RESEARCH ARTICLE

Effectiveness and Safety of Pemetrexed Versus Docetaxel as a Treatment for Advanced Non-small Cell Lung Cancer: a Systematic Review and Meta-analysis

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Abstract

Background: Our aim was to conduct a meta-analysis to compare the efficacy and safety of pemetrexed and docetaxel for non-small cell lung cancer (NSCLC). Materials and Methods: We systematically searched the Cochrane Library, PubMed, Embase, China Biology Medicine Database for randomized controlled trials (RCTs) comparing the efficacy and toxicities of pemetrexed versus docetaxel as a treatment for advanced NSCLC. We limited the languages to English and Chinese. Two reviewers independently screened articles to identify eligible trials according to the inclusion and exclusion criteria and assessed the methodological quality of included trials, and then extracted data. The meta-analysis was performed using STATA12.0. Results: Six RCTs involving 1,414 patients were identified. We found that there was no statistically significant differences in overall response rate, survival time, progression-free survival, disease control rate, and 1-2yr survival rate ($p>0.050$) but it is worthy of mention that patients in the pemetrexed arms had significantly higher 3-yr survival rate ($P=0.002$). With regard to the grade 3 or 4 hematological toxicity, compared with docetaxel, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia, and leukocyts toxicity ($p<0.001$). There was no significant difference in anemia between the two arms ($p=0.08$). In addition, pemetrexed led to higher rate of grade 3-4 thrombocytopenia toxicity ($p=0.03$). As for the non-hematological toxicities, compared with docetaxel, pemetrexed group had lower rate of grade 3-4 diarrhea and alopecia. Conclusions: Pemetrexed was almost as effective as docetaxel in patients with advanced NSCLC. At the same time, pemetrexed might increase the 3-yr survival rate. As for safety, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia, leukocytes, diarrhea and alopecia toxicity. However, it was associated with a higher rate of grade 3-4 thrombocytopenia.

Keywords: Non-small-cell-lung- cancer - pemetrexed - docetaxel - meta-analysis

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Introduction

Lung Cancer is a major public health problem all over the world. It was reported that there were more than 225 000 new cases of lung cancer and more than 160,000 deaths due to lung cancer in the United States in 2012 (Siegel et al., 2012). In China, the annual new cases are predicted to reach 1,000,000 by the year 2025 (Sun et al., 2013). Of all the lung cancer patients, non-small cell lung cancer (NSCLC) comprises approximately 80%, and the majority present with locally advanced or metastatic disease (Fathi et al., 2008). Unfortunately, the 5-year survival rate of patients with metastatic NSCLC is less than 10% (Govindan et al., 2006). Systemic therapy for advanced NSCLC has been improved largely over the last two decades, and now platinum-based (doublet) chemotherapy is generally considered the standard first-line therapy for patients with advanced NSCLC, but three meta analysises evaluate the efficacy and safety of epidermal growth factor receptor (EGFR) as first-line treatment in patients with advanced NSCLC, the result showed that compared with placebo, EGFR significantly increases objective tumor response rate and progression-free survival (Zhang et al., 2011; Qi et al., 2012; Alimujiang et al., 2013). At the same time, cell toxic drugs like docetaxel and pemetrexed were used as alternatives as well. Docetaxel is the first drug approved as a second-line treatment for advanced NSCLC. Pemetrexed is a multi-targeted inhibitor of three

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key enzymes in the folate metabolic pathway: thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT) (Calvert et al., 1999; Adjei et al., 2004). It was approved in numerous countries as first-line therapy in combination with cisplatin, as single-agent second-line therapy, or as single-agent maintenance therapy for patients with advanced non-squamous NSCLCyears ago (Baldwin et al., 2009). But recently, pemetrexed has been approved by U.S. Food and Drug Administration (FDA) as a second-line treatment for advanced NSCLC as well. Several clinical trials have investigated the effectiveness and safety of the two anticancer drugs, but most of these trials are based on small samplings, which provided inadequate statistical power to evaluate the effectiveness and safety of the two drugs. What's worse, some studies even produced conflicting results, especially in aspects of the toxicities. Thus, we want to conduct a systematic review and meta-analysis for all the eligible randomized studies comparing the effectiveness and safety of pemetrexed and docetaxel to get a more credible result. To our knowledge, there has no systematic review or meta-analysis comparing these two drugs at present.

