Indirect comparison of the efficacy and safety of gefitinib and cetuximab-based therapy in patients with advanced non-small-cell lung cancer

JIFENG TANG[1,2], HENA ZHANG[1,2], JIANZHOU YAN[1,2] and RONG SHAO[1,2]

[1]The Research Center of National Drug Policy and Ecosystem; [2]School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, Jiangsu 211198, P.R. China

Received November 13, 2013; Accepted September 9, 2014

DOI: 10.3892/mco.2014.424

Abstract. The aim of this study was to systematically evaluate the efficacy and safety of gefitinib and cetuximab-based therapies in patients with advanced non-small-cell lung cancer (NSCLC). The studies to be used for the comparisons were selected from the available literature on gefitinib and cetuximab-based therapies compared to conventional chemotherapy in patients with advanced NSCLC. The meta-analysis was performed with RevMan 5.0 software and the Bucher approach was applied to conduct the indirect comparisons. A total of 4 studies, including 935 patients, on gefitinib therapy vs. conventional chemotherapy and 4 studies, including 1,015 patients, on cetuximab-based therapy vs. conventional chemotherapy, were used for indirect comparisons. As regards efficacy, the risk ratio (RR) of objective response rate and 1-year survival rate between gefitinib and cetuximab-based therapies in patients with advanced NSCLC were 0.99 [95% confidence interval (CI): 0.75-1.32; P=0.9584] and 0.85 (95% CI: 0.71-1.01; P=0.0696), respectively, and the mean difference of progression-free survival and overall survival (OS) were -0.15 (95% CI: -0.90 to 0.60; P=0.6946) and -1.84 (95% CI: -3.53 to -0.15; P=0.0331), respectively. As regards safety, the RR of grade 3/4 adverse events (AEs) was 0.29 (95% CI: 0.19-0.44; P=0.0001). The results demonstrated that cetuximab-based therapy was superior to gefitinib therapy in terms of OS and inferior to gefitinib therapy in terms of AEs, whereas there were no significant differences in terms of efficacy and safety between the two therapies on other endpoints adopted for advanced NSCLC. However, further well-designed randomized controlled trials and continuous studies are required to confirm our findings.

Correspondence to: Professor Rong Shao, School of International Pharmaceutical Business, China Pharmaceutical University, 639 Longmian Road, Jiangning District, Nanjing, Jiangsu 211198, P.R. China
E-mail: shaorong118@163.com

Key words: gefitinib, cetuximab, chemotherapy, indirect comparison, meta-analysis, non-small-cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for 80-85% of lung cancer cases (1). Chemotherapy combined with radiotherapy are traditionally used for the treatment of NSCLC. Over the last few years, targeted therapy has been gradually applied for the treatment of NSCLC and has been proven to be effective to a certain extent (2). Among the targeted drugs used for NSCLC, those acting on the epidermal growth factor receptor (EGFR) are attracting increasing attention, such as the tyrosine kinase inhibitor (TKI) gefitinib (Iressa; AstraZeneca, London, UK) and the monoclonal antibody cetuximab (Erbitux; Merck, Darmstadt, Germany). These two dtugs have similar mechanisms of action against NSCLC. In clinical practice, gefitinib may be administered orally alone, while cetuximab is administered intravenously in combination with chemotherapy. Gefitinib and cetuximab-based therapies have been proven to be effective for advanced NSCLC to a certain extent (3,4); however, there is currently no systematic review directly based on these two therapies and the differences between them in terms of efficacy and safety have not been determined.

Indirect comparisons are undertaken to address such issues. Using the same intervention as a bridge, the two therapies are compared with the intervention through a direct meta-analysis and, on the basis of the results, indirect comparisons are subsequently conducted. With conventional chemotherapy as the intervention, we performed a systematic evaluation for gefitinib and cetuximab-based therapies based on the most updated results of these studies and weighed the two therapies indirectly against the clinical benefits and toxicities, with the aim of providing references for clinical decisions for patients with advanced NSCLC.

Materials and methods

Literature search. Several engines, including Medline, Embase, Elsevier, the Cochrane Library Register of Controlled Trials and the Science Citation Index, were searched for randomized controlled trials (RCTs) using the keywords 'random/trial', 'gefitinib', 'cetuximab', 'chemotherapy' and

'non-small-cell lung cancer/NSCLC'. The deadline for trial publication eligible for the analysis was April 30, 2013.

