Int J Clin Exp Med 2017;10(6):8709-8719
www.ijcem.com /ISSN:1940-5901/IJCEM0053945

Review Article

Toxicity comparisons of eight chemotherapy regimens in the treatment of metastatic/advanced non-small-cell lung cancer: a network meta-analysis

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Received March 27, 2017; Accepted May 10, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: To compare the toxicity of different first-line chemotherapy regimens in the treatment of stage III/IV non-small-cell lung cancer (NSCLC) by network meta-analysis. The PubMed, Cochrane Library and EMBASE were searched. Randomized controlled trials (RCTs) concerning different first-line chemotherapy regimens for stage III/IV NSCLC from the day of databases establishment to August, 2016 were included into the study. Direct and indirect comparisons were combined by using network meta-analysis to evaluate the combined odds ratio (OR) and draw the surface under the cumulative ranking (SUCRA) curve of toxicity of different first-line chemotherapy regimens. A total of 12 qualified RCTs about ten first-line chemotherapy regimens (Gemcitabine, Cisplatin + Gemcitabine, Paclitaxel + Gemcitabine, Carboplatin + Gemcitabine, Carboplatin + Paclitaxel, Vinorelbine + Gemcitabine, Cisplatin + Gemcitabine + Vinorelbine, Vinorelbine + Carboplatin, Docetaxel + Gemcitabine, Dicycloplatin + Paclitaxel) were included into the study. According to network meta-analysis, the hematologic toxicity of Gemcitabine, Paclitaxel + Gemcitabine and Docetaxel + Gemcitabine regimens was lower, while that of Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens was higher. The incidence of hematologic toxicity of Paclitaxel + Gemcitabine and Docetaxel + Gemcitabine regimens was lower, while Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens had higher incidence of hematologic toxicity.

Keywords: Non-small-cell lung cancer, first-line chemotherapy, toxicity, randomized controlled trial, network meta-analysis

Introduction

Lung cancer is one of the most common malignant tumors, of which non-small-cell lung cancer (NSCLC) accounts for about 80%-85% [1]. Patients with early-stage NSCLC may be cured by surgical resection, followed by adjuvant chemotherapy [2]. However, a substantial proportion of patients with NSCLC are initially diagnosed with stage III/IV disease [3]. As the main approach for NSCLC, radiotherapy was adopted exclusively until the 1990s when the advantage of radiotherapy combined with chemotherapy was established by CALGB8433 [4]. In the past decades, the standard first-line treatment for advanced NSCLC consisted of platinum-based doublet therapy [5]. However, there is generally a brief period of disease control after the response to first-line chemotherapy, and most of patients will die because of disease progression, but the 5-year survival rate is very low (less than 5%) [6]. Consequently, it is necessary to identify more effective and tolerable treatments to delay progression and improve survival in advanced-stage NSCLC [7].

Currently, platinum-based combination chemotherapy is regarded as the standard in first-line therapy in the majority of patients with advanced NSCLC [8]. The drugs paired with platinum include microtubule-targeted agents (paclitaxel, docetaxel, or vinorelbine) and DNA-damaging agents (gemcitabine or irinotecan) [9]. Unfortunately, over the past decade, we have seen a plateau in clinical outcome whereby the median survival seldom exceeds 8 to 10 months, 1-year survival rates of 35% to 40% and 2-year survival rates of 10% to 15% at best. Attempts to add a third agent to platinum combinations or to extend treatment beyond four to

six cycles or to institute non-cross-resistant consolidation has yet to enhance outcome [10]. These platinum-based regimens bring modest benefits but also adverse effects, which may cause distressing symptoms and prevent further therapies. Studies have suggested that efficacy and toxicity of platinum-based chemotherapy vary greatly between individuals [11]. Thus, the identification of predictive markers for optimal individualized therapy with better efficacy and minimal toxicity remains a continuing challenge in the treatment of NSCLC [12].

In the present study, different first-line chemotherapy regimens in the treatment of stage III/IV NSCLC were searched out from relevant databases to compare their toxicities by performing this network meta-analysis, and to calculate the current clinical data to screen more effective chemotherapy regimens.