Materials and Methods

Search strategy

We identified eligible trials by an electronic search of Cochrane library, PubMed, Embase, ISI Web of Knowledge, China Biology Medicine disc using the following terms: (lung cancer OR lung tumor OR lung neoplasm) AND (pemetrexed OR alimta). The time searched was from the establishment time of the databases to March 15, 2013. At the same time, we searched Google, Medical Martix and Baidu for the relevant studies as well as a hand-search. We limited the language to English and Chinese.

Eligibility criteria

Study design Eligible studies must meet the following four criteria: *i*) Clinical controlled trials with a parallel design comparing pemetrexed versus docetaxel or pemetrexed-based doublet versus docetaxel-based with the same doublet in advanced NSCLC patients. *ii*) They had to be randomized controlled trials, and the blinded and un-blinded ones were all eligible. *iii*) Studies with available full text articles. *iv*) Sufficient data on overall response rate (ORR), median survival time, progression-free survival (PFS), disease control rate (DCR), 1-3yr survival rate and toxicities resulted in the two different treatments.

Population studied Patients met the following criteria were considered eligible: *i*) Histological or cytological confirmation of NSCLC with stage IIIB or IV disease. *ii*) Patients with an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, and with adequate bone marrow, renal, and hepatic function. *iii*) Patients older than 18 years old.

Data collection

Two investigators (Long Ge, Wenhui Huang) scanned all titles and abstracts to exclude studies failed to meet the including criteria, and then obtained and reviewed the full text reports of all the candidate trials. Finally, they conducted data extraction using a standardized pre-piloted form which collected information about the author, the population studied, number of the patients, methodological evaluation, interventions and outcomes. One of the investigators did the data collection and entry, and the other was in charge of the checking. Disagreements were solved though discussion with a third author (Jinhui Tian).

Quality assessment

The quality of trials was assessed with the methods recommended by the Cochrane Collaboration for assessing risk of bias (Higgins et al., 2005). The criteria used for quality assessment were sequence generation of allocation, allocation concealment, blinding, use of intent-to-treat analysis, and the proportion of patients lost to follow-up. Two investigators independently assessed the studies according to the same criteria. Disagreements were resolved by consensus.

Statistical analysis

The meta-analysis was done in line with recommendations from the STATA 12.0 when data met the requirements for pooling. Otherwise, we conducted descriptive analysis. Heterogeneity was assessed with χ^2 test (α=0.1) and I^2 statistics. When there was no statistics heterogeneity among studies (p>0.10, I^2<50%), we used fixed effect model; if there were (p<0.10, I^2>50%), we would try to find the cause. If there was no clinical/methodological heterogeneity, we changed to random effect model. We calculated the dichotomous variable results with pooled odds ratio (OR), and the continuous variable results were calculated with weight mean differences (WMD); 95% confidence intervals (CI) were also reported.

Results

Search results and baseline characteristics of included trials

Totally, 827 literatures were detected through search process and 614 were left after removing duplication. 442 were left after scanning all titles and abstracts. Of which, 429 were excluded for their study design not fitting in with the including criteria and seven were excluded for the low quality. Finally, we included six studies (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013), which containing 1, 414 patients. Of all the patients 927 (65.6%) were male. More details are presented in Table 1.

Quality of included studies

All the six RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported adequate generation of the allocation sequence, but none of the studies reported allocation concealment. Four (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Li et al., 2012) of them

Table 1. Baseline Characteristics of Included Trials

Study	Therapy	n	Age Median (y)	Male (%)	StageIIIb (%)	Stage IV (%)	Pathological diagnosis (%)
Chen et al., 2008	PEM	34	56	67.6	23.5	76.5	Ade: (58.8), Squ: (35.2), others : (5.9)
	Doc	33	55	63.6	18.2	81.8	Ade: (66.7), Squ: (30.3), others (3.0)
Hanna et al., 2004	PEM	283	59	68.6	NR	74.9	Ade: (64.4), Squ: (27.6)
	Doc	288	57	75.3	NR	74.7	Ade: (49.3), Squ: (32.3)
Jose et al., 2011	PEM/Carb	106	60.1	60.4	16	84	Ade: (84.9), others (15.1)
	Doc/Carb	105	58.9	47.6	21.9	78.1	Ade: (86.7), others (13.3)
Li et al., 2012	PEM	106	58.2	63.2	34	66	NSCC (40.6), Squ: (17.9), Missing (41.5)
	Doc	102	55.6	72.5	39.2	59.8	NSCC (33.3), Squ: (24.5), Missing (42.2)
Socinski et al., 2010	PEM/Carb	74	66	55	7	93	Ade: (58.0), Squ: (30.0), others (12.0)
	Doc/Carb	72	65	58	8	92	Ade: (60.0), Squ: (19.0), others (21.0)
Sun et al., 2013	PEM	107	55.9	68.2	22.4	75.7	Ade: (70.1), Squ: (25.2), others (4.7)
	Doc	104	55.8	58.7	17.3	80.8	Ade: (70.2), Squ: (24.0), others (5.8)