Study selection. The relevant studies were carefully selected using the following criteria: i) RCTs published in English; ii) patients with advanced (stage IIIB/IV) NSCLC and no obvious abnormalities of other organs; iii) comparison of gefitinib therapy vs. conventional chemotherapy (one or more combinations of cisplatin, carboplatin, docetaxel, gemcitabine, pemetrexed and vinorelbine) and cetuximab-based therapy vs. conventional chemotherapy; and iv) all or part of the data on objective response rate (ORR), 1-year survival, progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were provided. Studies were excluded by any of the following criteria: i) objective unrelated to this study; ii) phase I clinical trial; iii) no controlled clinical trials; iv) no or insufficient mature data; and v) reviews, comments and case reports.

Data extraction and conversion. According to the recommended guidelines of the Cochrane Handbook for Systematic Reviews (5), the extraction form, created with Microsoft Excel, included author, year of publication, interventions, sample size, dose, clinical efficacy and AEs.

As for the data that could not be adopted directly, appropriate transforming was required. For qualitative data, number of events = effective sample size x event rate. For quantitative data, the conversion methods were as follows: When the confidence interval (CI) was provided within a group, i) if the sample size was ≥100, under the 95% CI, standard deviation (SD) = $\sqrt{N}$ x (upper limit of CI - lower limit of CI)/3.92); ii) if the sample size was ≤60, 3.92 was replaced with 2 x t value; iii) if the sample size was 60-100, either method was applicable. When CI was provided between the groups, standard error (SE) was estimated first with the method described above, where $N = n_1 + n_2$, and then SD was calculated with the formula $SD = SE/\sqrt{1/n_1 + 1/n_2}$ (6).

Quality assessment. An open assessment of the trials was performed with the Jadad scale (7). The Jadad score ranged between 0 and 5 points with the major indicators of attrition and exclusions, randomization method and blinding. Studies scoring ≥3 were considered to be of high quality (8).

Statistical methods. Treatment A and C were compared with the intervention B and the direct evidence of AB and CB were obtained to conduct the indirect comparisons of AC (9). A meta-analysis was used to obtain the pooled AB and pooled CB using RevMan 5.0 software (The Cochrane Collaboration, Oxford, UK). The statistics were risk ratio (RR) for dichotomous variables and mean difference (MD) for numerical variables, together with the 95% CI. If the test for heterogeneity indicated good homogeneity (P>0.1 or I^2≤50%) between trials, the fixed-effects model was applied with the Mantel-Haeszel method (10); in the opposite case (P≤0.1 or I^2>50%), the random-effects model [DerSimonian and Laird method (11)] was used.

The Bucher approach was applied for indirect comparisons. A comparison of A and C was conducted through the difference between pooled AB and pooled CB, namely $d_{AC} = d_{AB} - d_{CB}$. The pooled effect size was measured by lnRR for dichotomous variables and MD for numerical variables. The variance of d_{AC} equaled the sum of the variance of AB and CB, namely $Var(d_{AC}) = Var(d_{AB}) + Var(d_{CB})$. For $Var(d_{AB})$ and $Var(d_{CB})$, the computational formula was $Var(d) = [(\text{upper limit of CI} - \text{lower limit of CI})/3.92]^2$. For dichotomous variables, 95% CI of $d_{AC} = \exp [d_{AC} \pm 1.96 \sqrt{Var(d_{AC})}]$ and for numerical variables, 95% CI of $d_{AC} = d_{AC} \pm 1.96 \sqrt{Var(d_{AC})}$. The hypothesis test was set for the results, as follows: H_0, $d_{AC}=0$; H_1, $d_{AC}\neq0$; and $Z_{AC}=|d_{AC}|/\sqrt{Var(d_{AC})}$, where Z_{AC} exhibited a standard normal distribution as a test statistic. The null hypothesis was rejected if P<0.05 (Z_{AC}>1.96), i.e., if the effects between A and C exhibited a statistically significant difference (12).

