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ORIGINAL ARTICLE

Meta-analysis of docetaxel-based doublet versus docetaxel alone as second-line treatment for advanced non-small-cell lung cancer

Wei-Xiang Qi · Zan Shen · Yang Yao

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Abstract
Purpose To compare docetaxel-based doublet with single-agent docetaxel as second-line treatment in non-small-cell lung cancer (NSCLC).
Methods We systematically searched for randomized clinical trials that compared docetaxel-based doublet with single-agent docetaxel in patients with histologically proven non-small-cell lung cancer. The primary end point was overall survival (OS). Secondary end points were progression-free survival, overall response rate, 1-year survival rate, and grade 3 or 4 toxicity. Data were extracted from the studies by two independent reviewers. The meta-analysis was performed by Stata version 10.0 software (Stata Corporation, College Station, TX, USA).
Results Eight randomized clinical trials (totally 2,126 patients) were eligible. Meta-analysis showed that there was significant improvement in PFS (HR 0.81, 95% CI 0.69–0.96, $P = 0.013$) and overall response rate (OR 1.42, 95% CI 1.13–1.80, $P = 0.03$) in docetaxel-based doublet group, compared with docetaxel alone, though the pooled HR for overall survival (HR 0.93, 95% CI 0.80–1.07, $P = 0.308$) showed no significant difference between the two groups. However, there were more incidences of grade 3 or 4 neutropenia (OR 1.2, 95% CI 1.00–1.45, $P = 0.05$), thrombocytopenia (OR 4.53, 95% CI 1.75–11.75, $P = 0.002$), and diarrhea (OR 1.78, 95% CI 1.16–2.74, $P = 0.008$) in docetaxel-based doublet group. With regard to the risk of grade 3 or 4 anemia (OR 1.95, 95% CI 0.62–6.17, $P = 0.25$), fatigue (OR 1.09, 95% CI 0.75–1.59, $P = 0.66$), and nausea and vomiting (OR 1.75, 95% CI 0.78–3.91, $P = 0.17$), there was no significant difference between the two groups.
Conclusions This was the first meta-analysis of docetaxel-based doublet versus single-agent docetaxel as second-line therapy in the treatment of non-small-cell lung cancer. The results indicated that docetaxel-based doublet therapy did not gain any benefit in survival but significantly improved PFS and better ORR versus single-agent docetaxel. However, more incidences of grade 3 or 4 neutropenia, thrombocytopenia, and diarrhea were observed in docetaxel-based doublet group.

Keywords Non-small-cell lung cancer · Second-line therapy · Docetaxel · Meta-analysis

W.-X. Qi · Z. Shen · Y. Yao (✉)
Department of Oncology, The Sixth People Hospital, Medical College of Shanghai Jiao Tong University, Shanghai 200233, China
e-mail: qwxzlk@163.com

Introduction

Lung cancer is one of the most common malignancies and the leading cause of cancer-related deaths in the world [1, 2], and more than 1.3 million new cases of lung cancer occur every year. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases, and most patients (80%) present with locally advanced or metastatic disease [3].

During the last decade, first-line chemotherapy for the treatment of patients with inoperable locally advanced or/and metastatic NSCLC has been substantially improved with the introduction of new cytotoxic agents such as vinorelbine, gemcitabine, paclitaxel, docetaxel, and pemetrexed. However, patients with non-small-cell lung cancer (NSCLC) inevitably relapse after first-line chemotherapy and require second-line chemotherapy. Docetaxel alone is the current standard as second-line chemotherapy

for advanced NSCLC. The recommended regimen of docetaxel 75 mg/m^2 given i.v. every 3 weeks as second-line therapy has been associated with median survival times of 5.7–7.5 months [4, 5] and is also associated with better quality-of-life outcomes compared with best supportive care [6]. Docetaxel monotherapy for recurrent NSCLC after first-line chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease control, and minimal survival advantage [4, 5].

