docetaxel was superior to erlotinib in terms of PFS in NSCLC harboring EGFR-mutations(HR0.70, 95%CI: 0.53-0.94, p=0.016), though the survival data was immature. As a result, more trials were still needed to identify patients who will most likely benefit from the EGFR-TKIs therapy in the era of individualized therapy.

As the main aims of treatments in the metastatic setting were to prolong life, provide cancer-related symptom relief, minimize treatment-related toxicity, and improve quality of life, toxicity was particularly relevant for patients with advanced NSCLC. Finding of our study indicated that there were fewer incidences of grade 3 or 4 neutropenia, febrile neutropenia and neurotoxicity in EGFR-TKI monotherapy group, but more incidences of grade 3 or 4 rash were observed in EGFR-TKI monotherapy group. With regard to the risk of grade 3 or 4 diarrhea, mucositis, nausea and vomiting, equivalent frequencies were found between the two groups. Therefore, EGFR-TKIs were associated with less toxicity and better tolerability compared with standard second-line chemotherapy. In view of this, we believe that erlotinib and gefitinib could be considered as an effective option in second-line treatment, owing to their toxicity profile.

Several limitations had to be mentioned in relation to this meta-analysis. Firstly, this meta-analysis was not based on individual patient data. And meta-analyses based on published data tended to overestimate treatment effects compared with individual patient data analyses. In addition, it precluded a more comprehensive analysis such as adjusting for baseline factors and other differences that existed between the trials from which the data were pooled. However, analyses using individual patient data might include fewer studies if all authors did not agree to submit their full databases to the analyzing group. Another drawback of analyses based on individual patient data was the time-consuming review process. Therefore, the results must be interpreted cautiously, as an individual patient data-based meta-analysis would give more reliable estimation than one based on abstracted data. Secondly, both docetaxel and pemetrexed as second-line chemotherapy for NSCLC patients were included in this meta-analysis, which contributed to increase the clinical heterogeneity of the meta-analysis, but clinical heterogeneity might improve the generalizability of the observed heterogeneity. Thirdly, EGFR-mutation is a major determinant of efficacy for EGFR-TKIs, but we did not do subgroup-analysis according to EGFR-mutation because limited data on EGFR-mutation could be available. Finally, in the meta-analysis of published studies, publication bias was important because trials with positive results were more likely to be published and with null results tend not to be published. Our paper observed no publication bias and involved six studies with null results.

In conclusion, our meta-analysis confirmed that the efficacy of EGFR-TKIs monotherapy were comparable to standard second-line chemotherapy for patients with advanced NSCLC, and EGFR-TKIs were associated with less toxicity and better tolerability. Moreover, our data also demonstrated that EGFR-TKIs monotherapy tended to be more effective in East Asian patients in terms of PFS and ORR compared with standard second-line chemotherapy. These results should help inform decisions about patient management and design of future trials.

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References

Begg CB, Mazumdar M (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, **50**, 1088-101.

Cufer T, Vrdoljak E, Gaafar R, et al (2006). Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. *Anticancer Drugs*, **17**, 401-9.

Ciuleanu T, Stelmakh L, Cicenas S, et al (2012). Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol*, **13**, 300-8.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

Fossella FV, DeVore R, Kerr RN, et al (2000). Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*, **18**, 2354-62.

Garassino MC, Martelli O, Bettini A, et al (2012). TAILOR: A phase III trial comparing erlotinib with docetaxel as the second-line treatment of NSCLC patients with wild-type (wt) EGFR. *J Clin Oncol*, **30**, abstr LBA7501.

Jiang H (2009). Overview of gefitinib in non-small cell lung cancer: an Asian perspective. *Jpn J Clin Oncol*, **39**, 137-50.

Jiang J, Huang L, Liang X, et al (2011). Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials. *Acta Oncol*, **50**, 582-8.

Kim ES, Hirsh V, Mok T, et al (2008). Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*, **372**, 1809-18.

Kim ST, Uhm JE, Lee J, et al(2012). Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer*, **75**, 82-8.

Lee DH, Park K, Kim JH, et al (2010). Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. *Clin Cancer Res*, **16**, 1307-14.

Li H, Zhuang Y, Xiu Y, et al (2010). Second-line treatment with gefitinib or docetaxel for advanced non-small cell lung cancer. *Chin J Clin Oncol*, **37**, 16-8 (article in chinese).

Maruyama R, Nishiwaki Y, Tamura T et al (2008). Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol*, **26**, 4244-52.

Moher D, Pham B, Jones A, et al (1998). Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*, **352**, 609-13.

Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Parmar MK, Torri V, Stewart L (1998). Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*, **17**, 2815-34.

Passaro A, Cortesi E, de Marinis F (2011). Second-line treatment of non-small-cell lung cancer: chemotherapy or tyrosine kinase inhibitors? *Expert Rev Anticancer Ther*, **11**, 1587-97.

Qi WX, Shen Z, Yao Y (2012). Meta-analysis of docetaxel-based doublet versus docetaxel alone as second-line treatment for advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol*, **69**, 99-106.

Qi WX, Tang LN, He AN, et al (2012). Effectiveness and safety of pemetrexed-based doublet versus pemetrexed alone as second-line treatment for advanced non-small-cell lung cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*, **138**, 745-51.

Rossi A, Ricciardi S, Maione P, et al (2009). Pemetrexed in the treatment of advanced non-squamous lung cancer. *Lung Cancer*, **66**, 141-9.

Schiller JH, Harrington D, Belani CP, et al (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*, **346**, 92-8.

Shepherd FA, Dancey J, Ramlau R, et al (2000). Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*, **18**, 2095-103.

Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al (2005). Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*, **353**, 123-32.

Stinchcombe TE, Socinski MA (2009). Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. *J Thorac Oncol*, **4**, 243-50.

Sun JM, Lee KH, Kim SW, et al (2012). Gefitinib versus pemetrexed as second-line treatment in patients with nonsmall cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01): An open-label, phase 3 trial. Cancer 2012.

Thatcher N, Chang A, Parikh P, et al(2005). Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*, **366**, 1527-37.

Uhm JE, Park BB, Ahn MJ, et al (2009). Erlotinib monotherapy for stage IIIB/IV non-small cell lung cancer: a multicenter trial by the Korean Cancer Study Group. *J Thorac Oncol*, **4**, 1136-43.

Vamvakas L, Agelaki S, Kentepozidis NK, et al (2010). Pemetrexed (MTA) compared with erlotinib (ERL) in pretreated patients with advanced non-small cell lung cancer (NSCLC): Results of a randomized phase III Hellenic Oncology Research Group trial. *J Clin Oncol*, **28**, abstr 7519.

Vandenbroucke JP (1998). Bias in meta-analysis detected by a simple, graphical test. Experts' views are still needed. *BMJ*, **316**, 469-70.

Yang CH (2008). EGFR tyrosine kinase inhibitors for the treatment of NSCLC in East Asia: present and future. *Lung Cancer*, **60**, S23-30.

Zintzaras E, Ioannidis JP (2005). Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol*, **28**, 123-37.