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Original Article

Efficacy and safety of non-platinum based doublets chemotherapy compared with platinum-based doublets chemotherapy in advanced non-small-cell lung cancer (NSCLC): a meta-analysis

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Abstract: Purpose: The aim of this study was to compare the efficacy and safety between doublets of third generation agents (non-platinum) and doublets of platinum plus a third-generation agent (platinum-based) for the therapy of advanced non-small-cell lung cancer (NSCLC). Methods: A meta-analysis was performed to evaluate studies comparing non-platinum based doublets with platinum-based doublets in advanced NSCLC using the fixed effects model or the random effects model. 12 studies including 3366 patients were eligible for the analysis of overall response rate, stable disease, progressive disease, 1-year survival rate and grade 3-4 toxicities. The results of meta-analysis were expressed as risk ratio (RR) with their corresponding 95% confidence intervals (95% CI). A subgroup meta-analysis was performed by comparing Gemcitabine-Docetaxel doublets with platinum-based doublets. Results: Twelve studies were eligible and evaluated in the meta-analysis. Results demonstrated that the efficacy of overall response rate, stable disease, progressive disease and 1-year survival rate have no significant difference between non-platinum based doublets and platinum-based doublets (RR=1.06, 95% CI=0.94-1.18, P=0.33; RR=0.94, 95% CI=0.84-1.06, P=0.32; RR=1.02, 95% CI=0.94-1.10, P=0.64; RR=1.00, 95% CI=0.90-1.11, P=1.00, respectively). Non-platinum based doublets significantly improved grade 3-4 neutropenia, anemia and nausea/vomiting (RR=1.50, 95% CI=1.27-1.77, P<0.00001; RR=2.61, 95% CI=1.52-4.49, P=0.0005; RR=3.60, 95% CI=1.99-6.48, P<0.0001; respectively). The other grade 3-4 toxicities were comparable between the two groups. Subgroup analysis results were correspondence with the overall research. Conclusion: Non-platinum based doublets showed similar efficacy with platinum-based doublets, but significantly improved grade 3-4 neutropenia, anemia and nausea/vomiting. Subgroup analysis of Gemcitabine-Docetaxel doublets versus platinum-based doublets showed the same results.

Keywords: NSCLC, chemotherapy, platinum, third-generation agent, gemcitabine, docetaxel

Introduction

Non-small cell lung cancer is the most common type of lung cancer and accounts for at least 80% of all lung cancer cases [1]. Unfortunately most NSCLC patients are diagnosed at an advanced stage, approximately 25%-30% patients present a locally advanced disease, and approximately 40%-50% patients present a metastatic disease [2].

Chemotherapy including third-generation agents combination and platinum plus third-generation agent combination are major treatments for advanced NSCLC. Platinum-based, especially cisplatin-based combination with third-generation agent therapies emerged as the worldwide standard treatment for advanced NSCLC with a good performance status and advanced disease, and were recommended as the first-line chemotherapy for advanced NSCLC by ASCO and NCCN [3-6]. However, platinum-based regimens have considerable toxicities including nausea and vomiting, renal toxicity, ototoxicity and neuropathy and are intolerant for a part of patients [7]. Third-generation agents such as gemcitabine, docetaxel, vinorebine and pemetrexed have been developed in

the past decades and have a promising levels of anti-tumor activities. Several randomized clinical trials have compared platinum-based regimens with non-platinum based regimens and indicated that non-platinum based chemotherapy was comparable with platinum-based chemotherapy for efficacy, but non-platinum based chemotherapy with less toxicities. However, the results were still inconclusive.

The present meta-analysis aims to quantify the treatment efficacy and safety of non-platinum based doublets versus platinum-based doublets in advanced NSCLC using randomized clinical trials. As the combination of gemcitabine and docetaxel is the most common third-generation combination therapy and presents promising efficacy and low toxicity, a subgroup analysis by gemcitabine+docetaxel doublets versus platinum-based doublets was conducted. The main outcomes of the analysis were overall response rate, stable disease, progressive disease, 1-year survival rate and grade 3-4 toxicities.

Methods

Search strategy and selection criteria

A literature search was performed in PubMed database, Embase database and Cochrane library. References lists of original articles were also examined for additional relevant trials. The search strategy included terms for NSCLC, gemcitabine, docetaxel, pemetrexed, vinorelbine and cisplatin (or carboplatin, oxaliplatin) and was limited to randomized controlled trials and human studies. The published language was limited to English and published years were not limited.

Trials that met all the following criteria were included in the analysis: randomized controlled trials, patients must be cytologically or pathologically confirmed of NSCLC, patients must be chemotherapy-naïve, comparing efficacy and safety of non-platinum based doublets (two third-generation agents combination) with platinum-based doublets (cisplatin/carboplatin/oxaliplatin combined with a third-generation agent). Studies using triplet regimens and sequential therapy were excluded. Treatments of NSCLC combined with other diseases or transfer parts, data not clear and could not get in touch with authors and reviews without original data were also excluded.

Selection and quality assessment

Studies were evaluated for eligibility and quality by two investigators independently and any discrepancies were resolved by consensus with a third expert. When more than one publication was identified from the same clinical trial, the most recent or complete report of that trial was used. The bias risk of trials was assessed with the components recommended by the Cochrane Collaboration: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other bias [8].

Data extraction and synthesis

All the data were independently extracted by two investigators with the use of standardized data-abstraction forms. Disagreements were resolved by discussion with an independent expert. The following information was sought from each paper, first author, publication year, numbers of patients, gender, age, diagnostic criteria, chemotherapy regimens, treatment schedules, study outcomes or endpoints (such as overall response rate, stable disease, progressive disease and 1-year survival rate) and adverse effects (grade 3-4 toxicities).

Statistical analysis

The meta-analysis was performed using the Review Manager 5.3 (RevMan) software (Cochrane Collaboration, Copenhagen, Denmark). Dichotomous variables were analyzed with estimation of risk ratio together with a 95% CI, and the continuous variables were analyzed with weighted mean difference (WMD) and a 95% CI. Pooled effect was calculated using either the fixed effects model or the random effects model. Statistical heterogeneity between trials was evaluated by I^2 and *P* value, with significance being set at $P<0.05$ and $I^2>50\%$. Sensitivity analysis was also performed by excluded some unique studies and test with total studies. Publication bias was assessed visually with a funnel plot.