A logical strategy for improving the efficacy of second-line treatment is to combine agents with different mechanism of action and toxicity. In first-line treatment, doublet chemotherapy is more effective than single agent, in terms of both objective response and OS [7]. Several randomized trials comparing docetaxel-based doublets with single-agent docetaxel as second line have been conducted in recent years. Most of these trials were characterized by a small sample size, with inadequate statistical power to exclude potentially clinically relevant differences in efficacy.

This meta-analysis was conducted to give an overview of the results of all eligible randomized trials comparing docetaxel-based doublet with single-agent docetaxel with the aim of investigating whether docetaxel-based doublet is more effective than single-agent docetaxel as second-line therapy in the treatment of patients with advanced or metastatic NSCLC. To our knowledge, so far, there has been no meta-analysis with a greater power of statistical comparisons to detect treatment differences.

Materials and methods

Search strategy

We searched, without language restrictions, PubMed (up to March 2011), Embase (1980 to March 2011), and the Cochrane Register of Controlled Trials using various combinations of different terms "NSCLC", "docetaxel", "taxotere", "randomized", and "second-line therapy". We also looked at posters from the annual meetings of the European Society of Medical Oncology (ESMO) and the American Society of Medical Oncology (ASCO) in the past 10 years.

Study selection

The relevant clinical trials were manually selected carefully based on the following criteria: (1) trails comparing docetaxel-based doublet with single-agent docetaxel; (2) patients were pathologically confirmed of NSCLC and previously treated; (3) randomized controlled trial (RCT); and (4) the study has included sufficient data for extraction.

Data extraction

Two independent investigators reviewed the publications and extracted the data. The following information was extracted from each article: (1) basic information from papers such as year of publication, journal name, and author name. (2) characteristics of patients such as age and study duration. (3) information of study designation such as sample size per group, study design, randomization scheme, inclusion criteria, and type of end point used. (4) information of treatment such as treatment modality, dose of chemotherapy, withdrawals, median overall survival (OS), 1-year survival, overall response rate, and adverse events (AEs). Available information was extracted, recorded to a data collection form, and entered into electronic database.

Data analysis

The analysis was undertaken on an intention-to-treat basis: patients were analyzed according to treatment allocated, irrespective of whether they received that treatment. The outcomes used were (1) OS, defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive; (2) PFS, defined as the time from random assignment to first documented progression; and (3) ORR, defined as the sum of partial and complete response rates according to the Response Evaluation Criteria in Solid Tumors [8].

Statistical analysis of the overall hazard ratio (HR) for OS and PFS, the odds ratio (OR) for overall response rate, 1-year survival rate, and grade 3 or 4 AEs was calculated using Stata version 10.0 software (Stata Corporation, College Station, TX, USA). When OS could not be extracted from the original reports directly in several RCTs, we deciphered them from the survival curve as reported by Parmar et al. [9]. Between-study heterogeneity was estimated using the χ^2-based Q statistic [10]. Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.05$ or $I^2 > 50\%$. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. Sources of heterogeneity were appraised by subgroup stratification analysis, based on several study characteristics, such as ethnicity and source of control individuals (population or hospital based). A statistical test with a P value less than 0.05 was considered significant. HR > 1 reflects more deaths or progression in docetaxel-based doublets group, and OR > 1 indicates

more toxicities, 1-year survival rate, and overall response rate in docetaxel-based doublets group and vice versa. The presence of publication bias was evaluated using the Begg and Egger tests [11, 12]. All P values were two sided. All CIs had a two-sided probability coverage of 95%.

Assessment of study quality

An open assessment of the trials was performed using the methods reported by Jadad and colleagues [13], which assessed the trials according to the following three questions: (1) whether reported an appropriate randomization method (0–2 scores); (2) whether reported an appropriate blinding method (0–2 scores); (3) whether reported withdrawals and dropouts (0–1 scores).