Material and methods

Literature search

From inception to August 2016, PubMed, Cochrane Library and EMBASE databases were performed by the computer-based retrieval combined with manual retrieval of related references of NSCLC. With the combination of key words and free words, the search terms included: chemotherapy, cisplatin, fluorouracil, innotecan, vinorelbine, gerncitabine, non-small-cell lung cancer (NSCLC), randomized controlled trials (RCTs), etc.

Study selection

The inclusion criteria were as follows: (1) study design should be randomized controlled trials (RCTs); (2) at least one measurable lesion in patients with stage III/IV NSCLC according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 [13]; (3) outcomes included the incidences of leukopenia, neutropenia, thrombocytopenia, anemia, constipation, diarrhea, fatigue and nausea/vomiting. The exclusion criteria were as follows: (1) patients with hepatic and renal insufficiency, active malignancy and gastrointestinal disease and any severe organic disorder were excluded; (2) the studies lacked of data integrity, non-RCTs, duplicate studies, conference reports, systematic reviews and abstracts, non-human studies non-English studies were excluded.

Data extraction and quality assessment

With the standard data collection forms, data from included studies was extracted by researchers independently. Any disagreements were resolved through discussion. The risk of bias of included RCTs was assessed by two researchers according to Cochrane Collaboration's tool [14]. This tool included 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and anything else ideally prespecified. In the assessment, a judgment of "yes" "no" or "unclear", each domain was assigned to designate respectively a low, high, or unclear risk of bias. If one or no domain was deemed "no" or "unclear", the study was thought to have a low risk of bias. If four or more domains were deemed "no" or "unclear", the study was regarded as a high risk of bias. If two or three domains were deemed "no" or "unclear", the study belonged to a moderate risk of bias [15]. Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK) was used to carry out quality assessment and investigation of publication bias.

Statistical analysis

Firstly, with R version 3.2.1 and the meta-package, pair-wise meta-analyses of direct evidence were conducted by the fixed-effects model. Our results showed the pooled estimates of odds ratio (OR) and 95% confidence interval (95% CI) of endpoint outcomes. Heterogeneity among these studies was tested by Chi-square test and I-square [16]. Secondly, R 3.2.1 software was used to draw network meta diagram, in which each node represented different interventions, the nodes sizes reflected sample sizes, and the thickness of line between nodes meant number of included studies. Thirdly, we implemented a random-effects network meta-analysis with the gemtc package, which modeled the relative effects (e.g. log-odds ratio) responding to a generalized linear model (GLM) under the Bayesian framework by connecting to JAGS, OpenBUGS or WinBUGS as first described by Lu and Ades [17] and improved by others [18, 19]. The study used the node-splitting method to evaluate the consistency of direct evidence and indirect evidence. If node-splitting result was $P > 0.05$, it was analyzed by the fixed effect Model. We calculated the probabili-

Table 1. The baseline characteristics for included studies

First author	Year	Country	Interventions		Sample size			Gender (M/F)		Age (years)	
			T1	T2	Total	T1	T2	T1	T2	T1	T2
Karampeazis A	2016	Greece	A	I	106	52	54	49/3	44/10	78.5 (70-92)	73.5 (70-82)
Liu KJ	2014	China	E	J	236	118	118	93/25	82/36	57 (34-71)	56 (32-71)
Morabito A	2013	Italy	A	B	56	28	28	23/5	23/5	63 (47-69)	63 (49-69)
Kusagaya H	2012	Japan	A	D	61	30	31	24/6	27/4	79 (76-85)	79 (76-88)
Flotten O	2012	UK	F	H	437	215	222	126/89	126/96	65 (44-87)	65 (43-83)
Kosmidis PA	2008	Greece	C	D	452	225	227	194/31	184/43	63 (42-82)	63 (36-83)
Langer C	2007	US	B	E	200	100	100	59/41	74/26	67 (42-81)	65 (45-80)
Esteban E	2007	Spain	B	G	154	78	76	71/7	70/6	58 (36-73)	59 (33-74)
Esteban E	2006	Spain	F	G	114	57	57	49/8	45/12	60 (38-75)	59 (37-72)
Sederholm C	2005	Sweden	A	D	334	170	164	88/82	98/66	66 (42-80)	66 (42-82)
Lilenbaum RC	2005	US	E	F	165	83	82	42/41	51/31	63 (38-86)	66 (42-86)
Chen YM	2005	Ireland	F	G	869	43	43	32/11	30/13	67.5 (32-80)	67.2 (44-78)

Notes: T = treatment; M = male; F = female; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel.