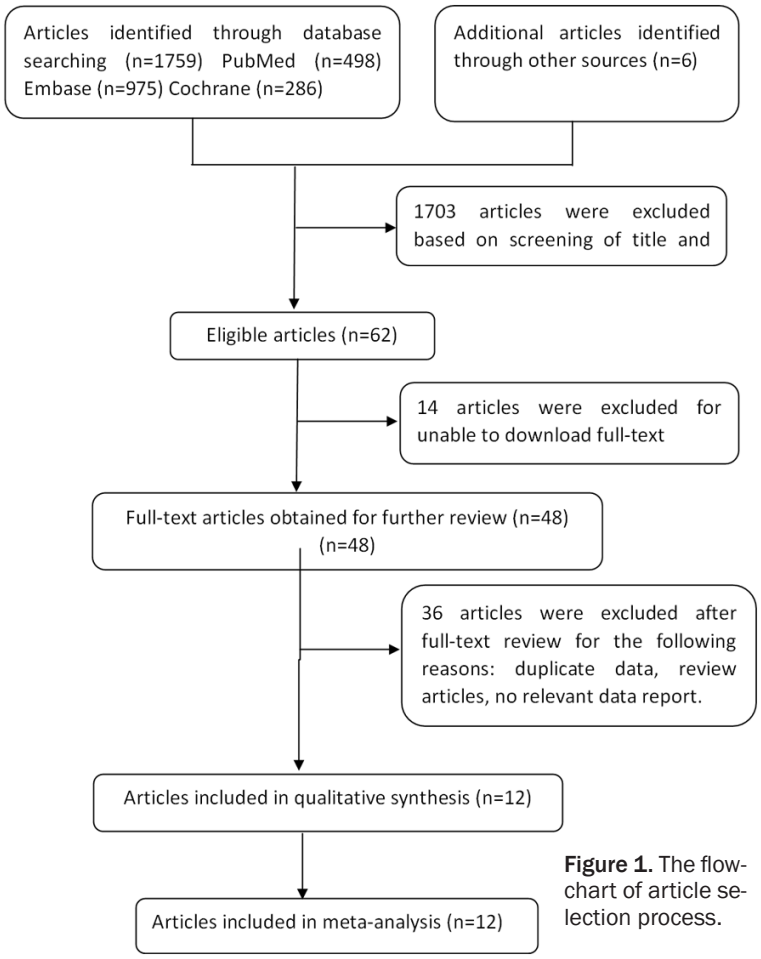


Figure 1. The flowchart of article selection process.

Results

Literature search, selection and assessment

The process of searching and evaluating the articles for inclusion in the meta-analysis was shown in **Figure 1**. One thousand seven hundred and fifty nine articles were identified originally through database searching, and 6 additional articles were identified through other sources. Sixty two records were eligible after screening of title and abstract. Fourteen articles were excluded for unable to download full-text and forty eight full-text articles were obtained for further review. Another thirty six articles were excluded after reviewing full-text for the following reasons: duplicate data, review articles and no relevant data report. Twelve articles were ultimately assessed and analyzed [9-20].

The bias risk of articles assessed with the components recommended by the Cochrane Collaboration is shown in **Figure 2**.

Baseline characteristics of the 12 studies

All the 12 studies meet the inclusion criteria. Five [11, 13-16] of the 12 studies were phase III clinical trials and four [9, 12, 18, 20] of the 12 studies were phase II clinical trials. The other three [10, 17, 19] of the 12 studies were randomized trials. The detailed regimens and baseline characteristics of the 12 studies were listed in **Table 1**.

Meta-analysis and subgroup analysis

3366 patients in 12 studies were evaluated in the meta-analysis, of whom 1678 were included in the non-platinum based doublets and 1688 patients were included in the platinum-based doublets. As shown in **Table 1**, the distribution of baseline characters like gender, age, diagnostic criteria and treatment schedules were found to be quite homogeneous. The pooled analysis data were used to evaluate the difference of efficacy (including overall response rate, stable disease, progressive disease and 1-year survival rate) and safety (including neutropenia, febrile neutropenia, leucopenia, anemia, thrombopenia, nausea/vomiting, constipation and diarrhea) between non-platinum based doublets and platinum-based doublets. A subgroup analysis comparing Gemcitabine-Docetaxel doublets with platinum-based doublets was evaluated in a further meta-analysis. 6 studies [12-14, 17-19] comparing Gemcitabine-Docetaxel doublets with platinum-based doublets were identified and evaluated in the subgroup analysis.

Overall response rate

Eleven of the 12 studies reported overall response rate data. The pooled RR for overall response rate did not display a difference between non-platinum doublets and platinum-