*Karnofsky performance status; Ade:adenocarcinoma; Squ:squamous; PEM: pemetrexed- 500 mg/m^2 d1, q3w; Doc : docetaxel-75 mg/m^2 d1, q3w; Carb: carboplatin

Table 2. Quality of Included Trials

Included Trials	Random allocation	Allocation concealment	Blinding	Intent-to-treat analysis	Lost to follow-up
Chen et al., 2008	Yes	Not report	Not report	Not report	Yes
Hanna et al., 2004	Yes	Not report	Not report	Yes	Yes
Jose et al., 2011	Yes	Not report	Open-label	Yes	Yes
Li et al., 2012	Yes	Not report	Not report	Not report	Yes
Socinski et al., 2010	Yes	Not report	Not report	Yes	Yes
Sun et al., 2013	Yes	Not report	Open-label	Yes	Yes

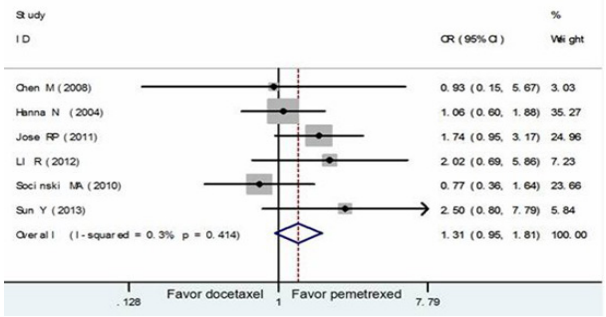

Figure 1. Forest Plot of Overall Response Rate

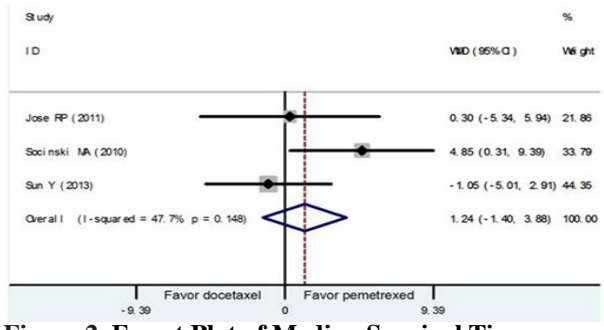

Figure 2. Forest Plot of Median Survival Time

didn't report blinding, and two (Rodrigues-Pereira et al., 2011; Sun et al., 2013) trials were open-label studies. Four (Hanna et al., 2004; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Sun et al., 2013) did the intent-to-treat analysis, but two (Chen et al., 2008; Li et al., 2012) of them didn't report that. All of the six RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported the patients lost to follow-up in detail. Table 2 presents the specific information.

Overall response rate

All the six RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported this outcome and 1, 400 patients were contained for this outcome (705 for pemetrexed group and 695 for docetaxel group). The rates in group pemetrexed and group docetaxel were 14.2% and 11.4% respectively. Result of the heterogeneity was p=0.414, I^2=0.3%. After an analysis with fixed effect model, we got the result OR=1.31, 95%CI: 0.95-1.81, p=0.102, which indicated no statistical significance between these two groups (Figure 1).

Median survival time

Five RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Sun et al., 2013) reported this outcome, which totally contained 1201 patients (602 for pemetrexed group and 599 for docetaxel group), two RCTs (Hanna et al., 2004; Chen et al., 2008) (which contained 633 patients , 315 for pemetrexed group and 318 for docetaxel group) only reported this outcome without confidence interval, so they can't be summarized in the forest plot, Hanna et al, (2004) reported the median survival time was 8.3 versus 7.9 months (p =not significant) for pemetrexed and docetaxel respectively. Chen et al (Chen et al., 2008) reported that being 8.1 versus 7.7 months (p=0.871). Data from the other three RCTs (Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Sun et al., 2013) containing 568 patients (287 for pemetrexed group and 281 for docetaxel group), were summarized in the forest plot (See Figure 2). The heterogeneity between the three trials was p=0.148, I^2=47.7%. After an analysis with fixed effect model, we got the result WMD: 1.24, 95%CI: -1.40 -3.88, p=0.357, which also showed no statistical significance between the two arms (Figure 2).

