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Gefitinib versus docetaxel in treated non-small-cell lung cancer: a meta-analysis

Abstract: The objective of this study was to perform a meta-analysis to evaluate the efficacy and toxicity of gefitinib and docetaxel in treated patients with non-small-cell lung cancer (NSCLC). Methods. A literature search was performed using PubMed and CNKI databases for relevant keywords and the Medical Subject Headings. After further full-text screening, 10 clinical trials were included in the final meta-analysis. Specific odds ratios (OR) and confidence intervals were calculated. Results. The outcomes of treatment efficacy included disease control rates, quality-of-life improvement rates, 3~4 grade adverse events. Comparing gefitinib to docetaxel for NSCLC patients, the pooled odds ratios (OR) of disease control rates was 1.09, (95% confidential index [CI] = 0.84–1.43), the pooled OR of quality-of-life improvement rates was 2.49, (95% CI = 1.77–3.49), the pooled OR of 3~4 grade adverse events was 0.49, (95% CI = 0.32–0.75). Conclusion. Gefitinib was found to significantly improve patients' quality-of-life and obviously decrease patients' adverse events of 3~4 grade. There is no difference of disease control rates between gefitinib and docetaxel.

Keywords: Docetaxel; Gefitinib; Meta-analysis; NSCLC

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1 Introduction

Lung cancer remains the most lethal cancer, which is a serious harm to human health [1].

Non-small-cell lung cancer (NSCLC) accounted for more than 80% of lung cancer, and advanced NSCLC is still an incurable disease [2]. As the standard second-line treatment of NSCLC, docetaxel and ifosfamide, vinorelbine, can significantly prolong the median survival, but their hematologic toxicity was significant [3, 4]. Pemetrexed as a second-line treatment compared with docetaxel, their efficacy is comparable and toxicity of pemetrexed is significantly reduced, but it is still cytotoxic drugs [5].The results of a series of clinical trials showed that the efficiency of chemotherapy was only 20% to 40% for advanced non-small-cell lung cancer and one year survival rate is only 35% to 45% [6, 7]. Gefitinib is an oral targeted molecular that inhibits tumor cell growth by targeting a specific enzyme on the epidermal growth factor receptor [8]. At present, gefitinib has been applied to clinical, but there is still a big controversy. This study aims to perform a meta-analysis to evaluate the clinical efficacy and safety of gefitinib and traditional therapeutic drug docetaxel in the treatment of advanced non-small cell lung cancer.

2 Methods

2.1 Searching method

We searched for relevant studies in PubMed and CNKI databases that were published between 2005 and 2017. The search terms and keywords used included "Docetaxel", "gefitinib", "NSCLC" and "non-small-cell lung cancer". Duplicate articles and unpublished studies from international meetings were excluded.

2.2 Inclusion criteria

Eligible references were selected carefully based on the following criteria: (1) studies comparing the efficacy and toxicity of gefitinib with docetaxel in the treatment of non-small cell lung cancer (NSCLC) randomized controlled trials; (2) patients with non-small-cell lung cancer and liver and kidney function, hematology, ECG no obvious abnormalities; (3) information collected including disease control rates, quality-of-life improvement rates, 3~4 grade adverse events.

2.3 Excluding standard

Non-clinical randomized controlled trials; Non-lung cancer research; To accept other anti-cancer treatment; Data description is not clear; data repeated reports of the larger sample size.