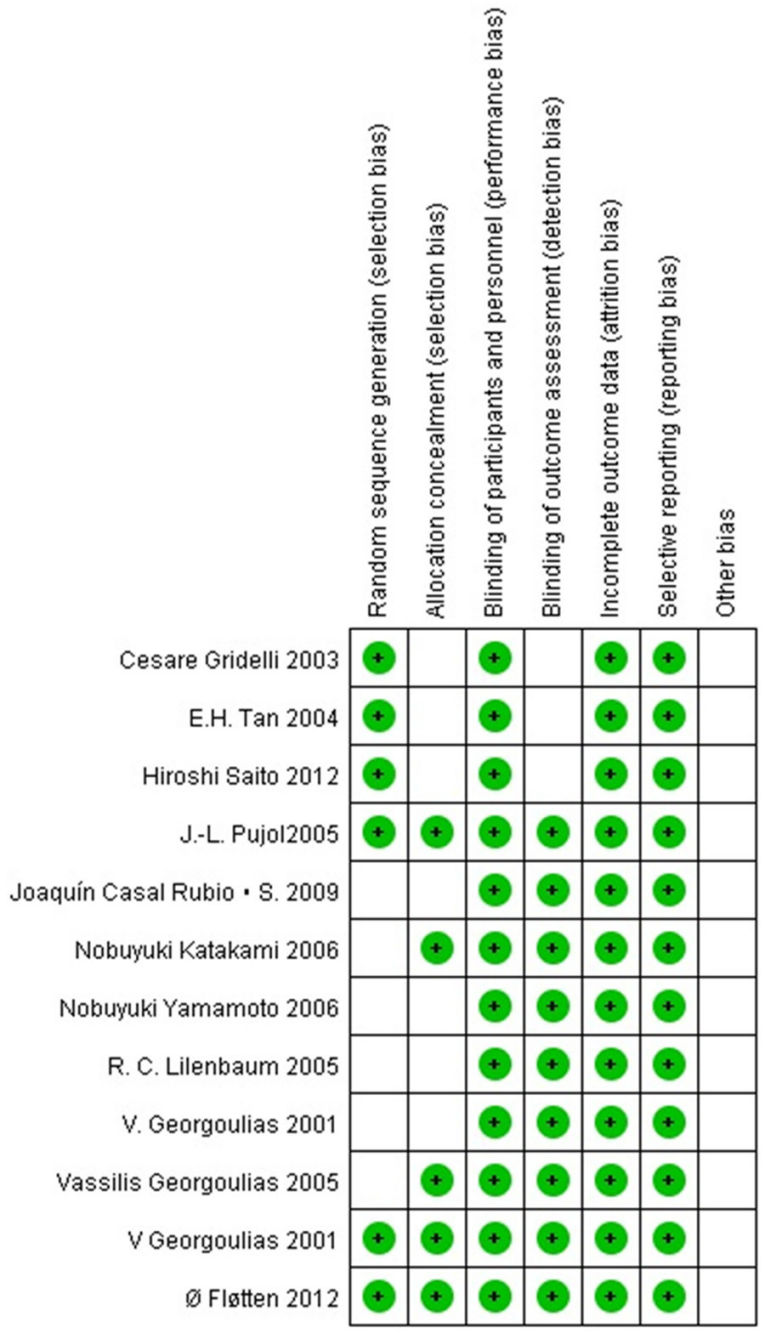


Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included studies. "-", high risk of bias; "+", low risk of bias; blank, unclear of bias.

based doublets (RR=1.06, 95% CI=0.94-1.18, P=0.33, **Figure 3A**). There was no significant heterogeneity between trials (P=0.52, I^2=0%), and the pooled RR for overall response rate was performed using the fixed effects model. Subgroup analysis by Gemcitabine-Docetaxel doublets compared with platinum-based doublets also did not display a difference of overall response rate (RR=1.08, 95% CI=0.94-1.24, P=0.27, **Figure 4A**).

Stable disease

Nine of the 12 studies reported stable disease data. The pooled RR for stable disease did not display a difference between non-platinum based doublets and platinum-based doublets (RR=0.94, 95% CI= 0.84-1.06, P=0.32, **Figure 3B**). There was no significant heterogeneity between trials (P=0.29, I^2=17%), and the pooled RR for overall response rate was performed using the fixed effects model. Subgroup analysis by Gemcitabine-Docetaxel doublets compared with platinum-based doublets also did not display a difference of stable disease (RR= 0.90, 95% CI=0.77-1.04, P= 0.15, **Figure 4B**).

Progressive disease

Nine of the 12 studies reported progressive disease data. The pooled RR for progress disease did not display a difference between non-platinum based doublets and platinum-based doublets (RR= 1.02, 95% CI=0.94-1.10, P= 0.64, **Figure 3C**). There was no significant heterogeneity between trials (P=0.67, I^2= 0%), and the pooled RR for overall response rate was performed using the fixed effects model. Subgroup analysis by Gemcitabine-Docetaxel doublets compared with platinum-based doublets also did not display a difference of progressive disease (RR=1.03, 95% CI=0.90-1.17, P=0.67, **Figure 4C**).

1-year survival rate

Nine of the 12 studies reported 1-year survival rate data. The pooled RR for 1-year survival

Table 1. Baseline characteristics of the 12 studies included in the meta-analysis

Studies	Regimens	No. Of patients	Age, range (years)	Male/ Female	Diagnostic criteria	Treatment schedules	Outcomes
Cesare Gridelli 2003	Gem+Vin	251	61 (37-74)	159/41	Histologically or cytologically	3 weeks*6	ORR, SD, PD, Ane, Leu, Neu, Thr, N/V
	Cis-based	250	62 (35-72)				
E.H. Tan 2004	Vin+Gem	157	59 (29-74)	238/78	Histologically or cytologically	3 weeks*2	ORR, SD, PD, 1-y SR, Neu, FNeu, Leu, Ane, Thr, N/V, Dia, Con
	Vin+Car	159	60 (30-75)				
Hiroshi Saito 2012	Gem+Vin	45	67 (34-76)	61/13	Histologically or cytologically	3 weeks*6	ORR, 1-y SR, Leu, Neu, FNeu, Ane, Thr, N/V, Dia
	Car+Pac	44	65 (20-77)				
J.L. Pujol 2005	Gem+Doc	155	60 (37-75)	248/63	Histologically or cytologically	3 weeks*8	ORR, SD, PD, 1-y SR, FNeu, Neu, Ane, Thr
	Cis+Vin	156	57 (39-74)				
Joaquín Casal RubioS. 2009	Gem+Doc	52	61.4 (52.4-70.4)	91.6/16.4	Histologically or cytologically	3 weeks*6	ORR, SD, PD, Ane, Leu, Neu, FNeu, N/V
	Cis+Gem	56	59.9 (50.1-69.7)				
Nobuyuki Katakami 2006	Gem+Doc	65	61 (49-75)	86/45	Histologically or cytologically	3 weeks*(2-3)	ORR, SD, PD, 1-y SR, Neu, FNeu, Leu, Thr, Ane, Dia, N/V
	Cis+Doc	68	65 (31-75)				
Nobuyuki Yamamoto 2006	Gem+Vin	64	62 (36-74)	85/43	Histologic subtypes	3 weeks*(3-6)	ORR, SD, PD, 1-y SR, Leu, Neu, Ane, Thr, FNeu, Dia, Con, N/V
	Car+Gem	64	60 (30-74)				
R.C. Lilenbaum 2005	Vin+Gem	82	66 (42-86)	93.17/71.83	Histologically or cytologically	3 weeks*6	ORR, SD, 1-y SR, Ane, Neu, Thr, Dia, Con, N/V
	Car+Pac	83	63 (48-86)				
V. Georgoulias 2001	Doc+Gem	155	62 (39-76)	262/34	Histologically or cytologically	3 weeks*(3-6)	ORR, PD, 1-y SR, Neu, Dia, Con, N/V
	Cis+Doc	162	60 (38-76)				
Vassilis Georgoulias 2005	Doc+Gem	209	63 (36-75)	365/48	Histologically or cytologically	3 weeks*(6-9)	ORR, SD, PD, 1-y SR, Ane, Neu, Thr, N/V, Dia
	Cis+Vin	204	64 (46-75)				
V. Georgoulias 2001	Gem+Doc	222	62 (39-75)	358/48	Histologically or cytologically	3 weeks*6	ORR, SD, PD, 1-y SR, Ane, Neu, Thr, N/V, Dia, Con
	Cis+Doc	219	61 (36-75)				
Ø Fløtten 2012	Vin+Gem	221	65 (44-87)	252/185	Histologically or cytologically	3 weeks*3	Ane, Neu, Thr, N/V, FNeu, Con
	Car+Vin	223	65 (43-83)				