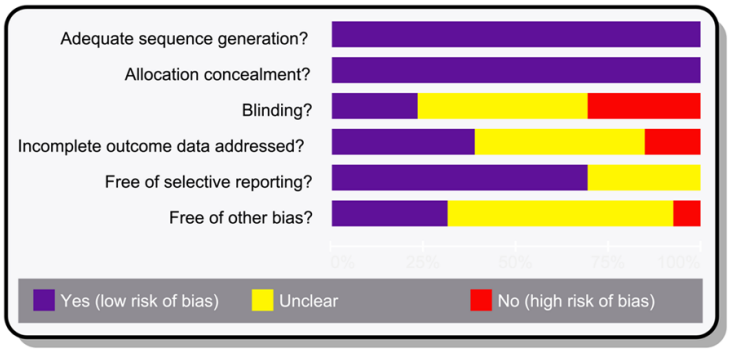

Figure 1. Cochrane system bias evaluation of included studies. Twelve eligible randomized controlled trials were analyzed in this network meta-analysis.

ty of each intervention being the most effective or safest treatment method based on a Bayesian approach using probability values summarized as surface under the cumulative ranking curve (SUCRA) in order to interpret ORs. The larger the SUCRA value, the better the rank of the intervention [20, 21]. The treatments were grouped by cluster analyses according to their similarity with regard to both outcomes [20]. R (V.3.2.2) package gemtc (V.0.6) as well as the Markov Chain Monte Carlo engine Open BUGS (V.3.4.0) were used to do all computations.

Results

The baseline characteristics of included studies

A total of 3879 relevant studies were initially retrieved. We firstly excluded 255 duplicate studies, 223 letters and reviews, 781 non-human studies and 555 non-English studies. After full-text review, of the rest 2065 studies, 567 non-cohort studies, 510 unrelated to stage III/IV NSCLC, 454 unrelated to first-line chemotherapy regimens, 521 unrelated to the index of toxicity and 1 without data integrity or with no data were ruled out. Finally, 12 RCTs were eligible to this meta-analysis [8, 22-32] (Figure S1). The 12 RCTs were published from 2005 to 2016. There were 10 studies in Caucasians and 2 in Asians, and all 12 RCTs were two-arm trials. The baseline characteristics of included studies were displayed in **Table 1**. The Cochrane risk of bias assessment of included studies was shown in **Figure 1**. These studies included 3234 patients with stage III/IV NSCLC, among which the majority of patients were treated with Carboplatin + Gemcitabine and Vinorelbine + Gemcitabine (**Figure 2**).

Pairwise meta-analysis for toxicities of ten first-line chemotherapy regimens for stage III/IV NSCLC

We conducted a direct-paired comparison of the incidence of toxicity of ten chemotherapy regimens during the treatment of stage III/IV NSCLC, and the results indicated that the incidences of leukopenia, neutropenia, thrombocy-

