Int J Clin Exp Med 2016;9(11):21057-21065
www.ijcem.com /ISSN:1940-5901/IJCEM0030827

Original Article

Gefitinib and docetaxel for the treatment of non-small cell lung cancer: a meta-analysis

Huiqing Yu[1], Aihong Zhang[2]

[1]*Department of Oncology, Chongqing Cancer Hospital, Chongqing 102206, P. R. China;* [2]*Department of Pharmacy, The Cancer Hospital Affiliated to Harbin Medical University, Harbin 150086, P. R. China*

Received April 19, 2016; Accepted September 25, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: To systematically evaluate the efficacy and safety of gefitinib and docetaxel in the treatment of non-small cell lung cancer. We searched the Cochrane Library (1993~2015.10), PubMed (1970~2015.10), CBM (1978~2015.10), CNKI (1996~2015.10), Wanfang Data (1999~2015.10), VIP database (1996~2015.10) and Google scholar by a computer, and manually searched relevant journals. The comparison between randomized controlled trials (RCTs) of gefitinib (treatment group) and docetaxel (control group) in the treatment of non-small cell lung cancer were collected. The data were independently extracted by two researchers according to inclusion and exclusion criteria. After evaluation of the research quality according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.0, meta-analysis was performed for the included literatures by RevMan 5.2 software. A total of 14 RCTs were included. Meta-analysis indicated that, compared to docetaxel, gefitinib could improve the total efficiency (RR=1.40, 95% CI (1.18, 1.65), $P<0.0001$) and the trial outcome index (TOI) improvement rate (RR=1.89, 95% CI (1.56, 2.29), $P<0.00001$), and decrease the incidence of neutropenia (RR=0.16, 95% CI (0.07, 0.36), $P<0.00001$) of non-small cell lung cancer patients. However, in terms of 1-year survival rate and disease control rate, there was no statistically significant difference ($P>0.05$). Compared to docetaxel, gefitinib shows more advantages. However, more high-quality studies are still required to verify its effectiveness and safety.

Keywords: Gefitinib, docetaxel, non-small cell lung cancer, randomized controlled trial, meta-analysis

Introduction

Lung cancer is one of the diseases seriously threaten human health, and the leading cause of cancer death [1]. According to the degree of differentiation and morphological characteristics of each type of lung cancer, it is currently divided into two categories, i.e. non-small cell lung cancer (NSCLC) and small lung cancer (SCLC). NSCLC accounts for 80% of lung cancer and included squamous cell carcinoma, adenocarcinoma, and large cell carcinoma [2]. For the NSCLC patients, more than half of them are diagnosed with advanced stage and lost the chance of operation [3].

Chemotherapy is still the most important treatment, which can prolong the survival time of part of the patients with advanced stage and recurrent lung cancer, and improve their quality of life [4]. Currently, combination of platinum drugs with the third generation chemotherapy drug gemcitabine (GP program) has become the standard first-line treatment of patients with advanced NSCLC [5]. However, the total efficiency and 1-year survival time of the GP program is still not satisfactory in the treatment of NSCLC, and its adverse reactions, such as thrombocytopenia and anemia, affect the compliance of patients [6].

Studies found that docetaxel showed more advantages in the treatment of lung cancer [7-9]. Therefore, American Society of Clinical Oncology (ASCO) recommends that docetaxel and pemetrexed can be used in chemotherapy if the patients still have a good performance status after failure of the first-line chemotherapy [10]. With the development of molecular targeted drugs, the treatment of NSCLC has a new breakthrough. Gifitinib (trade name Iressa) is an anilinoquinazoline compound and an oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which can inhibit the activation of EGFR, and thus inhibit cell cycle progression, accelerate cell apoptosis,

inhibit angiogenesis and inhibit tumor cell invasion and metastasis [11-13]. It has currently been used in clinic [14], but still has a lot of controversy compared with the traditional chemotherapy drugs docetaxel [15]. Therefore, we collected the published comparison between the randomized controlled trials (RCTs) of gefitinib and docetaxel in the treatment of NSCLC, and analyzed the efficacy and safety of gefitinib in the treatment of NSCLC using Cochrane systematic reviews.

Materials and methods

Inclusion and exclusion criteria

Type of study: RCTs, whether allocation concealment and blinding were used or not, were included. The research articles were full texts in Chinese or English.

Study object

Patients should meet the following criteria: clearly diagnosed as NSCLC by biopsy; received at least one course of chemotherapy, and their liver and kidney function, hematology and electrocardiogram had no obvious abnormalities; never received prior chemotherapy of any one of the two drugs as single or combination; whether had surgery was not considered; whether had tumor distant metastasis was not considered; race, age, sex and course of disease were not limited.