Gem indicates gemcitabine; Vin, vinorelbine; Doc, docetaxel; Pac, paclitaxel; Cis, cisplatinum; Car, carboplatin; ORR, Overall response rate; SD, Stable disease; PD, Progressive disease; 1-y SR, 1-year Survival Rate; Neu, Neutropenia; FNeu, Febrile neutropenia; Leu, Leucopenia; Ane, Anemia; Thr, Thrombopenia; N/V, Nausea/Vomiting; Con, Constipation; Dia, Diarrhea.

rate showed no difference between non-platinum doublets and platinum-based doublets (RR=1.00, 95% CI=0.90-1.11, P=1.00, **Figure 3D**) using a fixed effects model, and there was no significant heterogeneity (P=0.28, I^2=19%). Subgroup analysis by Gemcitabine-Docetaxel doublets compared with platinum-based doublets also did not display a difference of 1-year survival rate (RR=1.03, 95% CI=0.92-1.17, P=0.59, **Figure 4D**).

Grade 3-4 toxicities

As shown in **Figure 5**, respectively, grade 3-4 hematologic toxicity such as neutropenia (a), febrile neutropenia (b), leucopenia (c), anemia (d) and thrombopenia (e), and grade 3-4 non-hematologic toxicity such as nausea/vomiting (f), constipation (g) and diarrhea (h) between non-platinum based doublets and platinum-based doublets were analyzed. Grade 3-4 neutropenia, anemia and nausea/vomiting (RR=1.50, 95% CI=1.27-1.77, P<0.00001; RR=2.61, 95% CI=1.52-4.49, P=0.0005; RR=3.60, 95% CI=1.99-6.48, P<0.0001; respectively) were significantly improved in non-platinum based doublets compared with platinum-based doublets. Grade 3-4 febrile neutropenia, leucopenia, thrombopenia, constipation and diarrhea (RR=1.72, 95% CI=0.93-3.18, P=0.08; RR=1.35, 95% CI=0.92-1.97, P=0.13; RR=1.44, 95% CI=0.64-3.22, P=0.38; RR=1.05, 95% CI=0.40-2.77, P=0.92; RR=2.13, 95% CI=0.95-4.78, P=0.07; respectively) showed no significant difference between non-platinum based doublets and platinum-based doublets. There was significant heterogeneity between trials and the pooled RR for grade 3-4 toxicities were performed using the random effects model. In subgroup analysis, as shown in **Figure 6**, grade 3-4 neutropenia (a), anemia (b) and nausea/vomiting (c) (RR=1.43, 95% CI=1.14-1.80, P=0.002; RR=3.34, 95% CI=2.06-5.42, P<0.00001; RR=5.76, 95% CI=3.32-10.00, P<0.00001; respectively) were also significantly improved in Gemcitabine+Docetaxel doublets compared with platinum-based doublets. Grade 3-4 thrombopenia (d) and diarrhea (e) (RR=0.65, 95% CI=0.25-1.68, P=0.37; RR=