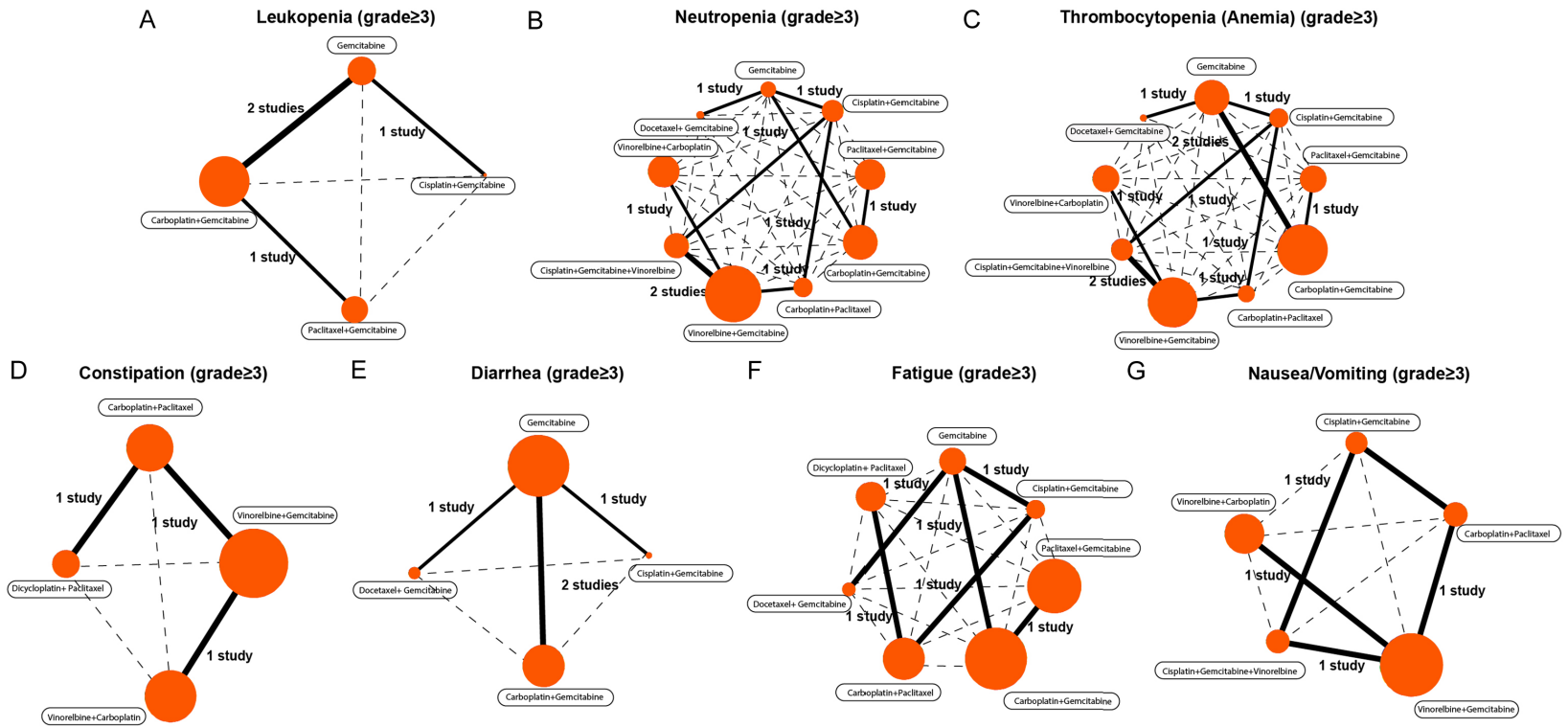

Figure 2. Evidence network plot of ten first-line chemotherapy regimens for stage III/IV NSCLC.

Table 2. OR values and *P* values of direct and indirect pairwise comparisons under four endpoint outcomes

Pairwise comparisons	Direct OR values				Indirect OR values				*P* values			
	Neu	Thr	Ane	Nau/Vom	Neu	Thr	Ane	Nau/Vom	Neu	Thr	Ane	Nau/Vom
E VS. B	2.80	0.20	0.70	0.18	1.30	1.80	0.38	0.06	0.518	0.601	0.766	0.621
G VS. B	1.20	1.00	0.58	1.00	2.60	0.09	1.10	2.80	0.530	0.576	0.784	0.665
F VS. E	0.33	0.07	0.98	1.20	0.15	0.72	0.62	0.38	0.470	0.585	0.838	0.605
G VS. F	2.70	5.60	1.40	13.00	1.30	71.00	0.93	5.00	0.473	0.594	0.881	0.654

Notes: OR = Odds ratio; Neu = Neutropenia; Thr = Thrombocytopenia; Ane = Anemia; Nau/Vom = Nausea/Vomiting; B = Cisplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine.