Intervention measures

Gefitinib was used for the treatment group and could be combined with conventional chemotherapy, while docetaxel was used for the treatment of the control group with other interventions consistent with the treatment group. The dosages and periods of treatment bygefitinib and other drugs were not limited.

Outcome measures

Main measures: 1-year survival rate, overall response rate (ORR), disease control rate (DCR), trial outcome index (TOI) improvement rate and incidence of neutropenia.

Document retrieval

The Cochrane Library (1993~2015.10), PubMed (1970~2015.10), CBM (1978~2015.10), CNKI (1996~2015.10), Wanfang Data (1999~2015.10), VIP database (1996~2015.10) and Google scholar were searched by a computer, and relevant journals were manually searched. The full-text references were obtained. Search terms: “Non-small cell lung cancer”, “NSCLC”, “gefitinib”, “irressa”, “docetaxel”, “randomized controlled trial”.

Quality assessment and data extraction

The reference quality was evaluated according to the quality standards of RCT in the Cochrane Handbook for Systematic Reviews of Interventions version 5.0 [16]. The main evaluation items were as follows: whether the random method was correct, whether the blinding method was used, whether the allocation concealment was used, whether there was loss of follow-up or withdrawal, if had, whether intention to treat analysis was used. Literature screening, literature quality evaluation and data extraction were independently performed by two researchers. Cross check was performed, and disagreement was resolved by discussion with a third researcher. The researcher firstly read the titles and abstracts of all the obtained references and excluded the trials that obviously did not meet the inclusion criteria. Then, the full texts of those references which might meet the inclusion criteria were read to determine if they actually met the inclusion criteria. The data was extracted using a self-made data extraction table.

Statistical analysis

Quantitative and qualitative analysis were performed for the collected data. The software RevMan 5.2 of the Cochrane Collaboration was used for meta-analysis. The clinical and methodological heterogeneities were first analyzed for the included researches, and the statistical heterogeneity was checked by χ^2 test and I^2 test. When $P>0.1$ and $I^2<50\%$, it indicated that there was no statistical heterogeneity between the researches, and thus the fixed effects model was used for the meta-analysis. When $P\leq0.1$ and $I^2\geq50\%$, it indicated that there was statistical heterogeneity between the researches, and thus the subgroup analysis (based on the possible factors with heterogeneity) or sensitivity analysis was used. If there was still heterogeneity, for the data that could be combined from the aspect of clinical significance, the meta-analysis was performed using random effects model, and

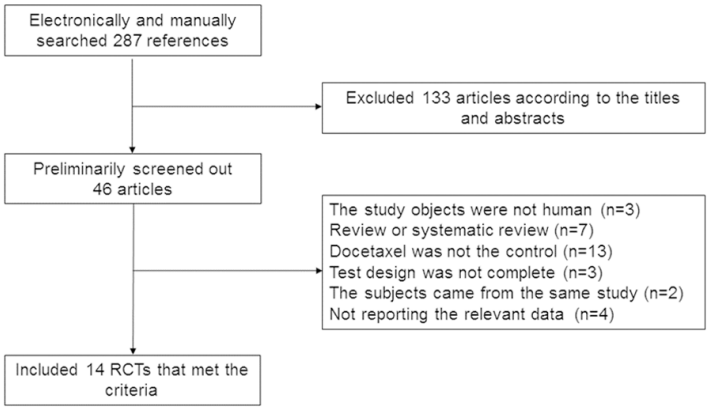

Figure 1. A scheme for the screening of literature. A total of 287 related references were found through computer and manual searches, and finally 14 RCTs were included.

the results should be interpreted with caution. Dichotomous variables were expressed with OR, and continuous variables were expressed with weighted mean differences (WMD). Interval estimate used 95% confidence interval (CI). Hypothesis testing used u test, and expressed with P. A *P* value ≤0.05 indicated there was statistical significance for the difference between two groups. The results of interval estimation and hypothesis testing were listed in the forest figure.

Results

Literature search results

A total of 287 related references were found through computer and manual searches. After removing 241 non-qualified references by eliminating repeated references and reading the titles and abstracts, 46 references were preliminarily screened out. After reading the full texts in further, duplicate publications and those literatures did not meet the inclusion criteria were excluded, and finally 14 RCTs were included [17-30] (**Figure 1**). The clinical data of the included studies were shown in **Table 1**.