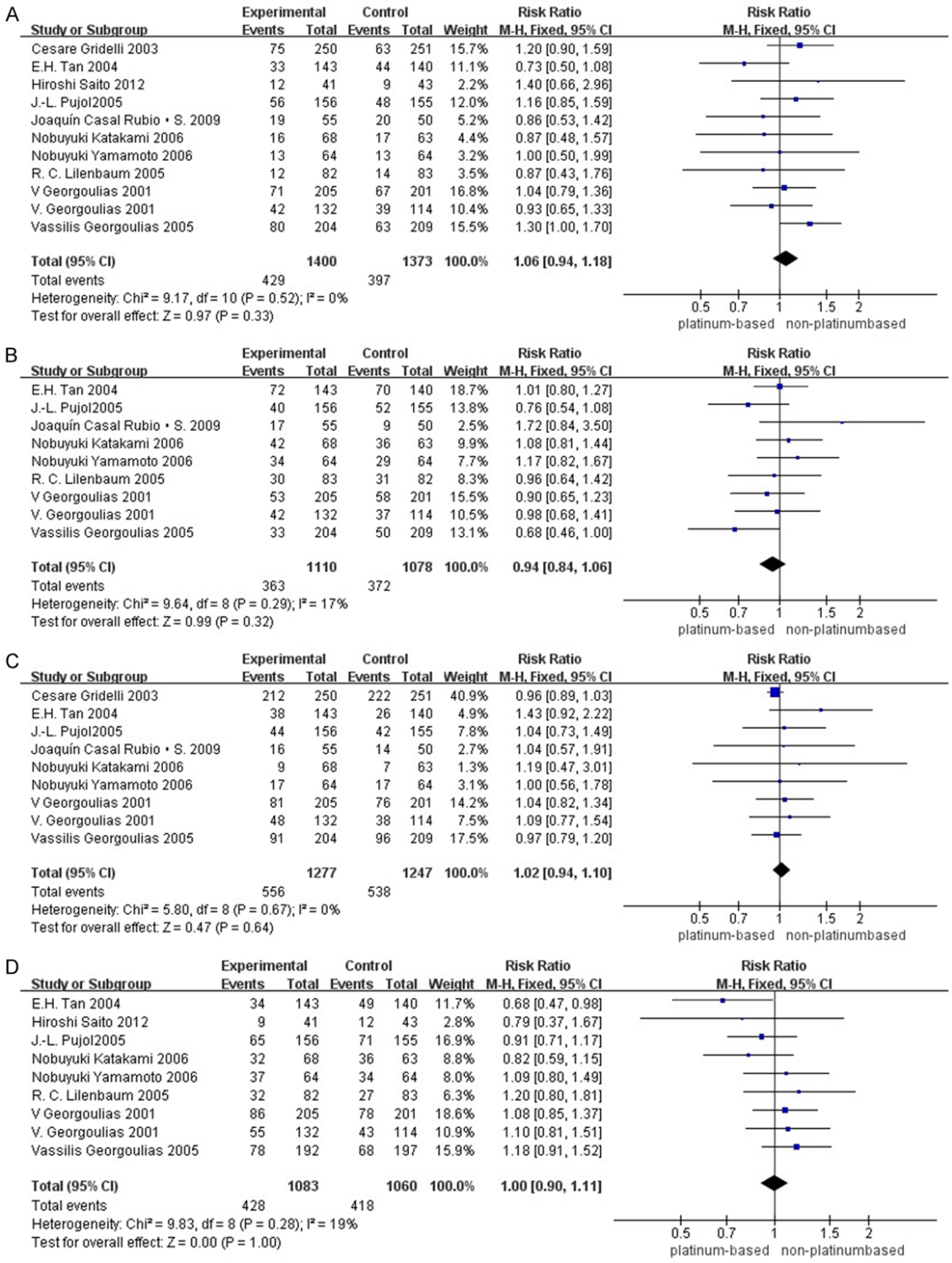


Figure 3. Comparison of the overall response rate (A), stable disease (B), progressive disease (C) and 1-year survival rate (D) between non-platinum based doublets and platinum-based doublets. Experimental, platinum-based; Control, non-platinum based.

2.53, 95% CI=0.74-8.64, P=0.14; respectively) showed no significant difference between Gemcitabine-Docetaxel doublets and platinum-based doublets.

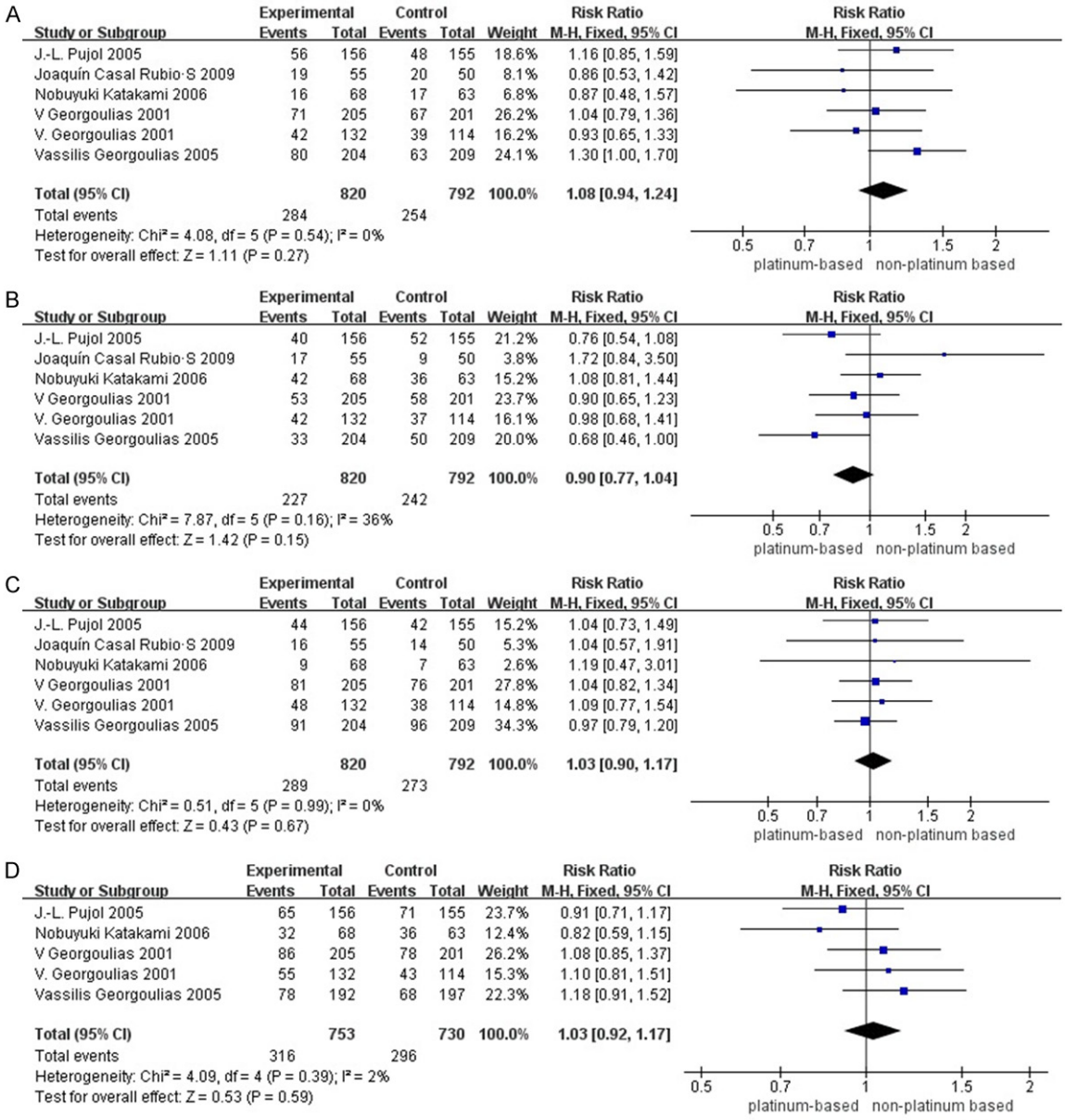


Figure 4. Subgroup comparison of the overall response rate (A), stable disease (B), progressive disease (C) and 1-year survival rate (D) between Gemcitabine-Docetaxel doublets and platinum-based doublets. Experimental, platinum-based; Control, Gemcitabine-Docetaxel.

Discussion

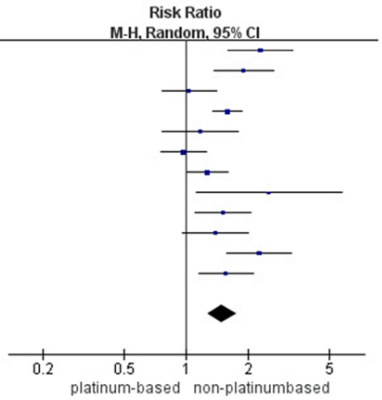
Third-generation agents combination therapy and platinum combined with third-generation agents therapy are common strategies in advanced NSCLC clinical treatments. Several randomized clinical trials have compared platinum-based regimens with non-platinum based regimens and indicated that non-platinum based chemotherapy was comparable with platinum-based chemotherapy for efficacy, but non-platinum based chemotherapy with less toxicities. However, the results were still inconclusive. As a result, a meta-analysis investigating the chemotherapy for patients with advanced NSCLC was conducted to avoid the cause of small sample sizes and help inform choices about patient management.