2.4 Data extraction

Two researchers selected independently the relevant literature, and then download and extracted all the data with the use of standardized data-abstraction forms. The study design of the literature according to the above inclusion criteria was included in the evaluation of the patients, the intervention measures and the observation results. The data were extracted from the first author, year of publication, disease control rates, quality-of-life improvement rates, 3~4 grade adverse events.
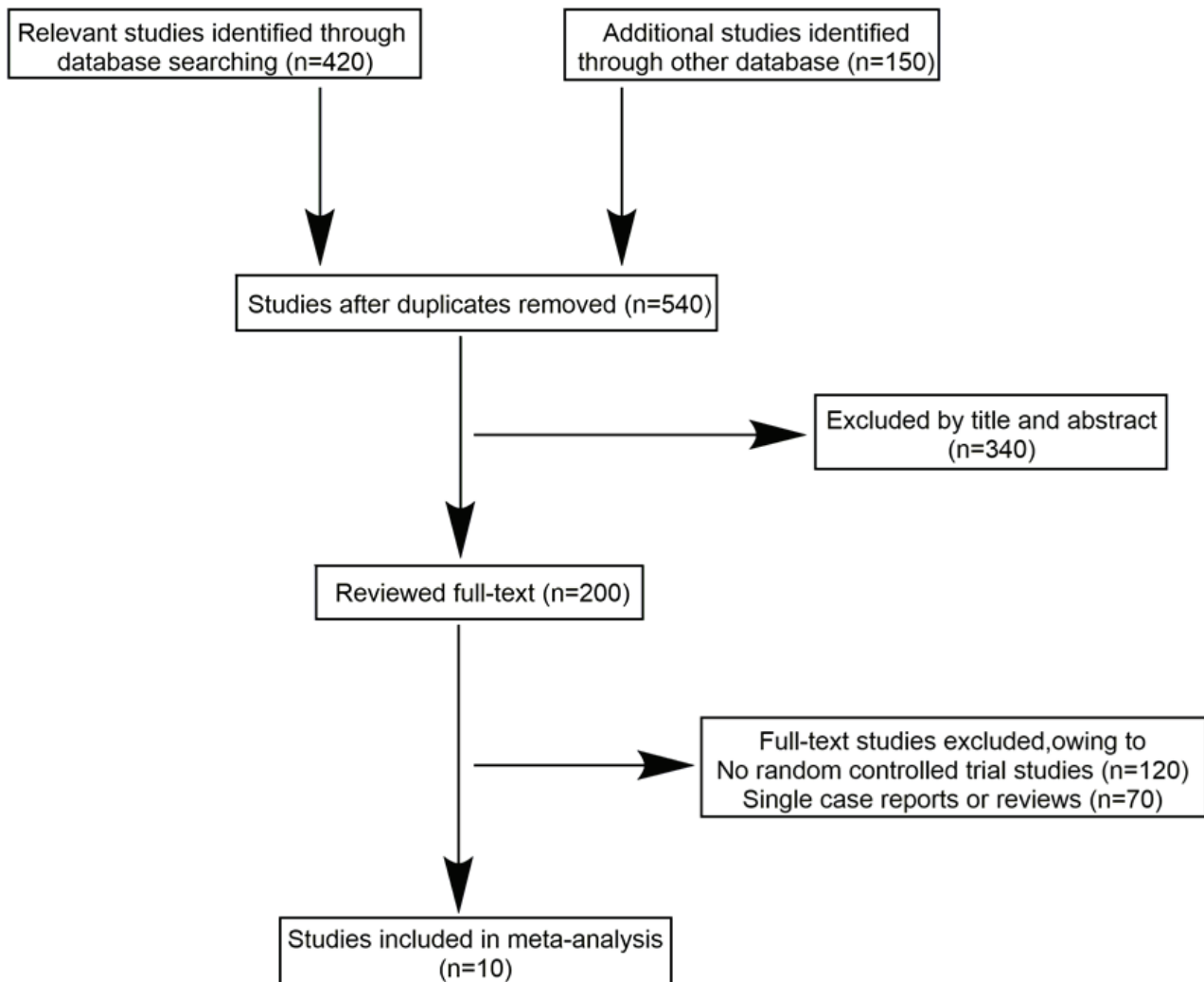