The methodological quality of the included studies

In the 14 included researches, 8 researches [17-19, 22, 23, 25, 27, 29] used adequate random methods, 3 researches [19, 22, 25] used correct allocation concealments, and no research used blind methods (**Table 2**).

Results of meta-analysis

1-year survival rate: There were 8 researches reported 1-year survival rate, including a total of 2519 patients. The result of the heterogeneity test was *P*=0.73 and I^2=0%, and thus the fixed effects model was used. The m*eta-analysis result showed that RR=0.91, 95% CI (0.83, 1.01) and *P*=0.07, and the difference had no statistical significance (**Figure 2**). The results indicated that the 1-year survival rate of gefitinib-treated NSCLC patients was not significantly different from that of the patients treated with docetaxel.

Overall response rate: There were 10 researches reported ORR, including 2416 patients. The result of the heterogeneity test was P=0.11 and I^2=38%, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.40, 95% CI (1.18, 1.65), P<0.0001, and the difference was statistically significant (**Figure 3**). The results indicated that the ORR for gefitinib-treated NSCLC patients were obviously better than that of the patients treated with docetaxel.

Disease control rate: There were 9 researches reported DCR, including 1004 patients. The result of the heterogeneity test was P=0.89 and I^2=0%, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.12, 95% CI (0.96, 1.29), P=0.15, and the difference had no statistical significance (**Figure 4**). The results indicated that the DCR of gefitinib for the treatment of NSCLC were not obviously better than that of docetaxel.

TOI improvement rate: There were 7 researches reported TOI improvement rate, including 2243 patients. The result of the heterogeneity test was P=0.08 and I^2=47%, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.89, 95% CI (1.56, 2.29), P<0.00001, and the difference had statistical significance (**Figure 5**). The results indicated that the TOI improvement of gefitinib-treated NSCLC patients was obviously better than that of the patients treated with docetaxel. Therefore, heterogeneous sources were analyzed. After excluding the studies by Sekine

Table 1. The features of the included studies

Study	Published language	Ethnicity	Study location	Intervention	Participant	Age median years (range)	Disease stage			Quality evaluation
							IIIa	IIIb	IV	
Cufer T 2006 [17]	English	Multicenter	Eslovenia	Gefitinib	68	-	-	-	-	High
				Docetaxel	73	-	-	-	-	
Edward S Kim 2008 [18]	English	Multicenter	Canada	Gefitinib	733	61	89	183	388	High
				Docetaxel	733	60	68	211	383	
Riichiroh Maruyama 2008 [19]	English	Asians	Japan	Gefitinib	245	-	-	47	159	High
				Docetaxel	244	-	-	50	150	
Xiong Huihua 2008 [20]	Chinese	Asians	China	Gefitinib	26	54	-	-	-	Low
				Docetaxel	25	54	-	-	-	
Shang Shuheng 2009 [21]	Chinese	Asians	China	Gefitinib	25	54	-	9	16	Low
				Docetaxel	25	52	-	8	17	
I Sekine 2009 [22]	English	Asians	Japan	Gefitinib	245	-	-	-	-	High
				Docetaxel	244	-	-	-	-	
Zhong Wei 2009 [23]	Chinese	Asians	China	Gefitinib	44	59	-	6	38	Low
				Docetaxel	34	56	-	1	33	
Zhang Yi 2009 [24]	Chinese	Asians	China	Gefitinib	26	66	-	-	-	Low
				Docetaxel	28	61	-	-	-	
Dae Ho Lee 2010 [25]	English	Asians	Korea	Gefitinib	82	57	-	-	-	High
				Docetaxel	79	58	-	-	-	
Li Hongmei 2010 [26]	Chinese	Asians	China	Gefitinib	50	50.7	-	29	21	High
				Docetaxel	48	48.2	-	29	19	
Sun Yan 2011 [27]	Chinese	Asians	China	Gefitinib	107	-	-	-	-	Medium
				Docetaxel	115	-	-	-	-	
Wang Yan 2011 [28]	Chinese	Asians	China	Gefitinib	32	60	-	7	25	Low
				Docetaxel	30	59	-	7	23	
Liu hailong 2012 [29]	Chinese	Asians	China	Gefitinib	40	66	-	-	-	Low
				Docetaxel	38	66	-	-	-	
Zhang Jing 2012 [30]	Chinese	Asians	China	Gefitinib	40	-	-	9	31	Low
				Docetaxel	40	-	-	7	33	