Progression-free survival

Four RCTs (Hanna et al., 2004; Chen et al., 2008; Rodrigues-Pereira et al., 2011; Sun et al., 2013) reported this outcome, which totally contained 1055 patients (528 for pemetrexed group and 527 for docetaxel group), Similarly, we didn't summarize data from one (Chen et al., 2008) of these four RCTs, which contained 62 patients, 32 for pemetrexed, and 30 for docetaxel group, because it reported this outcome, without confidence interval, This study reported the median progression-free survival time was 5.2 versus 5.5 months (p=0.086) for pemetrexed and docetaxel respectively. The other three RCTs (Hanna et al., 2004; Rodrigues-Pereira et al., 2011; Sun et al., 2013) containing 993 patients (496 for pemetrexed group and 497 for docetaxel group), were summarized in the

forest plot, the heterogeneity between the three trials was p=0.635, I^2=0%. After an analysis with fixed effect model, we got the result WMD: -0.59, 95%CI: -1.25-0.07, p=0.080. No statistical significance between the two arms was showed either.

Disease control rate

Five RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Li et al., 2012; Sun et al., 2013) reported this outcome directly or indirectly, which totally contained 673 patients (340 for pemetrexed group and 333 for docetaxel group), heterogeneity between the five trials was p=0.160, I^2=39.2%. After an analysis with fixed effect model, we got the result OR: 1.00, 95%CI: 0.79-1.26, p=0.969. Again, no statistical significance was presented between the two arms.

Survival rate

Three RCTs (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010) reported 1-yr survival rate, which totally contained 749 patients (371 for pemetrexed group and 378 for docetaxel group), result of the heterogeneity between the 3 trials was p=0.087, I^2=59.0%. After an analysis with random effect model, we got the result OR: 1.21, 95%CI: 0.89-1.65, p=0.218, which predicted no statistical significance on 1-yr survival rate between the two arms (See Figure 3). Only one RCT (Socinski et al., 2010) reported 2-yr and 3-yr survival rate, which contained 146 patients (74 for pemetrexed group and 72 for docetaxel group). Therefore, only summarized this study in the forest plot (See Figure 3), No statistical significance on 2-yr survival rate between the two arms was found, (OR=1.52, CI: 0.71-3.28, p=0.280). However, one point worth to be mentioned is that patients in pemetrexed arms showed significantly higher 3-yr survival rate (OR=8.073, CI: 2.10-30.96, p=0.002) (Figure 3).

Hematological and non-hematological toxicity (grade 3-4)

Table 3 is a summary of forest plot for grade 3-4 hematological and non-hematological toxicity. All the six trials (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported hematological toxicity, including neutropenia, anemia and thrombocytopenia. Five trials (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Sun et al., 2013) reported febrile neutropenia. Three trials (Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported leukocytes. Compared with docetaxel, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia and leukocytes toxicity (OR=0.16, 95%CI: 0.08-0.33, p<0.00001; OR=0.20, 95%CI: 0.10-0.41, p =0.0001; OR=0.22,

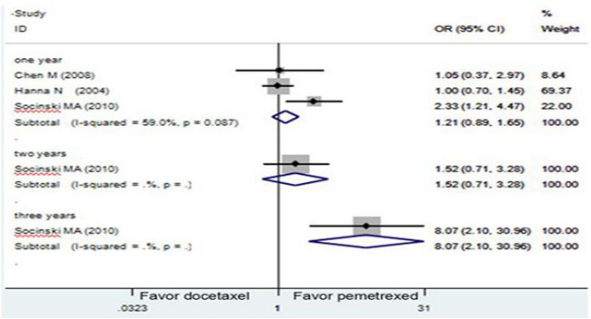

Figure 3. Forest Plot of 1-3yr Survival Rate

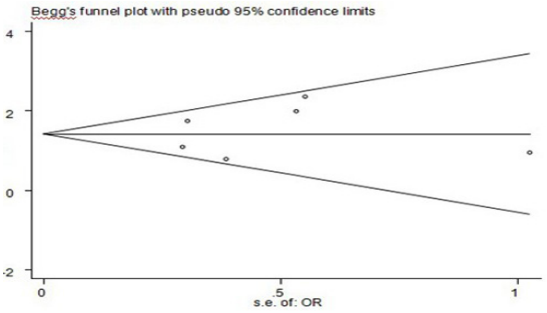

Figure 4. Forest Plot of Publication Bias

Table 3. Summary of Forest Plot for Grade 3-4 Hematological and Non-Hematological Toxicity