Results

Study identification and eligibility

After the selection procedure (Fig. 1), eight trials were considered eligible. The characteristics of these studies are listed in Table 1. Of these eight trials, three were phase III trials [14, 17, 18] and five were phase II trials [15, 16, 19–21]; a total of 2,126 patients from 17 clinical studies were available for analysis. The docetaxel was combined with drugs including vandetanib, gemcitabine, vinorelbine, irinotecan, carboplatin, and S-1. The total number of each trial varied from 60 to 1,391; Jadad score ranged from 3 points to 5 points.

Efficacy

Overall survival

The pooled hazard ratio for OS did not show significant difference in overall survival between docetaxel-based doublets with single-agent docetaxel group (HR 0.93, 95% CI 0.80–1.07; $P = 0.308$ Fig. 2). There is no significant heterogeneity ($P = 0.989$), and the pooled HR for OS was performed using fixed-effort model.

Progression-free survival

The pooled hazard ratio for PFS showed docetaxel-based doublet therapy significantly improved PFS (HR 0.81, 95% CI 0.69–0.96, $P = 0.013$, Fig. 3). There was significant heterogeneity ($P = 0.037$), and the pooled HR for PFS was performed using random-effort model.

Overall response rate

The pooled OR for overall response rate showed docetaxel-based doublet group significantly improved overall response rate (OR 1.42, 95% CI 1.13–1.80, $P = 0.03$, Fig. 4). There was no significant heterogeneity ($P = 0.558$), and the pooled OR for overall response was performed using fixed-effort model.

1-year survival rate

The pooled OR for 1-year survival rate showed docetaxel-based doublet group did not significantly improved 1-year