Table 2. The methodological quality of the included studies

Study	Randomization	Allocation concealment	Blinding	Incompleteness of data	Selective outcome reporting	Other sources of bias
Cufer T 2006 [17]	Yes	Unclear	Yes	Yes	No	Unclear
Edward S Kim 2008 [18]	Yes	Unclear	Yes	Yes	No	Unclear
Riichiroh Maruyama 2008 [19]	Yes	Yes	Yes	Yes	No	Unclear
Xiong Huihua 2008 [20]	Unclear	Unclear	Yes	Yes	No	Unclear
Shang Shuheng 2009 [21]	Unclear	Unclear	Yes	Yes	No	Unclear
I Sekine 2009 [22]	Yes	Yes	Yes	Yes	No	Unclear
Zhong Wei 2009 [23]	Yes	Unclear	Yes	Yes	No	Unclear
Zhang Yi 2009 [24]	Unclear	Unclear	Yes	Yes	No	Unclear
Dae Ho Lee 2010 [25]	Yes	Yes	Yes	Yes	No	Unclear
Li Hongmei 2010 [26]	Unclear	Unclear	Yes	Yes	No	Unclear
Sun Yan 2011 [27]	Yes	Unclear	Yes	Yes	No	Unclear
Wang Yan 2011 [28]	Unclear	Unclear	Yes	Yes	No	Unclear
Liu hailong 2012 [29]	Yes	Unclear	Yes	Yes	No	Unclear
Zhang Jing 2012 [30]	Unclear	Unclear	Yes	Yes	No	Unclear

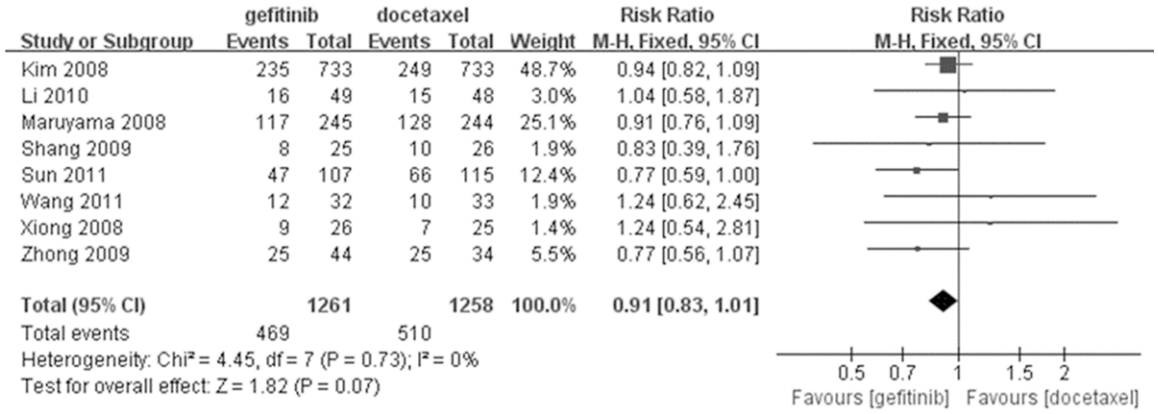

Figure 2. The meta-analysis of the 1-year survival rates of gefitinib *vs*. docetaxel for the treatment of NSCLC. It showed that RR=0.91, 95% CI (0.83, 1.01) and *P*=0.07, and the difference had no statistical significance.