Results

Description of selected studies. A total of 104 articles were retrieved during the primary search, of which 8 studies met the predetermined inclusion criteria. A total of 4 studies (13-16), including 935 patients who were randomized to receive either gefitinib therapy or conventional chemotherapy, and another 4 studies (17-20), including 1,015 patients who received either cetuximab-based therapy or conventional chemotherapy, were included in the study. The main characteristics of the 8 studies are summarized in Table I.

All 8 studies were RCTs, of which 7 studies applied the proper methods of randomization. Attrition and exclusions were illustrated in detail, while double-blind methods were not mentioned. The included studies were considered to be of high quality, scoring 3 on the Jadad scale, except one study (13). The quality assessment of the studies is presented in Table II.

Statistical analysis of efficacy and safety

ORR. A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of ORR. The pooled analysis of ORR using the fixed-effects model is presented in Fig. 1A and B. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 1.31 (95% CI: 1.02-1.68) and 1.32 (95% CI: 1.15-1.52), respectively. Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in ORR (RR=0.99; 95% CI: 0.75-1.32; P=0.9584; Table III).

Survival rate. A total of 2 studies (13,16) compared gefitinib therapy vs. conventional chemotherapy and 3 studies (17-19) compared cetuximab-based therapy vs. conventional chemotherapy in terms of 1-year survival rate. The pooled analysis of 1-year survival rate using the fixed-effects model is presented in Fig. 1C and D. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.93 (95% CI: 0.81-1.06) and 1.10 (95% CI: 0.98-1.25), respectively. Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in 1-year survival rate (RR=0.85; 95% CI: 0.71-1.01; P=0.0696; Table III).

PFS. A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conven-

Table I. Characteristics of the 8 studies included in the meta-analysis.

Study (year)	Group	Intervention	Treatment schedule	Phase	Cases	End point	(Refs.)
Kim *et al* (2008)	Treatment	Gefitinib	250 mg/day p.o.	III	733	a-e	(13)
	Control	Doc	75 mg/m^2 i.v.	III	729	a-e	
Mitsudomi *et al* (2010)	Treatment	Gefitinib	250 mg/day p.o.	III	88	a,c,e	(14)
	Control	Cis + Doc	80+60 mg/m^2 i.v.	III	89	a,c,e	
Morère *et al* (2010)	Treatment	Gefitinib	250 mg/day p.o.	II	43	a,c-e	(15)
	Control	Gem	1,250 mg/m^2 i.v.	II	42	a,c-e	
	Control	Doc	75 mg/m^2 i.v.	II	42	a,c-e	
Ahn *et al* (2012)	Treatment	Gefitinib	250 mg/day p.o.	II	40	a-c,e	(16)
	Control	Pem + Cis	500+75 mg/m^2 i.v.	II	33	a-c,e	
Rosell *et al* (2008)	Treatment	Cetuximab + Cis + Vin	400+80+25 mg/m^2 i.v.	II	43	a-e	(17)
	Control	Cis + Vin	80+25 mg/m^2 i.v.	II	43	a-e	
Butts *et al* (2007)	Treatment	Cetuximab + Gem + Cis	400+1,250+75 mg/m^2 i.v.	II	65	a-e	(18)
	Control	Gem + Cis	1,250+75 mg/m^2 i.v.	II	66	a-e	
Pirker *et al* (2009)	Treatment	Cetuximab + Cis + Vin	400+80+25 mg/m^2 i.v.	III	557	a-e	(19)
	Control	Cis + Vin	80+25 mg/m^2 i.v.	III	568	a-e	
Lynch *et al* (2010)	Treatment	Cetuximab + Doc + Carbo	400+75 mg/m^2 + curve ≤6 i.v.	III	338	a,c-e	(20)
	Control	Doc + Carbo	75 mg/m^2 + curve ≤6 i.v.	III	338	a,c-e	

[a]Objective response rate; [b]1-year survival rate; [c]progression-free survival; [d]overall survival; [e]grade 3/4 adverse events. Doc, docetaxel; p.o., *per os*; i.v., intravenously; cis, cisplatin; gem, gemcitabine; pem, pemetrexed; vin, vinorelbine; carbo, carboplatin.

Table II. Quality assessment of the 8 included studies by the Jadad scale.