	Pemetrexed	Docet-axel	Heterogeneity		OR (95%CI)	p value
			p value	I^2		
Grade 3-4 hematological toxicity						
Febrile Neutropenia	9/583	58/585	0.65	0	0.16 (0.08-0.33)	<0.00001
Neutropenia	78/710	268/714	<0.0003	78	0.20 (0.10-0.41)	0.0001
Leukocytes	27/339	92/334	0.49	0	0.22 (0.14-0.35)	<0.00001
Anemia	52/710v	24/712	0.03	59	2.30 (0.90-5.87)	0.08
Thrombocytopenia	47/710	12/712	0.07	54	3.70 (1.15-11.84)	0.03
Grade 3-4 non-hematological toxicity						
ALT*	6/466	1/475	0.22	35	3.31 (0.27-39.82)	0.35
Fatigue	23/604	24/607	0.75	0	0.97 (0.54-1.74)	0.91
Diarrhea	3/678	20/682	0.93	0	0.16 (0.05-0.5)	0.002
Nausea	12/604	9/610	0.99	0	1.36 (0.57-3.25)	0.49
Vomiting	7/572	6/580	0.77	0	1.01 (0.35-2.9)	0.98
Neurosensory	4/572	6/580	0.44	0	0.71 (0.22-2.27)	0.57
Stomatitis	4/498	4/508	0.64	0	1.02 (0.29-3.56)	0.97
Alopecia	3/233	18/229	0.5	0	0.16 (0.05-0.53)	0.003
Pulmonary	0/392	4/403	NA	NA	0.11 (0.01-2.13)	0.15
Rash	4/371	2/278	0.4	0	1.83 (0.39-8.68)	0.45
Allergy	0/201	4/199	0.68	0	0.19 (0.02-1.65)	0.13
Weight loss	18/371	4/378	NA	NA	5.01 (1.63-15.37)	0.005

ALT, alanine aminotransferase; NA, Not applicable

95%CI: 0.14-0.35, $p<0.00001$, respectively). There were no statistically significant differences on anemia toxicity between the two arms (OR =2.30, 95%CI: 0.90-5.87, $p=0.08$). It is worth to mentioned that pemetrexed led to higher rate of grade 3-4 thrombocytopenia toxicity (OR=3.70, 95%CI: 1.15-11.84, $p=0.03$) (See Table 3).

Some of the trials (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) reported non-hematological toxicity, including ALT, fatigue, diarrhea, nausea, vomiting, neurosensory, stomatitis, alopecia, pulmonary, rash, allergy and weight loss toxicity. Compared with docetaxel, pemetrexed led to lower rate of grade 3-4 diarrhea and alopecia toxicity (OR =0.16, 95%CI: 0.05-0.5, $p=0.002$; OR=0.16, 95%CI: 0.05-0.53, $p=0.003$, respectively). There were no statistically significant differences on ALT, fatigue, nausea, vomiting, neurosensory, stomatitis, pulmonary, rash, allergy and weight loss toxicity between the two arms (more details about OR value, 95%CI and p value were showed in Table 3).

Publication bias

We did our best to design the study in order to minimize the publication bias. Firstly, we made a comprehensive search strategy; Secondly, the inclusion criteria were executed strictly to selected papers; Thirdly, publication bias was detechted by several methods. According to the funnel, may be there is no publication bias in our study (Begg' test, $p=0.658$; Egger's test, $p=0.573$, Figure 4).