topenia and anemia of Paclitaxel + Gemcitabine regimen were relatively lower than Carboplatin + Gemcitabine regimen; while Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens showed higher incidences of neutropenia and thrombocytopenia than Vinorelbine + Gemcitabine regimen. Besides, comparing with Vinorelbine + Gemcitabine regimen, the incidence of constipation of Carboplatin + Paclitaxel regimen was correspondingly higher, and Cisplatin + Gemcitabine + Vinorelbine and Vinorelbine + Carboplatin regimens delivered higher incidences of nausea/vomiting (Table S1A and S1B).

Inconsistency tests of neutropenia, thrombocytopenia, anemia and nausea/vomiting in 12 RCTs

Inconsistency tests showed that the results of the direct and indirect evidence of these four outcomes were consistent, thus the consistency model was adopted (both $P > 0.05$) (**Table 2**).

The main results of network meta-analysis

This network meta-analysis indicated that the incidence of neutropenia of Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens were relatively higher than Vinorelbine + Gemcitabine regimen (OR = 4.05, 95% CI = 1.29~12.27; OR = 2.46, 95% CI = 1.06~5.73, respectively) (**Table 3** and **Figure 3**). However, there was no significant difference in the incidences of leukopenia, thrombocytopenia, anemia, constipation, diarrhea, fatigue and nausea/vomiting among ten first-line chemotherapy regimens (Table S2).

SUCRA values of the incidences of toxicity of ten first-line chemotherapy regimens for stage III/IV NSCLC

As shown in **Table 4**, the SUCRA values demonstrated that Cisplatin + Gemcitabine regimen has the lowest incidences of leukopenia, thrombocytopenia and anemia (leukopenia: 43.50%; thrombocytopenia: 30.89%; anemia: 30.44%); while the incidences of neutropenia and thrombocytopenia of Paclitaxel + Gemcitabine regimen ranked the highest (neutropenia: 92.78%; thrombocytopenia: 74.11%). Besides, the SUCRA value of Carboplatin + Gemcitabine regimen of the incidences of diarrhea and fatigue was the highest (diarrhea: 72.00%; fatigue: 77.43%); meanwhile Carboplatin + Paclitaxel regimen ranked the highest incidences of constipation and nausea/vomiting (constipation: 84.00%; nausea/vomiting: 86.40%). Thus we could see the hematologic toxicity of Cisplatin + Gemcitabine regimen was relatively higher, while that of Paclitaxel + Gemcitabine regimen was relatively lower; and the non-hematologic toxicity of Carboplatin + Gemcitabine and Carboplatin + Paclitaxel regimens was relatively lower.

Cluster analysis of the incidences of neutropenia, thrombocytopenia and anemia of ten first-line chemotherapy regimens for stage III/IV NSCLC

The results of cluster analysis showed that the hematologic toxicity of Gemcitabine, Paclitaxel + Gemcitabine and Docetaxel + Gemcitabine regimens was relatively lower, while that of Cisplatin + Gemcitabine, Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens was relatively higher (**Figure 4**).

Discussion

In the study, the randomized controlled trials (RCTs) concerning ten first-line chemotherapy regimens (Gemcitabine, Cisplatin + Gemcitabine, Paclitaxel + Gemcitabine, Carboplatin + Gemcitabine, Carboplatin + Paclitaxel, Vinorelbine + Gemcitabine, Cisplatin + Gemcitabine + Vinorelbine, Vinorelbine + Carboplatin, Doce-

Table 3. Odds ratio and 95% confidence intervals of nine drug regimens in the treatment of stage III/IV non-small cell lung cancer in terms of neutropenia (grade ≥3)