Author (year)	Randomization	Blinding	Attrition and exclusions	Jadad score	(Refs.)
Kim *et al* (2008)	1	0	1	2	(13)
Mitsudomi *et al* (2010)	2	0	1	3	(14)
Morère *et al* (2010)	2	0	1	3	(15)
Ahn *et al* (2012)	2	0	1	3	(16)
Rosell *et al* (2008)	2	0	1	3	(17)
Butts *et al* (2007)	2	0	1	3	(18)
Pirker *et al* (2009)	2	0	1	3	(19)
Lynch *et al* (2010)	2	0	1	3	(20)

tional chemotherapy in terms of PFS. The pooled analysis of PFS using the fixed-effects model is presented in Fig. 2A and B. The MD for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.06 (95% CI: -0.56 to 0.68) and 0.21 (95% CI: -0.21 to 0.63). Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in PFS (MD=-0.15; 95% CI: -0.90 to 0.60; P=0.6946; Table III).

OS. A total of 2 studies (13,15) compared gefitinib therapy vs. conventional chemotherapy and 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of OS. The pooled analysis of OS using the fixed-effects model is presented in Fig. 2C and D. The MD for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was -0.51 (95% CI: -1.76 to 0.75) and 1.33 (95% CI: 0.19-2.46). Indirect comparisons between gefitinib and cetuximab-based therapies revealed that the latter exhibited a significant advantage over the former in terms of OS (MD=-1.84; 95% CI: -3.53 to -0.15; P=0.0331; Table III).

Grade 3/4 AEs. A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of 3/4 AEs. The pooled analysis of 3/4 AEs using the fixed-effects model is shown in Fig. 3A, while the results using the random-effects model are shown in Fig. 3B. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.67 (95% CI: 0.58-0.78) and 2.31 (95% CI: 1.55-3.44). Indirect comparisons between gefitinib and cetuximab-based therapies revealed that the former exhibited a significant advantage over the latter in terms of 3/4 AEs (RR=0.29; 95% CI: 0.19-0.44; P=0.0001; Table III).