Gemcitabine and docetaxel are the most active third-generation drugs approved for advanced NSCLC and the combination of gemcitabine

A

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cesare Gridelli 2003	77	241	34	246	7.9%	2.31 [1.61, 3.32]
E.H. Tan 2004	69	155	36	154	8.4%	1.90 [1.36, 2.66]
Hiroshi Saito 2012	27	40	28	43	8.9%	1.04 [0.76, 1.41]
J.-L. Pujol2005	130	156	81	155	11.4%	1.59 [1.35, 1.88]
Joaquín Casal Rubio • S. 2009	27	56	21	51	6.9%	1.17 [0.76, 1.79]
Nobuyuki Katakami 2006	43	68	41	63	9.8%	0.97 [0.75, 1.26]
Nobuyuki Yamamoto 2006	51	64	40	64	10.3%	1.27 [1.02, 1.60]
R. C. Lilenbaum 2005	18	83	7	82	3.1%	2.54 [1.12, 5.76]
V Georgoulias 2001	71	205	46	201	8.7%	1.51 [1.10, 2.08]
V. Georgoulias 2001	50	132	31	114	7.8%	1.39 [0.96, 2.02]
Vassilis Georgoulias 2005	71	192	32	197	7.9%	2.28 [1.58, 3.29]
Ø Fløtten 2012	78	221	48	213	8.9%	1.57 [1.15, 2.13]
Total (95% CI)		**1613**		**1583**	**100.0%**	**1.50 [1.27, 1.77]**
Total events	712		445			

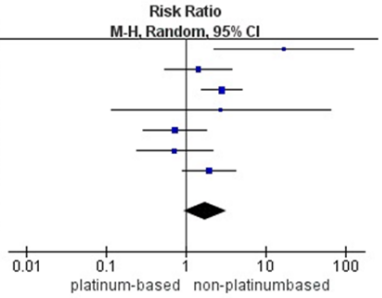
Heterogeneity: Tau² = 0.06; Chi² = 36.89, df = 11 (P = 0.0001); I² = 70%
Test for overall effect: Z = 4.82 (P < 0.00001)



B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
E.H. Tan 2004	17	155	1	154	7.0%	16.89 [2.28, 125.36]
Hiroshi Saito 2012	8	40	6	43	16.5%	1.43 [0.54, 3.77]
J.-L. Pujol2005	37	156	13	155	22.1%	2.83 [1.57, 5.11]
Joaquín Casal Rubio • S. 2009	1	56	0	51	3.3%	2.74 [0.11, 65.71]
Nobuyuki Katakami 2006	7	68	9	63	17.0%	0.72 [0.29, 1.82]
Nobuyuki Yamamoto 2006	5	64	7	64	14.8%	0.71 [0.24, 2.13]
Ø Fløtten 2012	18	221	9	213	19.2%	1.93 [0.89, 4.20]
Total (95% CI)		**760**		**743**	**100.0%**	**1.72 [0.93, 3.18]**
Total events	93		45			

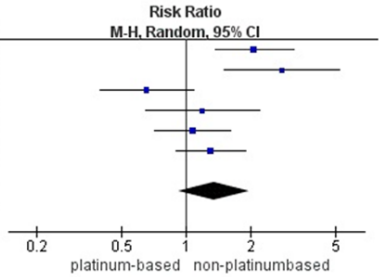
Heterogeneity: Tau² = 0.35; Chi² = 14.34, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 1.73 (P = 0.08)



C

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cesare Gridelli 2003	55	241	27	246	17.9%	2.08 [1.36, 3.18]
E.H. Tan 2004	34	155	12	154	14.3%	2.82 [1.52, 5.23]
Hiroshi Saito 2012	14	40	23	43	16.4%	0.65 [0.39, 1.09]
Joaquín Casal Rubio • S. 2009	17	56	13	51	14.4%	1.19 [0.64, 2.20]
Nobuyuki Katakami 2006	29	68	25	63	18.2%	1.07 [0.71, 1.62]
Nobuyuki Yamamoto 2006	34	64	26	64	18.8%	1.31 [0.90, 1.90]
Total (95% CI)		**624**		**621**	**100.0%**	**1.35 [0.92, 1.97]**
Total events	183		126			

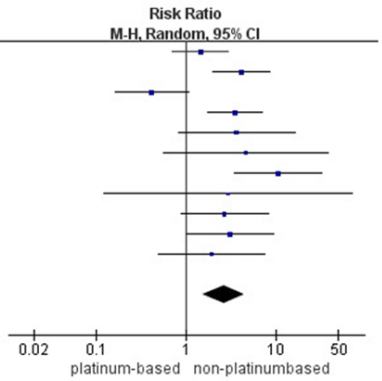
Heterogeneity: Tau² = 0.17; Chi² = 19.27, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 1.53 (P = 0.13)



D

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cesare Gridelli 2003	17	241	12	246	12.7%	1.45 [0.71, 2.96]
E.H. Tan 2004	33	155	8	154	12.5%	4.10 [1.96, 8.59]
Hiroshi Saito 2012	5	40	13	43	11.0%	0.41 [0.16, 1.06]
J.-L. Pujol2005	32	156	9	155	12.8%	3.53 [1.75, 7.15]
Joaquín Casal Rubio • S. 2009	8	56	2	51	7.2%	3.64 [0.81, 16.36]
Nobuyuki Katakami 2006	5	68	1	63	4.7%	4.63 [0.56, 38.57]
Nobuyuki Yamamoto 2006	32	64	3	64	9.5%	10.67 [3.44, 33.07]
R. C. Lilenbaum 2005	1	83	0	82	2.5%	2.96 [0.12, 71.72]
V Georgoulias 2001	11	205	4	201	9.6%	2.70 [0.87, 8.33]
Vassilis Georgoulias 2005	12	192	4	197	9.7%	3.08 [1.01, 9.38]
Ø Fløtten 2012	6	221	3	213	8.0%	1.93 [0.49, 7.61]
Total (95% CI)		**1481**		**1469**	**100.0%**	**2.61 [1.52, 4.49]**
Total events	162		59			