OR (95% CI)								
A	3.89 (0.25, 131.21)	0.26 (0.05, 1.72)	0.50 (0.12, 2.15)	9.10 (0.43, 367.41)	2.29 (0.10, 96.75)	5.70 (0.25, 217.89)	4.31 (0.16, 218.57)	0.97 (0.15, 6.94)
0.26 (0.01, 3.96)	B	0.06 (0.00, 2.13)	0.12 (0.00, 3.22)	2.23 (0.76, 6.56)	0.55 (0.17, 1.86)	1.39 (0.50, 4.00)	1.03 (0.21, 4.95)	0.23 (0.00, 10.67)
3.84 (0.58, 22.02)	15.71 (0.47, 685.09)	C	1.94 (0.65, 6.11)	36.33 (0.94, 1900.08)	9.00 (0.20, 512.53)	22.51 (0.54, 1230.01)	17.01 (0.33, 1148.75)	3.65 (0.27, 46.00)
1.99 (0.46, 8.16)	8.06 (0.31, 284.08)	0.52 (0.16, 1.53)	D	18.55 (0.58, 789.03)	4.57 (0.13, 221.29)	11.55 (0.34, 497.82)	8.61 (0.21, 502.35)	1.93 (0.17, 17.75)
0.11 (0.00, 2.32)	0.45 (0.15, 1.31)	0.03 (0.00, 1.07)	0.05 (0.00, 1.72)	E	0.25 (0.08, 0.77)	0.62 (0.20, 2.05)	0.48 (0.09, 2.13)	0.10 (0.00, 6.17)
0.44 (0.01, 10.36)	1.83 (0.54, 5.74)	0.11 (0.00, 4.99)	0.22 (0.00, 7.65)	4.05 (1.29, 12.27)	F	2.46 (1.06, 5.73)	1.89 (0.59, 5.56)	0.40 (0.01, 28.20)
0.18 (0.00, 4.04)	0.72 (0.25, 2.02)	0.04 (0.00, 1.85)	0.09 (0.00, 2.94)	1.62 (0.49, 5.13)	0.41 (0.17, 0.94)	G	0.76 (0.18, 2.82)	0.16 (0.00, 11.13)
0.23 (0.00, 6.09)	0.97 (0.20, 4.87)	0.06 (0.00, 2.99)	0.12 (0.00, 4.75)	2.10 (0.47, 10.56)	0.53 (0.18, 1.68)	1.32 (0.35, 5.48)	H	0.22 (0.00, 16.65)
1.03 (0.14, 6.83)	4.36 (0.09, 298.60)	0.27 (0.02, 3.77)	0.52 (0.06, 5.95)	10.12 (0.16, 540.58)	2.49 (0.04, 150.52)	6.29 (0.09, 336.51)	4.62 (0.06, 304.44)	I

Notes: OR = Odds ratio; 95% CI = confidence intervals; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine.