Figure 1: The study selection process

Table 1: Baseline characeristics of included studies

Study	Intervention	Participants	Gender(M/F)	Age(range)
Cufer, 2006 [15]	Gefitinib	68	47/21	34~85
	Docetacel	75	51/22	29~83
Li, 2010 [16]	Gefitinib	50	30/20	28~79
	Docetacel	48	29/19	
Liu,2012 [17]	Gefitinib	40	Not reported	28~79
	Docetacel	38	Not reported	
Kim, 2008 [18]	Gefitinib	733	466/267	27~84
	Docetacel	733	488/245	20~84
Xiong, 2008 [19]	Gefitinib	26	Not reported	33~72
	Docetacel	25	Not reported	
Zhong, 2009 [20]	Gefitinib	44	21/23	32~74
	Docetacel	34	18/16	28~78
Lee, 2010 [21]	Gefitinib	82	55/27	21~74
	Docetacel	79	45/34	20~73
Morere, 2010 [22]	Gefitinib	43	38/5	45~79
	Docetacel	42	33/9	30~79
Zhang, 2009 [23]	Gefitinib	26	12/14	34~84
	Docetacel	28	20/8	40~79
Maruyama, 2008 [24]	Gefitinib	245	151/94	Not reported
	Docetacel	244	151/93	Not reported

2.5 Statistical analysis

The summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by using RevMan (version 5.3). A random-effects (EF) model was adopted. We defined significant heterogeneity as being that of the chi-square test p value <0.1 or an I^2 measure >50%, based on a statement from the Cochrane Handbook {Higgins, 2011 #32}.

3 Results

3.1 Literature searches and study characteristics

Figure 1 shows the study selection process. After a preliminary screening of the retrieved literature and further screening, we obtained 10 studies. The basic information for the 10 eligible studies is summarized in Table 1. The funnel plots for each outcome did not show any publication bias (data not shown).

Table 2: Quality assessment of included studies

Study	Period	Jadad's quality scores
Cufer, 2006	October 2003-June 2004	3
Li, 2010	Not reported	3
Liu,2012	January 2007 - August 2011	3
Kim, 2008	March 2004 - February 2006	2
Xiong, 2008	May 2004 - February 2006	2
Zhong, 2009	April 2002 - June 2006	3
Lee, 2010	September 2005-September 2006	2
Morere, 2010	December 2004-June 2007	2
Zhang, 2009	October 2006 - December 2007	1
Maruyama, 2008	September 2003-January 2006	2

3.2 Quality assessment

The Jadad scale, a 5-point scale system, was used to evaluate the methodological quality of trials, which assessed randomization (0–2 points), double-blind (0–2 points), and follow-up (0–1 points) [9]. The Jadal scale has total scores ranged from 0 to 5, and clinical trials are defined as "good" when the score is from 3 to 5. The quality of these enrolled trials was scored according to Jadad's scale and listed in Table 2.

3.3 Meta-analysis of the disease control rates of gefitinib and docetaxel

Disease control rates were reported in seven studies (Fig. 2). The pooled OR from these 9 studies was 1.09 (95% CI, 0.84-1.43). The I^2 estimate of the variance between the studies is 0% and P = 0.49, which showed low heterogeneity. According to our analysis, the disease control

rates between gefitinib and docetaxel was not significant (P = 0.51).

3.4 Meta-analysis of the quality-of-life improvement rates of gefitinib and docetaxel

The quality-of-life improvement rates were reported in five studies (Fig. 3). The pooled OR from these 5 studies was 2.49 (95% CI, 1.77-3.49). The I^2 estimate of the variance between the studies is 0% and P = 0.48, which showed low heterogeneity. According to our analysis, the quality-of-life improvement rates between gefitinib and docetaxel was significant (P < 0.01).