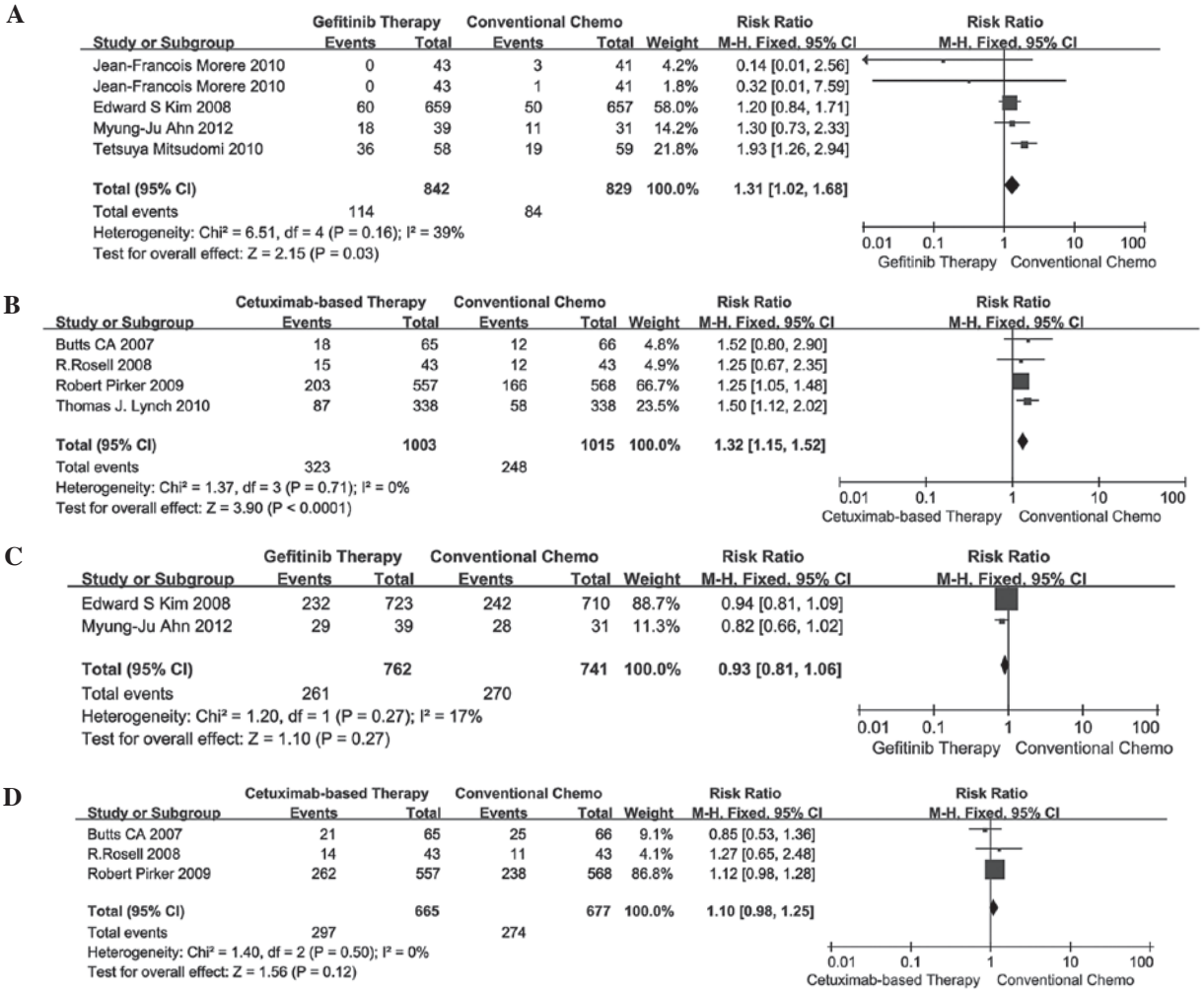

Figure 1. Meta-analysis of the risk ratio (RR) for (A and C) gefitinib therapy vs. conventional chemotherapy and (B and D) cetuximab-based therapy vs. conventional chemotherapy in terms of objective response rate (ORR) and 1-year survival rate, respectively. (A) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of ORR. (B) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of ORR. (C) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of 1-year survival rate. (D) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of 1-year survival rate. Chemo, chemotherapy; CI, confidence interval.

Table III. Results of indirect comparisons between gefitinib and cetuximab-based therapies.

Indicator	RR/MD	95% CI	P-value
Objective response rate	0.99	0.75 to 1.32	0.9584
One-year survival rate	0.85	0.71 to 1.01	0.0696
Progression-free survival	-0.15	-0.90 to 0.60	0.6946
Overall survival	-1.84	-3.53 to -0.15	0.0331
Grade 3/4 adverse events	0.29	0.19 to 0.44	0.0001

RR, risk ratio; MD, mean difference; CI, confidence interval.

Discussion

As demonstrated by the indirect comparisons, cetuximab-based therapy was found to be superior to TKIs, such as gefitinib, regarding efficacy. A recently published meta-analysis recommended that gefitinib therapy not be used for the management of patients with advanced NSCLC in the first-line setting (21). Other studies also reported that the activity of EGFR-TKIs may be restricted to a subset of tumors with specific molecular characteristics, highlighting the need for appropriate patient selection (22,23). Furthermore, certain studies proved the OS benefit of cetuximab-based therapy and suggested that advanced NSCLC patients with high EGFR gene expression may benefit more from cetuximab-based therapy (24).

As regards safety, gefitinib appears to be superior to cetuximab-based therapy in terms of 3/4 AEs. Despite the limitations of the safety indicator itself, one plausible explanation for this discrepancy is the difference in the administration methods, i.e., the oral administration of gefitinib is considered to be safer compared to the intravenous administration of cetuximab. Another possible reason is that gefitinib is more uncomplicated and controllable compared to cetuximab-based therapy containing several chemotherapeutic drugs, such as cisplatin, docetaxel and gemcitabine, which is associated with more risks.

The indirect comparison adopted in our study is controversial. Certain investigators have suggested that indirect comparison compromises the randomness of original RCTs and inevitably induces bias (25). In the study of Bucher *et al* (26),