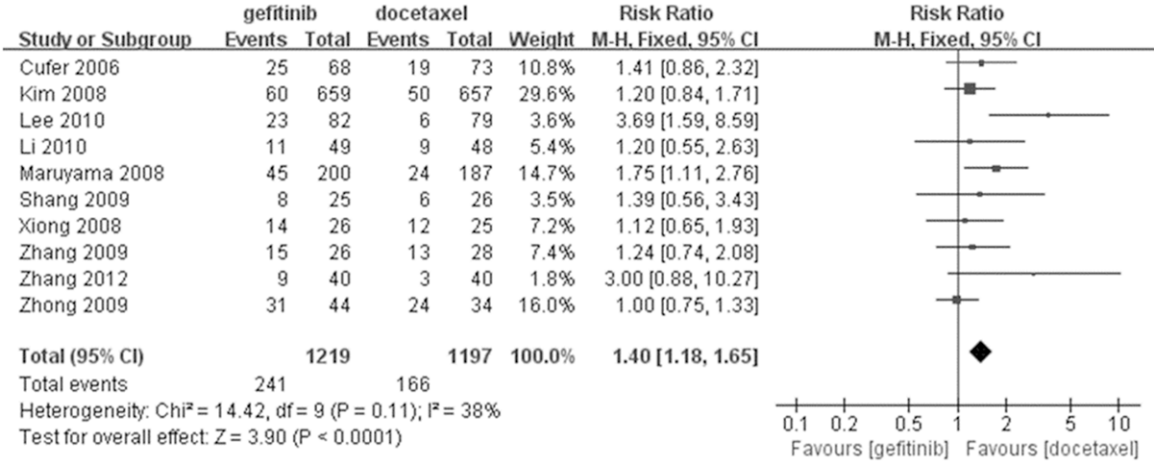

Figure 3. The meta-analysis of the overall response rates of gefitinib *vs*. docetaxel for the treatment of NSCLC. It showed that RR=1.40, 95% CI (1.18, 1.65), *P*<0.0001, and the difference was statistically significant.

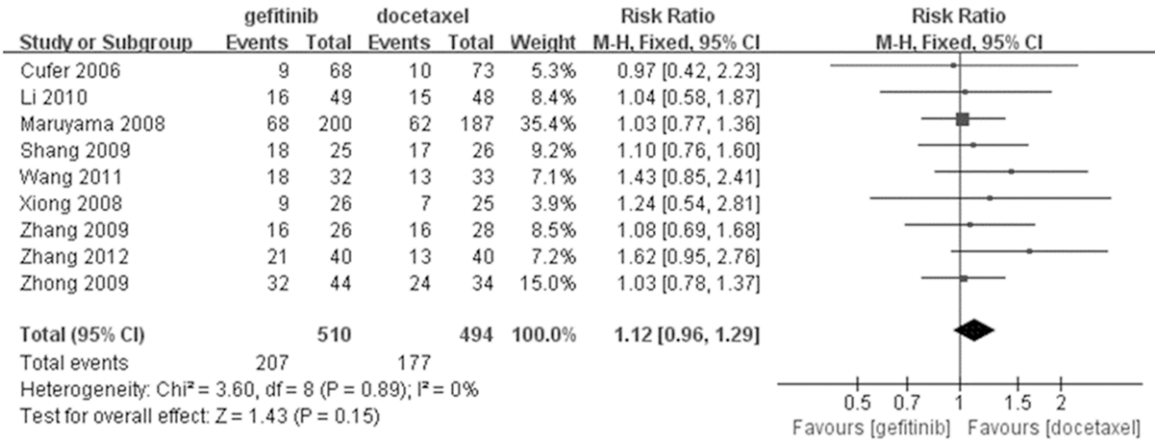

Figure 4. The meta-analysis of the disease control rates of gefitinib *vs*. docetaxel for the treatment of NSCLC. It showed that RR=1.12, 95% CI (0.96, 1.29), *P*=0.15, and the difference had no statistical significance.

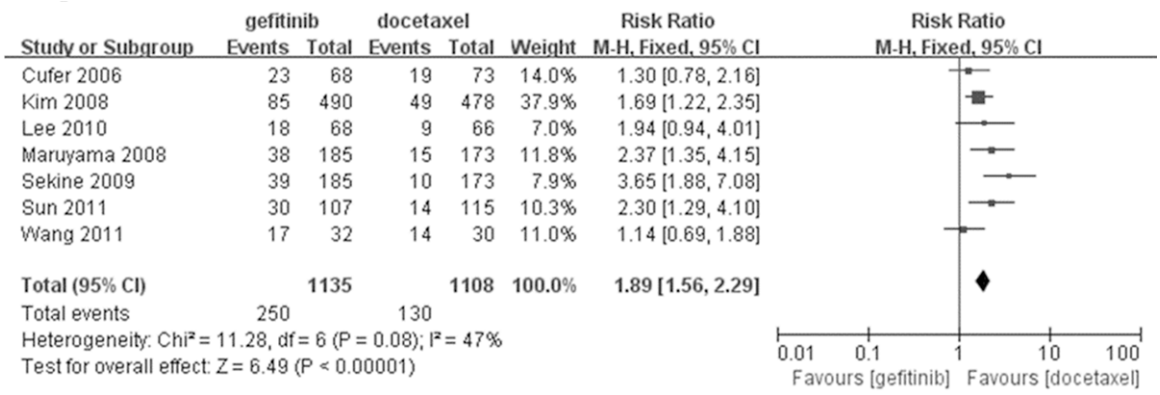

Figure 5. The meta-analysis of the TOI improvement rates of gefitinib *vs*. docetaxel for the treatment of NSCLC. It showed that RR=1.89, 95% CI (1.56, 2.29), *P*<0.00001, and the difference had statistical significance.