3.5 Meta-analysis of the 3~4 grade adverse events of gefitinib and docetaxel

The 3~4 grade adverse events was reported in six studies (Fig. 3). The pooled OR from these 6 studies was 0.49 (95%
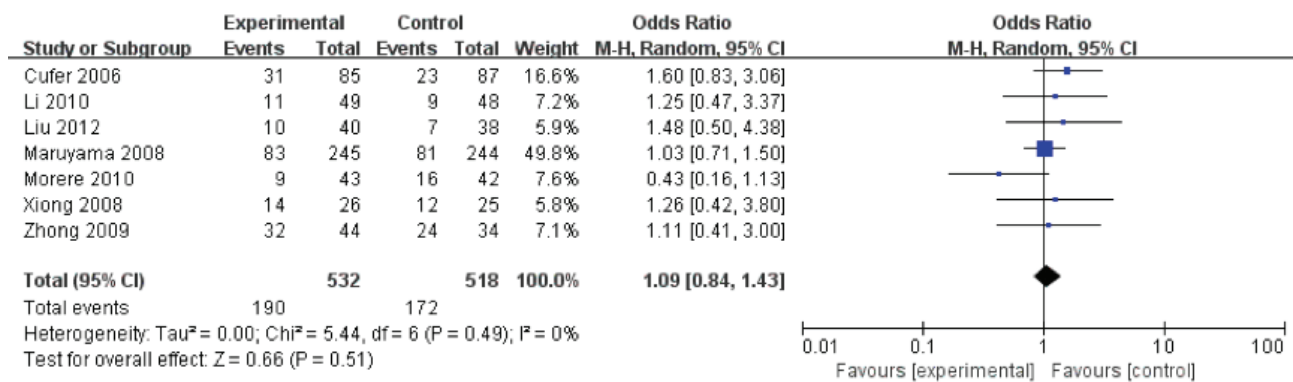

Figure 2: The comparison for the disease control rates between geftinib and docetaxel group
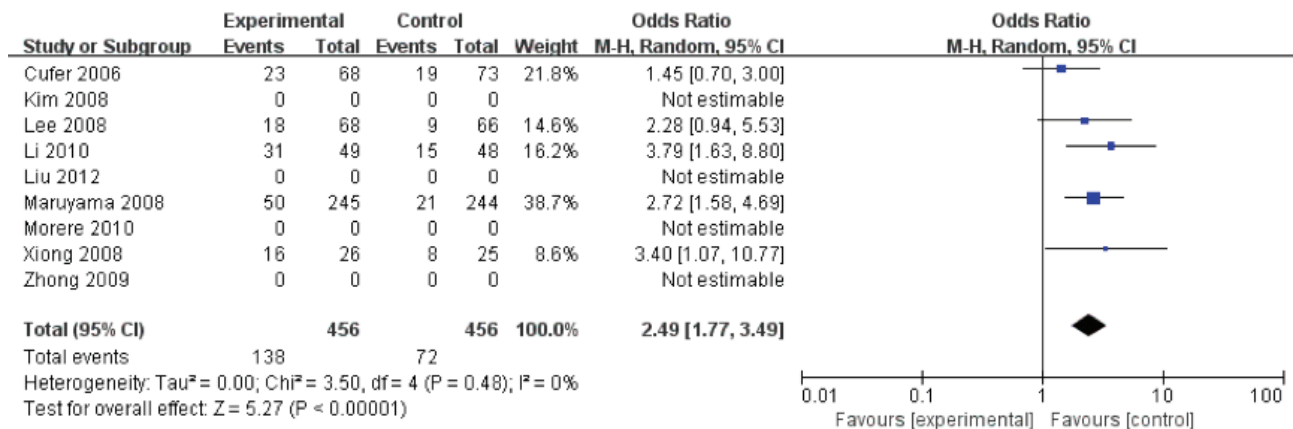

Figure 3: The comparison for the quality-of-life improvement rates between geftinib and docetaxel group

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Cufer 2006	6	68	19	73	13.3%	0.28 [0.10, 0.74]
Kim 2008	178	729	260	715	43.8%	0.57 [0.45, 0.71]
Lee 2008	12	81	10	76	15.1%	1.15 [0.46, 2.84]
Li 2010	0	0	0	0		Not estimable
Liu 2012	0	0	0	0		Not estimable
Maruyama 2008	99	245	199	244		Not estimable
Morere 2010	10	43	23	41	14.3%	0.24 [0.09, 0.61]
Xiong 2008	8	26	12	25	10.7%	0.48 [0.15, 1.51]
Zhong 2009	1	44	2	34	2.8%	0.37 [0.03, 4.28]
Total (95% CI)		**991**		**964**	**100.0%**	**0.49 [0.32, 0.75]**
Total events	215		326			