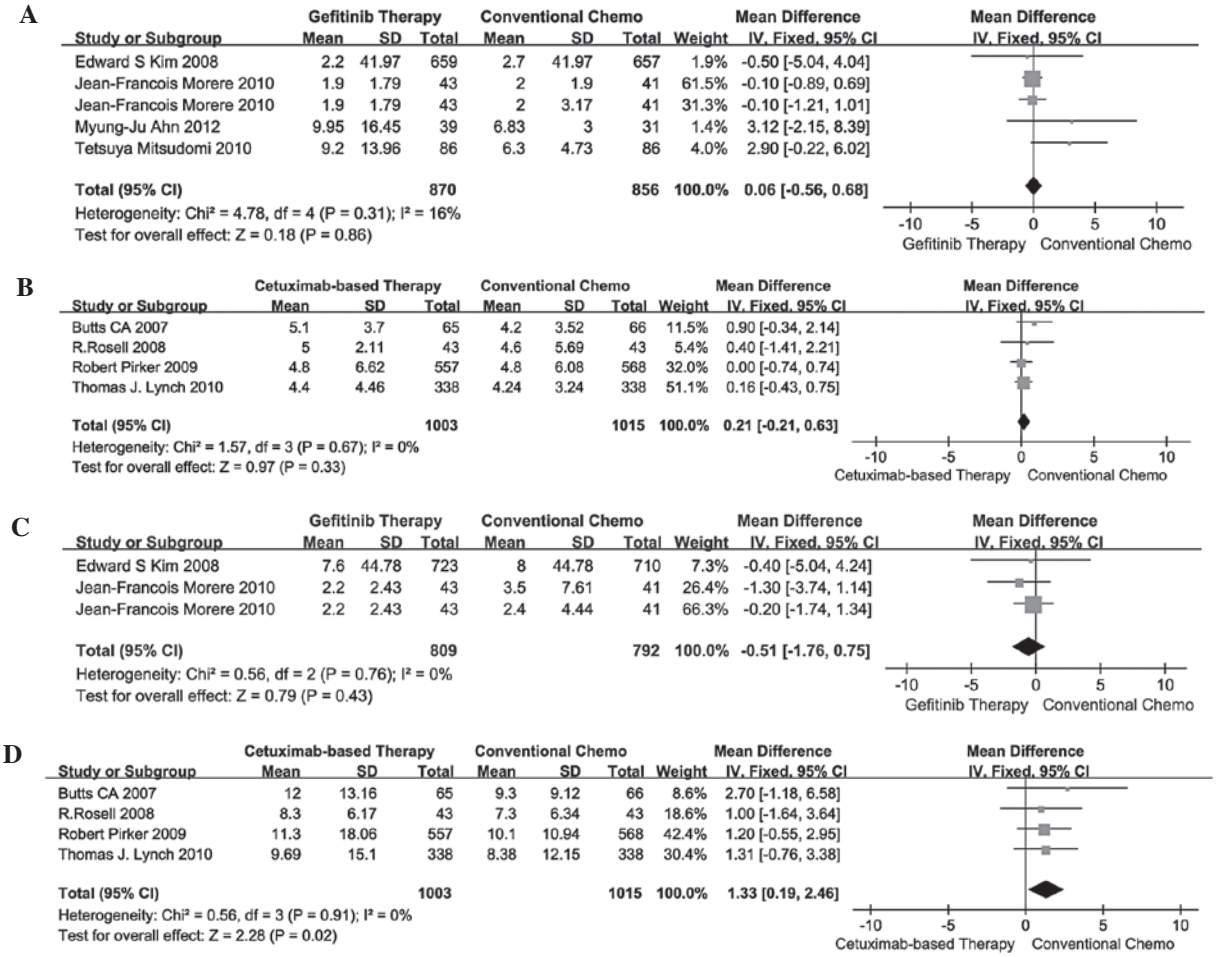

Figure 2. Meta-analysis of the mean difference (MD) for (A and C) gefitinib therapy vs. conventional chemotherapy and (B and D) cetuximab-based therapy vs. conventional chemotherapy in terms of progression-free survival (PFS) and overall survival (OS), respectively. (A) Summary data and MD of gefitinib therapy vs. conventional chemotherapy in terms of PFS. (B) Summary data and MD of cetuximab-based therapy vs. conventional chemotherapy in terms of PFS. (C) Summary data and MD of gefitinib therapy vs. conventional chemotherapy in terms of OS. (D) Summary data and MD of cetuximab-based therapy vs. conventional chemotherapy in terms of OS. Chemo, chemotherapy; SD, standard deviation; CI, confidence interval.