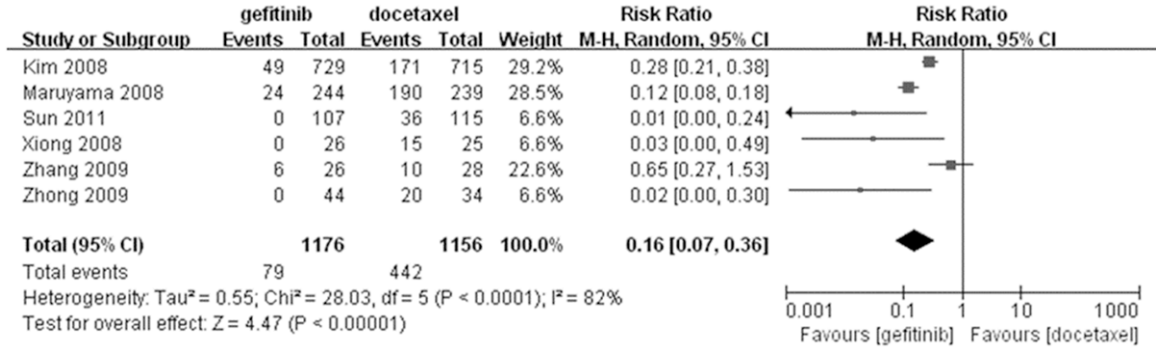

Figure 6. The meta-analysis of the incidence of neutropenia of gefitinib *vs*. docetaxel for the treatment of NSCLC. It showed that RR=0.16, 95% CI (0.07, 0.36), *P*<0.00001, and the difference had statistical significance.

[22] and Maruyama [19], the heterogeneity reduced to 10%. The reason may be that the research objects in these two references were mainly Japanese population. After excluding these two researches, the combined RR analytical result was 1.65 [95% CI (1.33, 2.04), P<0.0001], which had no influence on the final conclusion.

Incidence of neutropenia: There were 6 researches reported the incidence of neutropenia, including 2332 patients. The result of the heterogeneity test was *P*<0.0001 and I^2=82%, and thus the random effects model was used. Meta-analysis result showed that RR=0.16, 95% CI (0.07, 0.36), *P*<0.00001, and the difference had statistical significance (**Figure 6**). The results indicated that the incidence of neutropenia of gefitinib-treated NSCLC patients was obviously lower than that of the patients treated with docetaxel. Due to the large heterogeneity of the included studies, the sources of heterogeneity were analyzed. After excluding the study by Kim [18], the heterogeneity decreased to 31%. The reason may be that the objects in all the other 5 references were Asian population, but the objects in Kim's study [18] mixed many races. After excluding this study, the combined RR analytical result was 0.06 [95% CI (0.02, 0.17), P<0.00001], which had no influence on the final conclusion.

Discussion

Chemotherapy is mainly used for the treatment of advanced NSCLC. Currently used third-generation first-line chemotherapy for the treatment of advanced NSCLC has an effective rate of 35%, 1-year survival rate of 35% and 2-year survival rate of 20% [31]. For the second-line chemotherapy after the failure of the first-line chemotherapy, the National Comprehensive Cancer Network (NCCN) guideline recommends docetaxel and pemet-

rexed, and pemetrexed is only recommended for the non-squamous cell carcinoma patients [32]. Docetaxel is a new anti-microtubule drug, whose microtubule stabilizing effect is twice greater than that of taxol. It is a cell cycle specific drug and can block the cell in M phase. It also can interfere with cell mitosis, and thus kill tumor cells [33]. However, drug-resistant cell lines increased after the failure of first-line chemotherapy, its efficacy is limited. References reported that the tumor objective response rate of docetaxel as second-line chemotherapy was only 5.5%~6.7%, the median tumor progression free time was only 8.5~10.6 weeks, the median survival time was only 5.7~7.5 months [34]. In addition, docetaxel chemotherapy requires higher physical state for the patients. Many patients have a physical score >2 after the failure of the first-line chemotherapy, who cannot receive further chemotherapy [35]. In the treatment of lung cancer, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is a research hotspot in recent years. Gefitinib, erlotinib, vandetanib and a large number of other targeted drugs show good clinical efficacy and low toxic and side effects [36]. The results of this study showed that gefitinib could obviously improve the overall response rate and TOI improvement rate, and reduce the hematological toxicity.