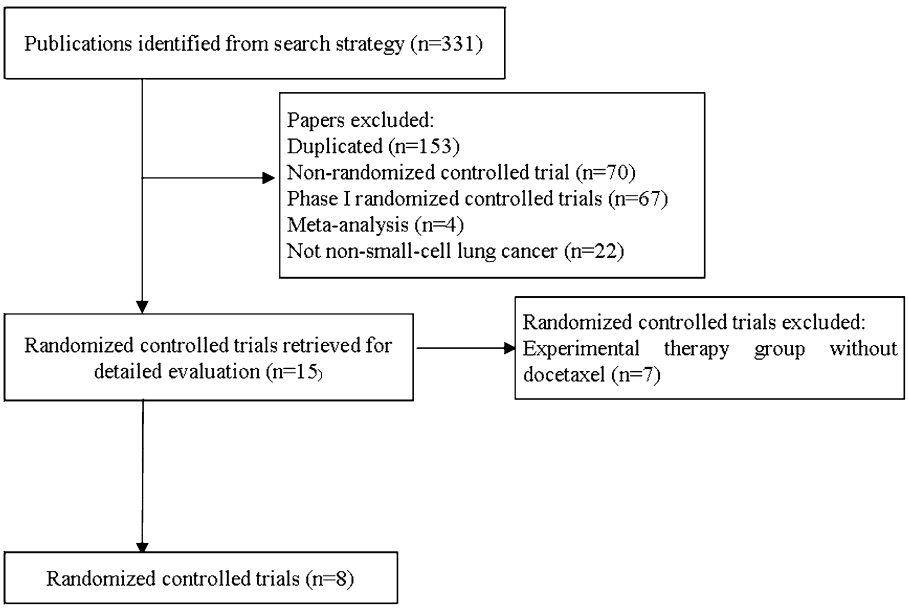

Fig. 1 Studies eligible for inclusion in the meta-analysis

Table 1 Baseline characteristics of included studies

Authors	Year	Design	Patients, no.	Comparison arms	Comments	Jadad score
Herbst et al. [14]	2010	Phase III	1,391	Vandetanib plus docetaxel vs. docetaxel	The addition of vandetanib to docetaxel provides a significant improvement in PFS	5
Gebbia et al. [15]	2009	Phase II	84	Docetaxel plus gemcitabine or vinorelbine vs. docetaxel	Docetaxel alone is still the standard second-line treatment for NSCLC	3
Pectasides et al. [16]	2005	Phase II	130	Docetaxel plus irinotecan vs. docetaxel	The administration of irinotecan with docetaxel in platinum-refractory NSCLC prolonged TTP	3
Takeda et al. [17]	2009	Phase III	130	Docetaxel plus gemcitabine vs. docetaxel	Prematurely interrupted for relevant toxicity	3
Pallis et al. [18]	2010	Phase III	132	Docetaxel plus carboplatin vs. docetaxel	The docetaxel/carboplatin combination was associated with a significant clinical benefit in terms of PFS	3
Heymach et al. [19]	2007	Phase II	127	Vandetanib plus docetaxel vs. docetaxel	The addition of vandetanib to docetaxel provides a significant improvement in PFS	5
Wachters et al. [20]	2005	Phase II	108	Docetaxel plus irinotecan vs. docetaxel	Addition of irinotecan to docetaxel does not improve response rate and increases gastrointestinal toxicity	3
Segawa et al. [21]	2010	Phased II	60	Docetaxel plus S-1 vs. docetaxel	Docetaxel alone is still the standard second-line treatment for NSCLC	3

survival rate (OR 1.09, 95% CI 0.92–1.28, $P = 0.328$, Fig. 5). There was no significant heterogeneity ($P = 1$), and the pooled OR for 1-year survival rate was performed using fixed-effort model.

Safety

There were more incidences of grade 3 or 4 neutropenia, thrombocytopenia, and diarrhea in docetaxel-based doublet group. With regard to the risk of grade 3 or 4 anemia, fatigue, nausea, and vomiting, equivalent frequencies were found between the two groups (Table 2).

Publication bias

A number of steps were included in the study design to minimize the potential for publication bias. Firstly, the search strategy was extensive; secondly, papers were selected strictly according to inclusion criteria; thirdly, publication bias was detected by several methods. Publication bias was not found according to funnel plot (Begg's test, $P = 0.621$; Egger test, $P = 0.223$; Fig. 6).

Discussion

Platinum-based chemotherapy was the standard first-line treatment for locally advanced or metastatic non-small-cell lung cancer (NSCLC). However, nearly all patients exposed to first-line chemotherapy eventually experience progression. At present, docetaxel alone was the current standard as second-line chemotherapy for advanced NSCLC, but the benefit was modest.

In 2009, Di Maio et al. [22] for the first time conducted a meta-analysis to investigate whether doublet chemotherapy was more effective than single agent as second-line treatment of NSCLC; the results showed that doublet chemotherapy significantly increased response rate (RR, 2.24; 95% CI, 1.43–3.53) and progression-free survival (HR, 0.79; 95% CI, 0.68–0.91), but was more toxic and did not improve overall survival (HR, 0.92; 95% CI, 0.79–1.08). Although the study was a meta-analysis of individual patient's data, chemotherapy of included studies consisted of docetaxel, irinotecan, cisplatin or pemetrexed, and different drugs included in the study might affect the results; therefore, we conducted this meta-analysis focused on docetaxel or docetaxel-based doublet therapy. The aim was to investigate whether docetaxel-based doublet was superior to single-agent docetaxel as second-line treatment in non-small-cell lung cancer.

The systematic literature search identified eight relevant RCTs comparing docetaxel-based doublet versus docetaxel alone, which was based on individual patient data from