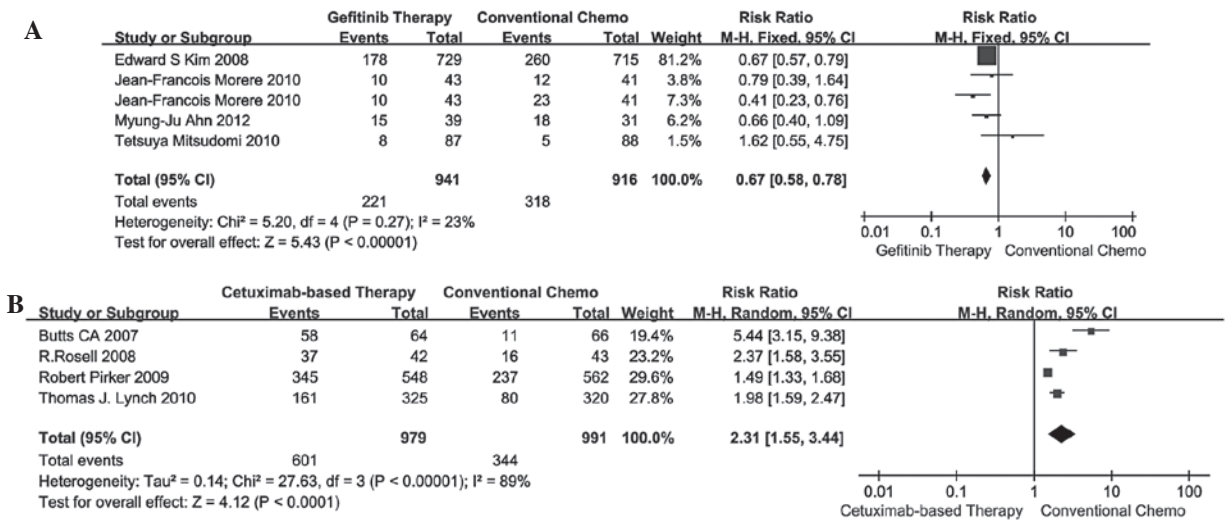

Figure 3. Meta-analysis of the risk ratio (RR) for (A) gefitinib therapy vs. conventional chemotherapy and (B) cetuximab-based therapy vs. conventional chemotherapy in terms of grade 3/4 adverse events (3/4 AEs). (A) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of 3/4 AEs. (B) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of 3/4 AEs. Chemo, chemotherapy; CI, confidence interval.

indirect comparison was associated with significantly more bias compared to direct comparisons, while Song *et al* (27) reached the opposite conclusion with 3 case studies. Another study by Song *et al* (28) further confirmed the reliability of the results of

indirect comparison. Indirect comparison remains a reasonable option in the absence of direct comparison of two drugs and a number of medical journals, such as JAMA, Lancet and BMJ have accepted the findings of indirect comparison (12).

However, our results must be interpreted with caution, as there were certain limitations to our study. Although each of the 8 included studies was considered to be of high quality, the total number of articles was insufficient to draw a credible conclusion. The sample size of included trials was also insufficient for a funnel plot to detect publication bias. Due to the lack or inconformity of patient selection regarding details such as gender, age, smoking history and race, subgroup analyses were not feasible. The analyses also revealed some heterogeneity within the study results, such as safety data of cetuximab-based therapy. One must also consider the limitation on methodology of indirect comparisons and the lack of unpublished or ongoing RCTs.

Despite all the limitations, our results may contribute to a better understanding of gefitinib and cetuximab-based therapies in patients with advanced NSCLC. Based on the present meta-analysis and indirect comparisons, we concluded that cetuximab-based therapy may be associated with a more significant improvement in OS compared to gefitinib therapy, while gefitinib was superior in terms of safety, with a lower incidence of grade 3/4 AEs. There were no significant differences between gefitinib and cetuximab-based therapies in terms of ORR, 1-year survival rate and PFS in patients with advanced NSCLC. Further studies are required to confirm our findings and evaluate the cost-effectiveness of the two therapies, in order to provide a better reference for clinical practice.

Acknowledgements

We would like to thank Professor Feng Yu and Dr Hongchao Li of the China Pharmaceutical University for their assistance with the writing of this manuscript.