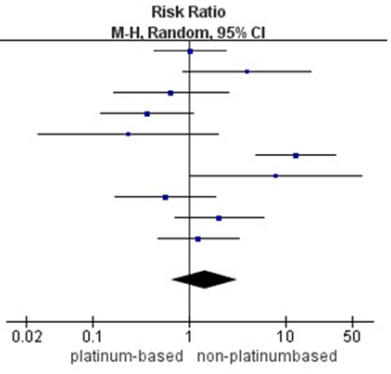
Heterogeneity: Tau² = 0.47; Chi² = 26.54, df = 10 (P = 0.003); I² = 62%
Test for overall effect: Z = 3.47 (P = 0.0005)



E

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cesare Gridelli 2003	10	241	10	246	11.8%	1.02 [0.43, 2.41]
E.H. Tan 2004	8	155	2	154	9.1%	3.97 [0.86, 18.42]
Hiroshi Saito 2012	3	40	5	43	9.8%	0.65 [0.16, 2.53]
J.-L. Pujol2005	4	156	11	155	10.8%	0.36 [0.12, 1.11]
Nobuyuki Katakami 2006	1	68	4	63	6.9%	0.23 [0.03, 2.02]
Nobuyuki Yamamoto 2006	52	64	4	64	11.4%	13.00 [5.00, 33.82]
R. C. Lilenbaum 2005	8	83	1	82	7.2%	7.90 [1.01, 61.78]
V Georgoulias 2001	4	205	7	201	10.4%	0.56 [0.17, 1.88]
Vassilis Georgoulias 2005	10	192	5	197	11.1%	2.05 [0.71, 5.89]
Ø Fløtten 2012	9	221	7	213	11.4%	1.24 [0.47, 3.27]
Total (95% CI)		**1425**		**1418**	**100.0%**	**1.44 [0.64, 3.22]**
Total events	109		56			

Heterogeneity: Tau² = 1.25; Chi² = 39.70, df = 9 (P < 0.00001); I² = 77%
Test for overall effect: Z = 0.88 (P = 0.38)



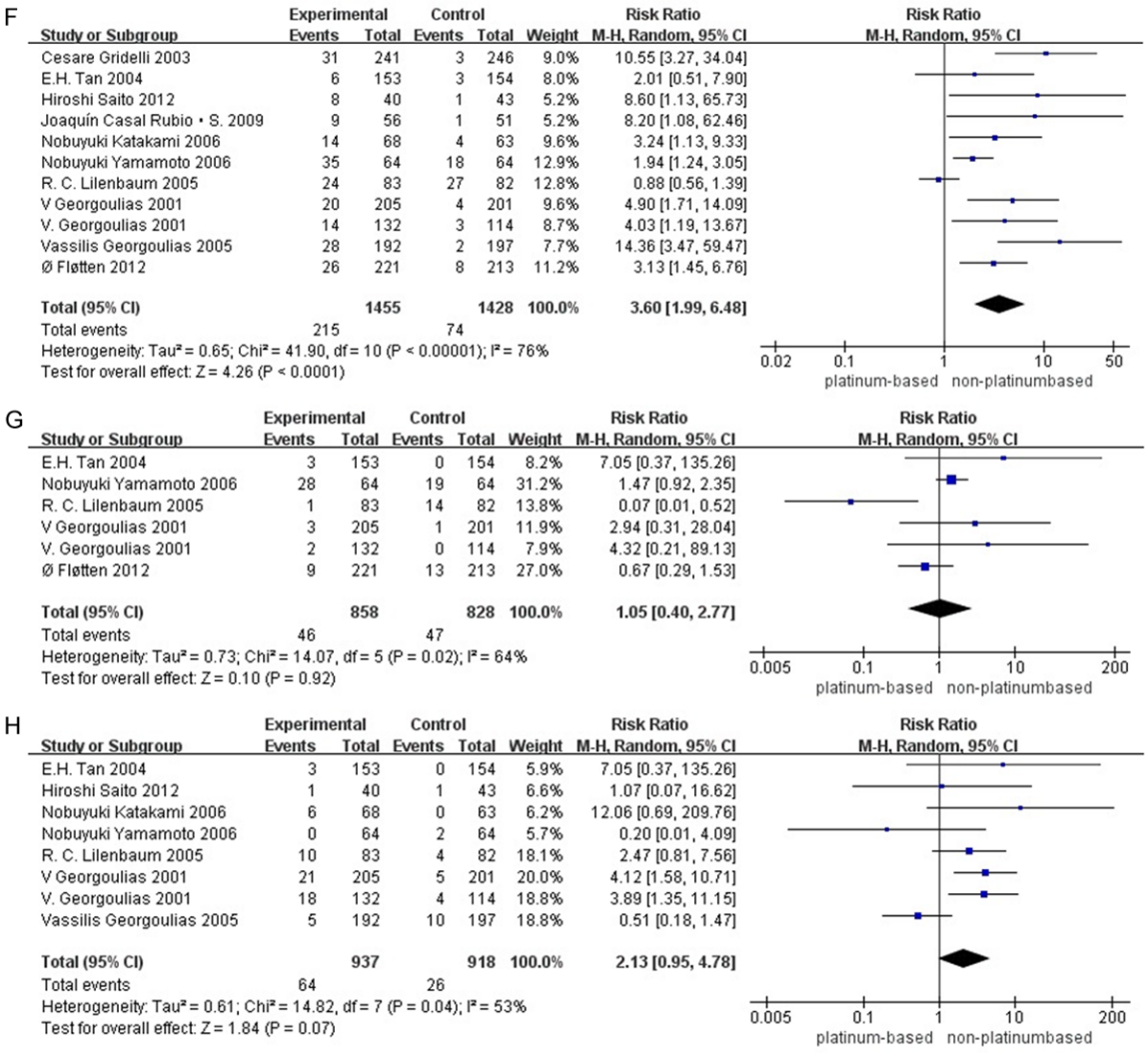


Figure 5. Comparison of neutropenia (A), febrile neutropenia (B), leucopenia (C), anemia (D), thrombopenia (E), nausea/vomiting (F), constipation (G) and diarrhea (H) between non-platinum based doublets and platinum-based doublets. Experimental, platinum-based; Control, non-platinum based.

and docetaxel is the most common third-generation combination therapy and presents promising efficacy and low toxicity. A subgroup analysis by gemcitabine+docetaxel doublets versus platinum-based doublets was conducted.