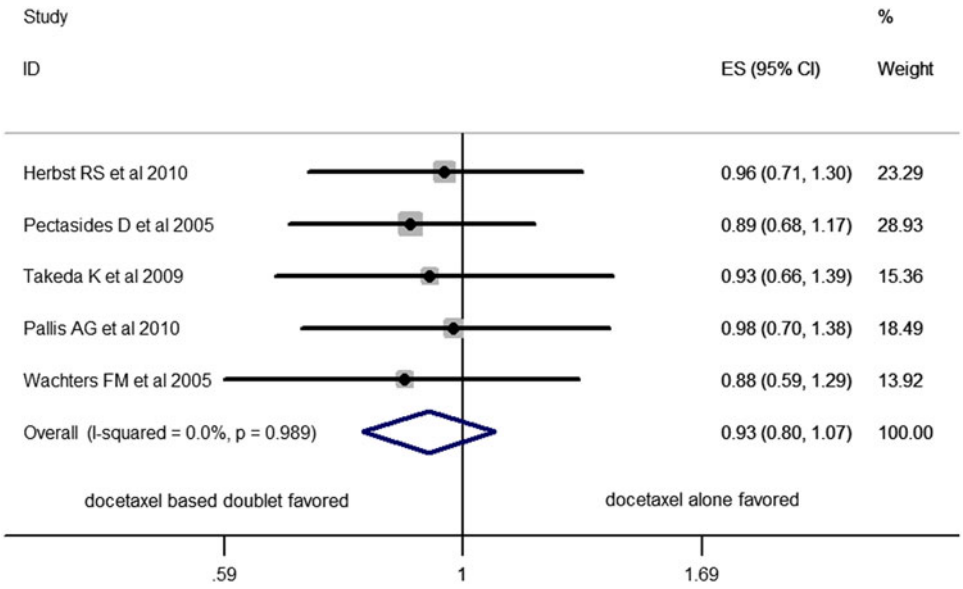

Fig. 2 Fixed-effects model of hazard ratio (95% confidence interval) of overall survival associated with docetaxel-based doublet compared with docetaxel alone

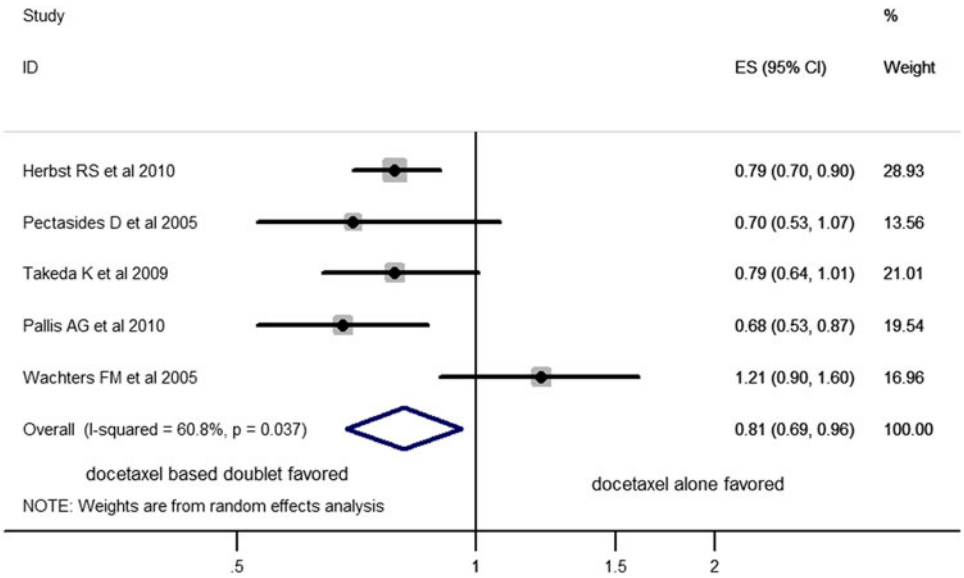

Fig. 3 Random-effects model of hazard ratio (95% confidence interval) of progression-free survival associated with docetaxel-based doublet compared with docetaxel alone

patients enrolled in RCTs done by independent investigators. The meta-analysis showed a markedly increased PFS (HR 0.81, 95% CI 0.69–0.96, $P = 0.013$) and overall response rate (OR 1.42, 95% CI 1.13–1.80, $P = 0.03$) in patients who received docetaxel-based doublets therapy. However, this increase in activity did not translate in increase in OS and 1-year survival compared with docetaxel single-agent treatment, which were consistent with Di Maio et al.' study.