Heterogeneity: Tau² = 0.09; Chi² = 7.70, df = 5 (P = 0.17); I² = 35%
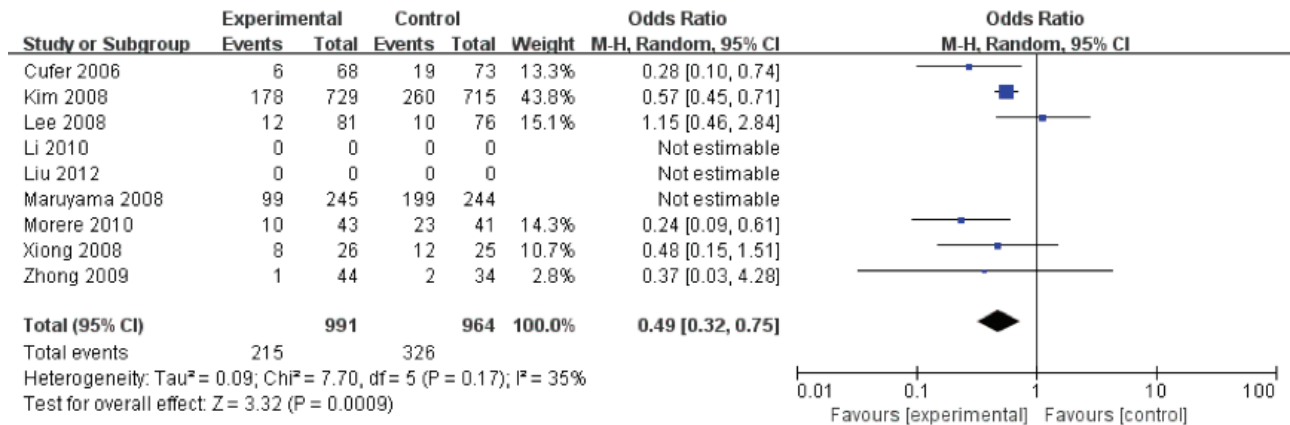Test for overall effect: Z = 3.32 (P = 0.0009)

Figure 4: The comparison for the 3~4 grade adverse events between geftinib and docetaxel group

CI, 0.32-0.75). The I² estimate of the variance between the studies is 35% and P = 0.17, which showed low heterogeneity. According to our analysis, the 3~4 grade adverse events between gefitinib and docetaxel was significant (P < 0.01).

4 Discussion

As human epithelial cell cancer show that the epidermal growth factor receptor (EGFR) family is aberrantly activated, and high expression of EGFR and poor prognosis of lung cancer is closely related [9]. Therefore, EGFR is an important molecular target. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) has become a hot topic in recent years. Gefitinib is a molecular targeted drug in the treatment of non-small cell lung cancer. Gefitinib competes with adenosine triphosphate at the ATP binding site in epithelial cells, blocking its tyrosine kinase activity, so EGFR signaling pathway were inhibited, and can induce tumor cell apoptosis [10]. The results of this study indicated that gefitinib had no inferior efficacy to docetaxel with an improvement of disease control rates. In this meta-analysis, we showed that gefitinib significantly improved life quality of patient. Besides, gefitinib decrease 3~4 grade adverse events significantly. Because disease control and quality of life were affected by subjective factors, we were not able to rule out the selection bias. Because of existence of bias, we still need high-quality research to prove its effectiveness. The study also indicated that safety and tolerability of gefitinib is superior to docetaxel group for non-small cell lung cancer. Most of the studies have confirmed that safety and tolerance of gefitinib is better than docetaxel group. In addition, some studies have shown that high expression of EGFR is also

considered a sensitive factor to gefitinib [11]. The results of intervention test failed to demonstrate that EGFR overexpression factor was more sensitive to gefitinib , and of course there were some different findings [12, 13]. Studies of EGFR mutations and case characteristics have also been reported in the literature [14], and their relationship with the efficacy of gefitinib remains to be studied further.

In summary, gefitinib has certain advantages for treatment of non-small cell lung cancer. It can be treated as non-small cell lung cancer conventional drugs. However, due to the use of gefitinib by the economic conditions and other effects and the quality of included literature in this study is uneven, we still need high-quality clinical research and economic evaluation support to evaluate clinical application of gefitinib.

Conflict of interest statement: Authors state no conflict of interest

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