Discussion

Docetaxel is the first drug approved as second-line treatment for advanced NSCLC and has been proved to play an important role as a standard second-line treatment for advanced NSCLC in Guo RR et al's meta-analysis (Guo et al., 2008), and his study also pointed out patients' compliance to docetaxel would be influenced by its hematological toxicity. In 2008, Scagliotti et al. (2008) first reported a large phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed, which found that pemetrexed significantly improved overall survival (OS) in non-squamous patients but significantly decreased OS in squamous patients. Based on this trial, pemetrexed was approved in numerous countries as first-line therapy in combination with cisplatin, or as single-agent second-line therapy, or as single-agent maintenance therapy for patients with advanced non-squamous NSCLC (Baldwin et al., 2009). Rencent trials (Hanna et al., 2004; Chen et al., 2008; Socinski et al., 2010; Rodrigues-Pereira et al., 2011; Li et al., 2012; Sun et al., 2013) demonstrated that compared with docetaxel, pemetrexed has the same ORR, survival time, and PFS. While in our meta-analysis, compared with docetaxel, we found there had no significantly difference on ORR, survival time, PFS, DCR and 1-2 yr survival rate, and for 3-yr survial, pemetrexed showed impressively better outcomes. But in case of the small sampling of the trial (Socinski et al., 2010), we should give more attention to the reliability of the two indexes, which are 2-yr and 3-yr survival rate. And give more analysis to them in the future trials.

Rencelty, there were also studies investigating treatment efficacies regarding tumor response and patient's performance status. They showed equivalent outcomes between pemetrexed and docetaxel. For example, Li et al. (2012) reported that pemetrexed had equivalent efficacy compared to docetaxel in the second-line treatment for Chinese NSCLC patients, which was similar to that showed in the study of Hanna et al. (2004). As for the safety, most of these studies are based on small samplings, which ensured inadequate statistical power to evaluate true safety of the two drugs. What's worse, some studies even produced conflicting results, especially in aspects of the toxicities. For example, Klionsky et al, (2012) reported that there was no significantly difference about thrombocytopenia between the two groups, while Shi X et al, (2013) reported pemetrexed caused higher rate of thrombocytopenia. More confusingly, Sun et al. (2013) reported an opposite result in their study. Another example is that Hanna, Li, Chen and Sun, et al (Hanna et al., 2004; Chen et al., 2008; Li et al., 2012; Sun et al., 2013) reported that there was no significantly difference on anemia between the two arms, but Socinski et al. (2010) reported that pemetrexed led to higher rate of anemia. After analyzing the pooled data, our review showed that pemetrexed caused less febrile neutropenia , but more thrombocytopenia toxicity compared with docetaxel, and there was no significant difference on anemia toxicity between the two groups. Therefore, performing a meta-analysis to evaluate the efficacy and safety of pemetrexed versus docetaxel in patients with advanced NSCLC is necessary.

Li et al. (2012) reported that pemetrexed seemed to slightly promote patients' average KPS score when comparing with docetaxel, Their subset analysis found that NSCLC patients who were older than 60 years old tended to benefit more from single pemetrexed treatment, since the study showed equivalent efficacies but less toxicity compared to docetaxel. Furthermore, their subset analysis showed that male patients are more likely to benefit from docetaxel while women from pemetrexed. Because of large proportion of data missing about subsets in current trials, we could't summarize more details into the forest plot. Hence future studies should not neglect subset analysis, such as age, gender, cancer stage, pathological subtypes, histological types and so on.

Certainly, there were some limitations in our study as well. For example, firstly, although pemetrexed and docetaxel have already been widely used as chemotherapy for advanced NSCLC, related RCT trial remain limited. Therefore, only a small number of studies were included in our review. Secondly, all the six trials included in our study didn't report allocation concealment, and four of them didn't report blinding and two of them were open-label trials, which might have resulted in an overestimation of the effect. Thirdly, all the samples of the included trials were too small, we are not sure about the effect which hasn't been overestimated or underestimated. Finally, the quality levels of most trials included were graded as "B", which may be at a high risk of bias. Considering all limitations above, it is not easy to control many

inherent risks from the base produced by the studies of interventions relating to pemetrexed and docetaxel. Hence the results of our review must be interpreted with caution.

In conclusion, as for the effectiveness in patients with advanced NSCLC, pemetrexed was almost as effective as docetaxel, and might increase the 3-yr survival rate. As for safety, pemetrexed led to lower rate of grade 3-4 febrile neutropenia, neutropenia, leukocytes, diarrhea and alopecia toxicity, and there were no statistically significant differences on anemia, ALT, fatigue, nausea, vomiting, neurosensory, stomatitis, pulmonary, rash, allergy and weight loss toxicity. It is worth to be pointed out is that pemetrexed led to higher rate of grade 3-4 thrombocytopenia toxicity.

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