Toxicity was particularly relevant in second-line treatment of advanced NSCLC, given the potential negative impact on benefit ratio and quality of life. Finding of our study indicated that there were more incidences of grade 3–4 neutropenia (OR 1.2, 95% CI 1.00–1.45, $P = 0.05$), thrombocytopenia (OR 4.53, 95% CI 1.75–11.75, $P = 0.002$), and diarrhea (OR 1.78, 95% CI 1.16–2.74, $P = 0.008$) in docetaxel-based doublet therapy. Compared with Di Maio et al.' study, there were more incidences of grade 3–4 diarrhea, but less incidences of grade 3–4 anemia in combination therapy group.

There were limitations in our analysis that should be considered when interpreting the data. First, the difference in treatment schedules contributes to increase the clinical heterogeneity of the meta-analysis, which makes the interpretation of a meta-analysis more problematic, and the drugs added to docetaxel in combination arm were different. Two trials were vandetanib, a newly targeted drug. Other trials were cytotoxic drugs. But clinical heterogeneity may improve the generalizability of the observed heterogeneity. Secondly, lack of blinding might have

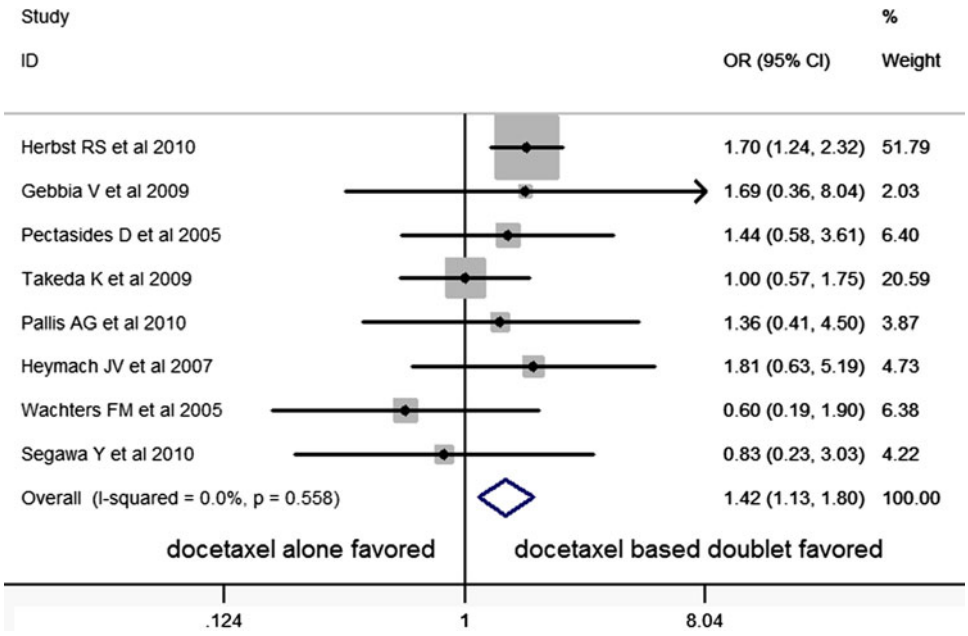

Fig. 4 Fixed-effects model of odds ratio (95% confidence interval) of overall response rate associated with docetaxel-based doublet compared with single-agent docetaxel