A large dataset of 3366 patients from 12 randomized clinical trials were enrolled in the meta-analysis and the efficacy and safety of third-generation agents doublets chemotherapy and platinum plus third-generation agent doublets chemotherapy were evaluated and compared. The present meta-analysis results demonstrated that non-platinum based doublets chemotherapy was comparable with platinum-based chemotherapy for efficacy including overall survival rate, stable disease, progressive disease and 1-year survival rate. Subgroup analysis including six studies also indicated that Gemcitabine+Docetaxel doublets were effectively equal to platinum-based doublets. However, both the overall analysis and the subgroup analysis showed significant improvement of grade 3-4 neutropenia, anemia and nausea/vomiting. A meta-analysis by Yong Yu [21] also demonstrated similar results. Gemcitabine+Docetaxel acquired similar survival with platinum-based regimens, but platinum-based regimens showed more grade 3-4 nausea/vomiting, anemia, neutropenia and febrile neutropenia.

In this study, third-generation doublets therapy seemed equal effective and less adverse

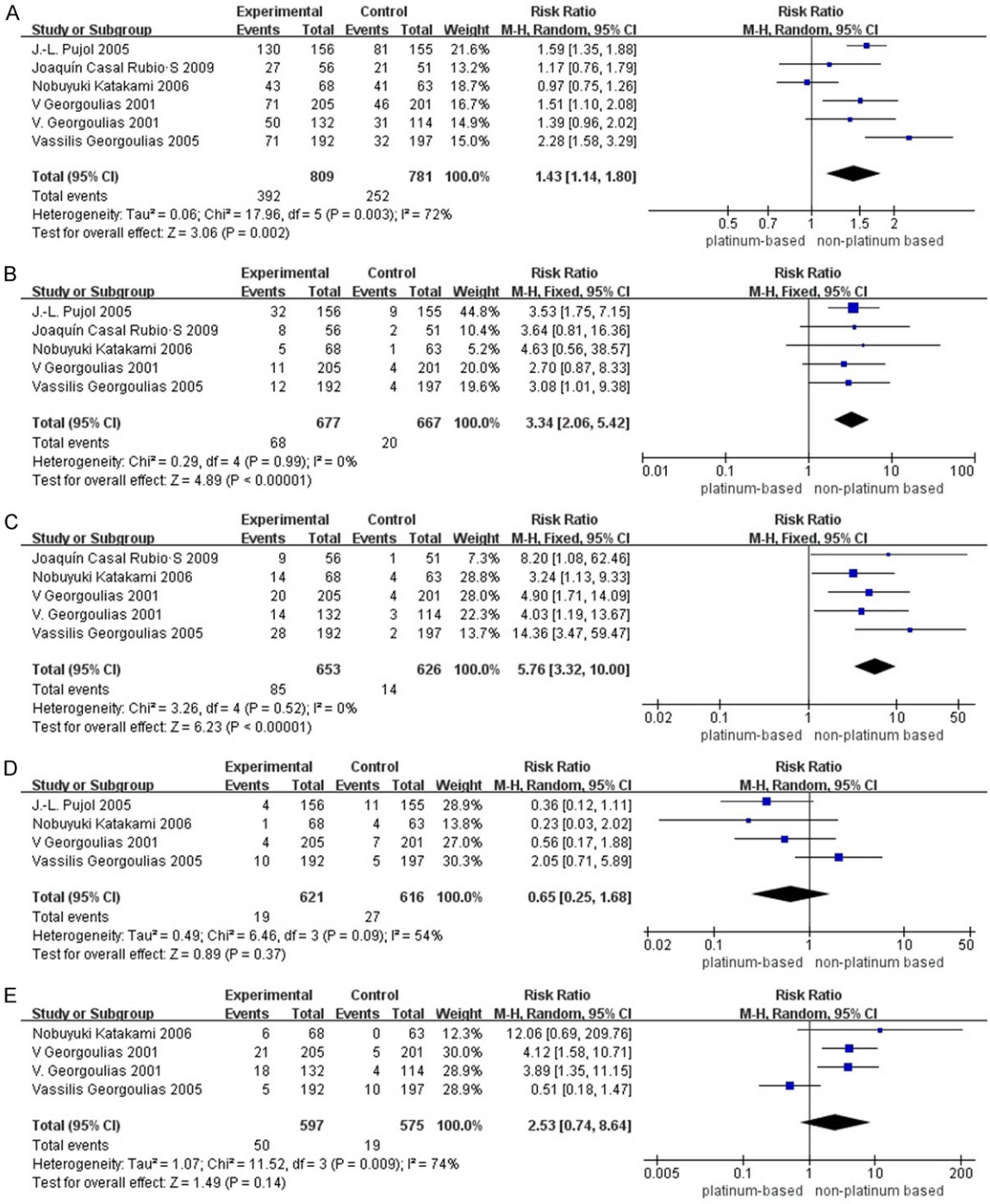


Figure 6. Subgroup comparison of neutropenia (A), anemia (B), nausea/vomiting (C), thrombopenia (D) and diarrhea (E) between Gemcitabine-Docetaxel doublets and platinum-based doublets. Experimental, platinum-based; Control, Gemcitabine-Docetaxel.

effects compared with platinum-based doublets, however, such results should be interpreted cautiously. 12 studies included in this study have some differences of regimens, sample sizes, dosages and treatment schedules. Because of these limitations, non-platinum based doublets could not definitively be concluded a priority for patients with advanced NSCLC. More high-quality randomized controlled trials and meta-analyses were still war-

ranted to investigate the dosages, schedules, and toxicities. The choice of a suitable treatment regimen for an individual patient with advanced NSCLC is dependent not only on treatment benefit but also on factors such as toxicity, administration and quality of life.

In conclusion, non-platinum based doublets showed equal efficacy compared with platinum-based doublets with less toxicities. It may be a prior choice for patients whom could not tolerant or are not suitable for platinum-based doublets therapy.

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Disclosure of conflict of interest

None.

Authors' contribution

ZWZ participated in the design of the study, performed the data analysis, and drafted the manuscript. YMZ participated in the design of the study. WQY and ZGL participated in the article retrieval, carried out the extraction of data, and assisted in the critical appraisal of included studies and assisted in writing up. All authors read and approved the final manuscript.

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