The RCTs included in this study had some defects in the research design, mainly in the following aspects: 1) only 8 studies described detailed randomized method, while the rest of the studies did not make full randomization of the study objects, which might result in selective bias; 2) insufficient attention to allocation concealment, which might exaggerate the treatment effect; 3) the use of blind method was too low, which might produce implementation bias and measurement bias; 4) the reasons for the loss of the case and follow-up and withdrawal were not described, which might affect the evaluation of therapeutic effects; 5) all the included studies did not explain the calculation of sample size, which would reduce the test efficiency; 6) the included studies did not describe the baseline in detail, which made it hard to judge the balance between groups. In addition, all studies were lack of economic evaluation. Therefore, further researches are needed to guide the clinical application of gefitinib.

In conclusion, gefitinib has some advantages in the treatment of NSCLC, and can be used as conventional drugs for NSCLC treatment. However, because the application of gefitinib is affected by economic conditions and the quality of the included literature is uneven, the clinical application of gefitinib needs supports from more high quality clinical studies and economic evaluations.

Acknowledgements

We would like to thank Mr. Changfu Li from The Cancer Hospital Affiliated to Harbin Medical University for his help in this study. We would like to thank Mr. Wuyong Zhong from Chongqing Cancer Hospital for his help in this study.

Disclosure of conflict of interest

None.

Address correspondence to: Aihong Zhang, Department of Pharmacy, The Cancer Hospital Affiliated to Harbin Medical University, No. 150 Haping Road, Nangang District, Harbin 150086, P. R. China. Tel: 0451-86298568; Fax: 0451-86298568; E-mail: cnq333@163.com

References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics. CA Cancer J Clin 2012; 62: 10-29.

[2] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346: 92-8.

[3] Hall RD, Le TM, Haggstrom DE and Gentzler RD. Angiogenesis inhibition as a therapeutic strategy in non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2015; 4: 515-23.

[4] Yin L, Liu JW, Guo YC and Qi J. Non-small cell lung cancer treatment status. Xian Dai Zhong Liu Yi Xue 2010; 18: 185-7.

[5] Rosell R, Gatzemeier U, Betticher DC, Keppler U, Macha HN, Pirker R, Berthet P, Breau JL, Lianes P, Nicholson M, Ardizzoni A, Chemaissani A, Bogaerts J and Gallant G. Phase III randomised trial comparing paclitaxel/carboplatin with paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. Ann Oncol 2002; 13: 1539-49.

[6] Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD Jr, Morse D, Abraham S, Rahman

A, Liang C, Lostritto R, Baird A and Pazdur R. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Gefitinib) tablets. Clin Cancer Res 2004; 10: 1212-8.

[7] Chung FT, Lee KY, Fang YF, Shieh MH, Lin SM, Yu CT, Lo YL, Lin TY, Kuo CH, Feng PH, Ni YL and Kuo HP. Low-dose weekly docetaxelis as tolerable as pemetrexed in previously treated advanced non-small-cell lung cancer. Chemotherapy 2011; 57: 147-50.

[8] Chen QQ, Ji XX, Zhou X, Shi QL, Yu HM, Fu HQ and Ji GP. Clinical observation of docetaxel or gemcitabine combined with cisplatin in the chemotherapy after surgery for stage II-III non-small cell lung cancer. Contemp Oncol (Pozn) 2015; 19: 323-6.

[9] Sugiura Y, Hashizume T, Kawai O, Ohkubo Y, Fusegawa H, Araki N, Kaseda S and Nemoto E. Complete Remission after Weekly Intravenous Nanoparticle Albumin-Bound Paclitaxel in Elderly Patients with Non-Small-Cell Lung Cancer. Gan To Kagaku Ryoho 2015; 42: 1095-7.

[10] Cromwell L, van der Hoek K, Melosky B and Peacock S. Erlotinib or docetaxel for second-line treatment of non-small cell lung cancer: a real-world cost-effectiveness analysis. J Thorac Oncol 2011; 6: 2097-103.

[11] Tan CS, Gilligan D and Pacey S. Treatment approaches for EGFR-inhibitor-resistant patients with non-small-cell lung cancer. Lancet Oncol 2015; 16: e447-59.

[12] Yano S. Molecular mechanisms of targeted drug resistance in lung cancer and its therapeutic strategy. Nihon Rinsho 2015; 73: 1378-83.

[13] Zhai H, Zhong W, Yang X and Wu YL. Neoadjuvant and adjuvant epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy for lung cancer. Transl Lung Cancer Res 2015; 4: 82-93.