References

1. Ozkaya S, Findik S, Dirican A and Atici AG: Long-term survival rates of patients with stage IIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Exp Ther Med 4: 1035-1038, 2012.
2. Mendelsohn J and Baselga J: The EGF receptor family as targets for cancer therapy. Oncogene 19: 6550-6565, 2000.
3. Ku GY, Haaland BA and de Lima Lopes G Jr: Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: meta-analysis of phase III trials. Lung Cancer 74: 469-473, 2011.
4. Lin H, Jiang J, Liang X, Zhou X and Huang R: Chemotherapy with cetuximab or chemotherapy alone for untreated advanced non-small-cell lung cancer: a systematic review and meta-analysis. Lung Cancer 70: 57-62, 2010.
5. Higgins JPT and Green S (eds): Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed June 3, 2013.
6. Liu M: Design and Implementation Methods of Systematic Reviews and Meta-analysis. People's Medical Publishing House, Beijing, pp86-89, 2011 (In Chinese).
7. Jadad AR, Moore RA, Carroll D, *et al*: Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1-12, 1996.
8. Schulz KF, Altman DG, Moher D, *et al*: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC Med 8: 18, 2010.
9. DerSimonian R and Laird N: Meta-analysis in clinical trials. Controlled clinical trials 7: 177-188, 1986.
10. Zhang HN, Yan JZ, Tang JF and Shao R: Indirect comparisons for efficacy of gefitinib and erlotinib in patients with non-small cell lung cancer. Chin J Pharm Econ 1: 15-19, 2013 (In Chinese).
11. Silagy C, Lancaster T, Stead L, *et al:* Nicotine replacement therapy for smoking cessation. The Cochrane Library, John Wiley & Sons, Oxford, 2004.
12. Liao WQ: Simulation Study of Multivariate Meta-analysis and Indirect Comparisons. Southern Medical University, Guangzhou, pp23-26, 2011 (In Chinese).
13. Kim ES, Hirsh V, Mok T, *et al*: Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 372: 1809-1818, 2008.
14. Mitsudomi T, Morita S, Yatabe Y, *et al*; West Japan Oncology Group: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 11: 121-128, 2010.
15. Morère JF, Bréchot JM, Westeel V, *et al*: Randomized phase II trial of gefitinib or gemcitabine or docetaxel chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2 or 3 (IFCT-0301 study). Lung Cancer 70: 301-307, 2010.
16. Ahn MJ, Yang JC, Liang J, *et al*: Randomized phase II trial of first-line treatment with pemetrexed-cisplatin, followed sequentially by gefitinib or pemetrexed, in East Asian, never-smoker patients with advanced non-small cell lung cancer. Lung Cancer 77: 346-352, 2012.
17. Rosell R, Robinet G, Szczesna A, *et al*: Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. Ann Oncol 19: 362-369, 2008.
18. Butts CA, Bodkin D, Middleman EL, *et al*: Randomized phase II study of gemcitabine plus cisplatin or carboplatin, with or without cetuximab, as first-line therapy for patients with advanced or metastatic non-small-cell lung cancer. J Clin Oncol 25: 5777-5784, 2007.
19. Pirker R, Pereira JR, Szczesna A, *et al*; FLEX Study Team: Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 373: 1525-1531, 2009.
20. Lynch TJ, Patel T, Dreisbach L, *et al*: Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol 28: 911-917, 2010.
21. Ibrahim EM: Frontline gefitinib in advanced non-small cell lung cancer: meta-analysis of published randomized trials. Ann Thorac Med 5: 153-160, 2010.
22. Paez JG, Jänne PA, Lee JC, *et al*: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304: 1497-1500, 2004.
23. Tsao MS, Sakurada A, Cutz JC, *et al*: Erlotinib in lung cancer - molecular and clinical predictors of outcome. New Engl J Med 353: 133-144, 2005.
24. Pirker R, Pereira JR, von Pawel J, *et al*: EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol 13: 33-42, 2012.
25. Caldwell DM, Ades AE and Higgins JP: Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331: 897-900, 2005.
26. Bucher HC, Guyatt GH, Griffith LE and Walter SD: The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 50: 683-691, 1997.
27. Song F, Harvey I and Lilford R: Adjusted indirect comparison may be less biased than direct comparison for evaluating new pharmaceutical interventions. J Clin Epidemiol 61: 455-463, 2008.
28. Song F, Altman DG, Glenny AM and Deeks JJ: Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 326: 472, 2003.