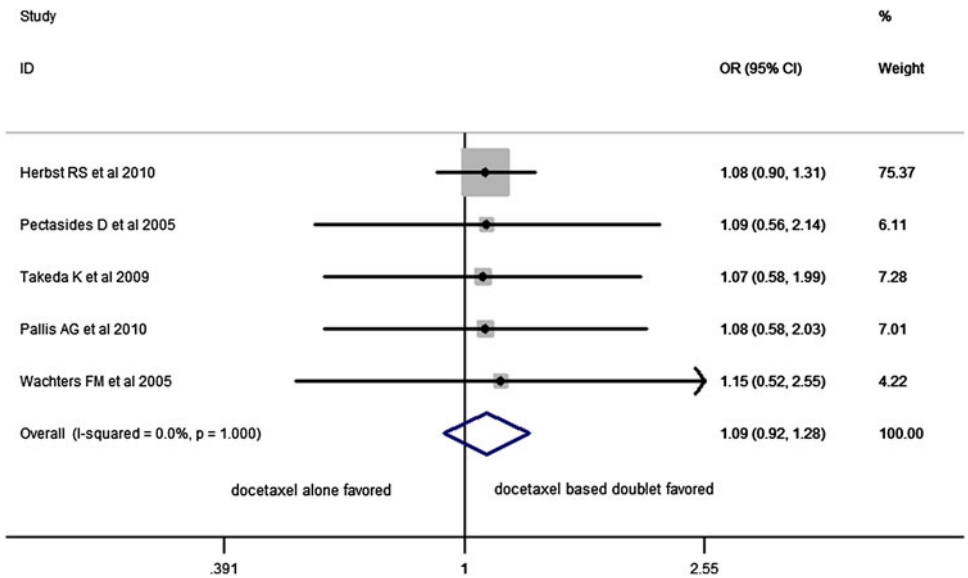

Fig. 5 Fixed-effects model of odds ratio (95% confidence interval) of 1-year survival rate associated with docetaxel-based doublet compared with single-agent docetaxel

Table 2 Outcome of grade 3 or 4 toxicity meta-analysis comparing docetaxel-based doublet with versus single-agent docetaxel

Toxicity	Trials	Docetaxel-based therapy with estramustine	Docetaxel-based therapy without estramustine	Heterogeneity		OR (95% CI)	*P* value
				P value	I^2		
Grade 3–4 neutropenia	7	334/1,061	276/1,029	0.11	42%	1.2 (1.00–1.45)	0.05
Grade 3–4 anemia	6	49/975	40/988	0.005	70.1%	1.95 (0.62–6.17)	0.25
Grade 3–4 thrombocytopenia	5	23/286	4/298	0.68	0	4.53 (1.75–11.75)	0.002
Grade 3–4 diarrhea	7	62/1,061	33/1,029	0.47	0	1.78 (1.16–2.74)	0.008
Grade 3–4 nausea and vomiting	4	18/253	9/218	0.56	0	1.75 (0.78–3.91)	0.17
Grade 3–4 fatigue	6	61/1,009	54/973	0.38	6%	1.09 (0.75–1.59)	0.66

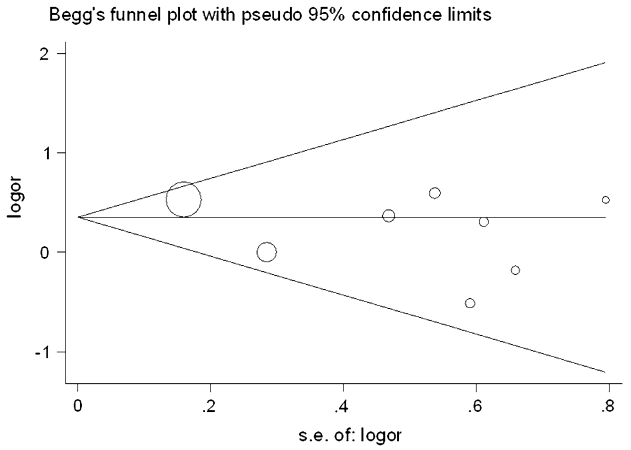

Fig. 6 Funnel plot of publication bias in the meta-analysis

resulted in an overestimate of the effects, although these trials included in the meta-analysis reported adequate randomization. Thirdly, as with any meta-analysis, the results were affected by the quality of the individual studies. Eight of the studies in our meta-analysis were RCTs, and while the number of included patients is small, insufficient patients might potentially limit detection of docetaxel-based doublet therapy effects. Finally, since the studies included in this analysis were from the West, the results need confirmation in Asia.

In conclusion, our meta-analysis did not support the use of docetaxel combination chemotherapy as second-line treatment for patients with NSCLC, based on an increase in toxicity without any gain in survival.

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