[14] Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE and Meyerson M. EGFR mutations in lung cancer correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-500.

[15] Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ and Kay AC. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003; 290: 2149-58.

[16] Higgins GPT and Green S. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration 2011; 9: 3.

[17] Cufer T, Vrdoljak E, Gaafar R, Erensoy I, Pemberton K; SIGN Study Group. 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 2006; 17: 401-9.

[18] Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, Li LY, Watkins CL, Sellers MV, Lowe ES, Sun Y, Liao ML, Osterlind K, Reck M, Armour AA, Shepherd FA, Lippman SM and Douillard JY. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. Lancet 2008; 372: 1809-18.

[19] Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K, Shinkai T, Negoro S, Imamura F, Eguchi K, Takeda K, Inoue A, Tomii K, Harada M, Masuda N, Jiang H, Itoh Y, Ichinose Y, Saijo N and Fukuoka M. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 2008; 26: 4244-52.

[20] Xiong HH, Zou YM and Xia S. Comparison of the efficacy of gefitinib and docetaxel for treatment of non-small cell lung cancer. Lin Chuang Nei Ke Za Zhi 2008; 25: 537-9.

[21] Shang SH, Ma TH and Li CH. Compare TP programs and gefitinib for treatment of non-small cell lung cancer. An Hui Yi Xue 2009; 30: 740-2.

[22] Sekine I, Ichinose Y, Nishiwaki Y, Yamamoto N, Tsuboi M, Nakagawa K, Shinkai T, Negoro S, Imamura F, Eguchi K, Takeda K, Itoh Y, Tamura T, Saijo N and Fukuoka M. Quality of life and disease-related symptoms in previously treated Japanese patients with non-small-cell lung cancer: Results of a randomized phase III study(V-15-32) of gefitinib versus docetaxel. Ann Oncol 2009; 20: 1483-8.

[23] Zhong W, Wang M, Zhang L, Zhang X and Li L. Gefitinib and docetaxel as second-line therapy for patients with advanced non-small cell lung cancer. Zhong Liu Xue Za Zhi 2009; 15: 508-11.

[24] Zhang Y. Gefitinib and docetaxel for the treatment of recurrent non-small cell lung cancer. Shou Du Yi Yao 2009; 16: 46-7.

[25] Lee DH, Park K, Kim JH, Lee JS, Shin SW, Kang JH, Ahn MJ, Ahn JS, Suh C and Kim SW. 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 2010; 16: 1307-14.

[26] Li H, Wang X and Hua F. Second-line treatment with gefitinib or docetaxel for advanced non-small cell lung cancer. Zhong Guo Zhong Liu Lin Chuang 2010; 30: 16-8.

[27] Sun Y, Wu Y, Li L, Liao M, Jiang G, Kim ES, Douillard JY, Milenkova T. Efficacy and safety of gefitinib or docetaxel in Chinese patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who had failed previous platinum-based first-line chemotherapy. Zhong Hua Zhong Liu Za Zhi 2011; 33: 377-80.

[28] Wang Y, Su L and Wang J. Comparison of gefitinib and docetaxel in treatment of advanced non-small cell lung cancer patients who have failed to previous chemotherapy. Guo Ji Hu Xi Za Zhi 2011; 31: 1221-4.

[29] Liu H, Lei H and Deng Q. Second-line treatment with gefitinib or docetaxel for advanced non-small cell lung cancer. Zhong Wai Yi Xue Yan Jiu 2012; 10: 7-8.

[30] Zhang J, Liu S, Zhang J, Ban L and Zhou T. Effect and cost-efficacy analysis of the second-line treatment of advanced non-small cell lung cancer. Lin Chuang Zhong Liu Xue Za Zhi 2012; 10: 908-11.

[31] Guan ZZ, Zhang L, Li LY, Jiang GL, Liu XY, Chu DT, Zhao HY and Li W. Efficacy of gefitinib on Chinese patients with locally advanced or metastatic non-small cell lung cancer: a clinical trial. Ai Zheng 2005; 24: 980-4.

[32] Sun Y and Zhou J. Manual of medical oncology, 4th Version. Beijing: People's Medical Publishing House Co. Ltd; 2006.

[33] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y and Berille J. 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 2000; 18: 2095-103.

[34] Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F and Hammershaimb L. Randomized phase III trial of docetaxel versus vinorelbine or if osfamidein patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18: 2354-62.

[35] Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L and Bunn PA Jr. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589-97.

[36] Fukuoda M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP and Baselga J. Multi-institutional randomized phase III trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 2003; 21: 2237-46.