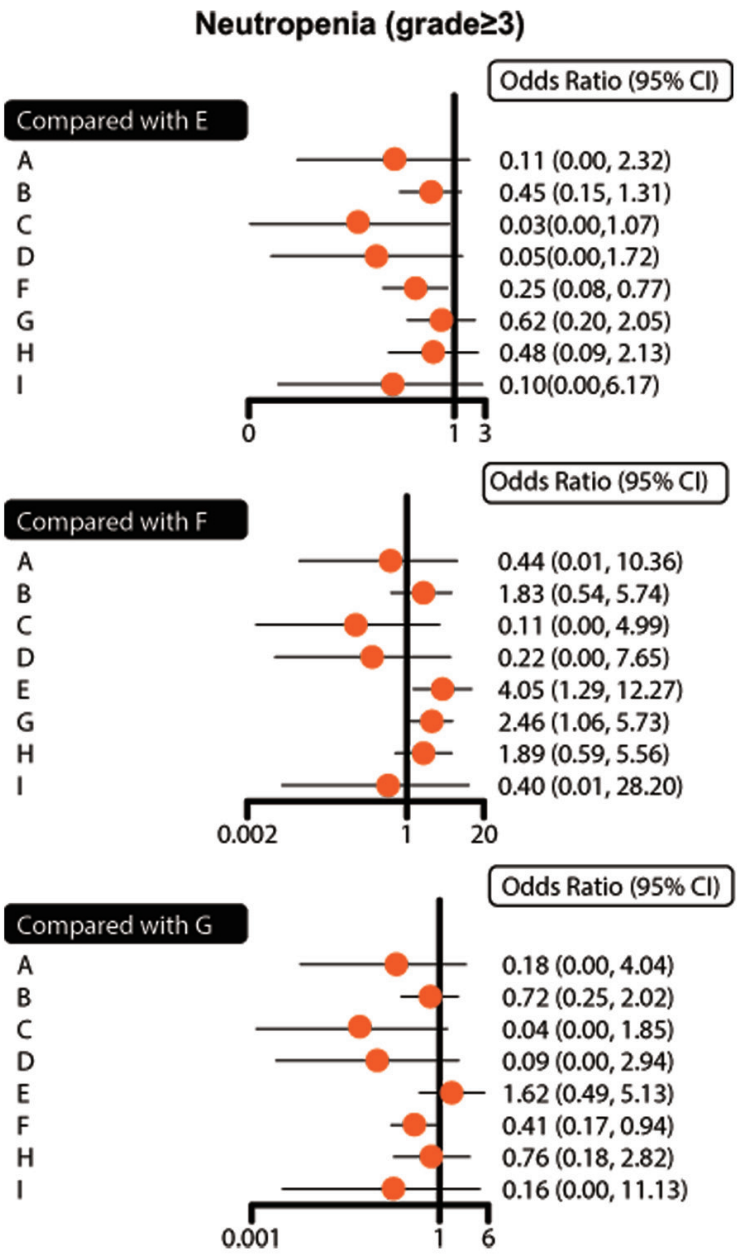

Figure 3. Forest plots of the incidence of neutropenia of ten first-line chemotherapy regimens for stage III/IV NSCLC. Notes: A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel; 95% CI = 95% confidence intervals.

taxel + Gemcitabine, Dicycloplatin + Paclitaxel) for stage III/IV Non-Small-Cell Lung Cancer (NSCLC) were included to perform a pairwise analysis and network meta-analysis. We drew a conclusion that the hematologic toxicity of Paclitaxel + Gemcitabine and Docetaxel + Gemcitabine regimens was relatively lower, while that of Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens were relatively higher [33-35].

The pairwise meta-analysis showed that the incidences of leukopenia, neutropenia, thrombocytopenia and anemia of Paclitaxel + Gemcitabine regimen were relatively lower than Carboplatin + Gemcitabine regimen, while Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens showed higher incidences of neutropenia and thrombocytopenia than Vinorelbine + Gemcitabine regimen. Clinical studies have shown that paclitaxel has been approved for the treatment of advanced NSCLC with a broad spectrum of anticancer activity [36]. Fang *et al*. conducted a clinical study of Abraxane plus platinum as first-line chemotherapy for stage III/IV NSCLC and verified that paclitaxel can reduce the risk of hypersensitivity reactions and blood toxicity induced by organic solvents when used in combination with albumin [1].

Additionally, the network meta-analysis found that the incidence of neutropenia of Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens were relatively higher than Vinorelbine + Gemcitabine regimen. By Tan *et al*.'s study, the platinum-free combination yielded incidence figures lower than those obtained with the Vinorelbine + Carboplatin combination, and the non-cisplatin containing treatment was significantly less toxic than standard cisplatin-based chemotherapy, according to both physicians' evaluation and to patients' assessment of quality of life items [37].

Table 4. SUCRA values of ten treatment modalities under eight endpoint outcomes

Treatments	SUCRA values (%)							
	Leukopenia	Neutropenia	Thrombocytopenia	Anemia	Constipation	Diarrhea	Fatigue	Nausea/ Vomiting
A	80.00	64.67	61.89	75.44	NR	54.25	63.00	NR
B	43.50	43.00	30.89	30.44	NR	61.25	32.00	39.20
C	77.50	92.78	74.11	77.44	NR	NR	69.86	NR
D	48.50	78.22	42.00	51.56	NR	72.00	77.43	NR
E	NR	18.22	46.33	43.89	84.00	NR	47.14	86.40
F	NR	63.22	69.89	55.22	37.00	NR	NR	86.00
G	NR	31.22	39.89	45.22	NR	NR	NR	34.60.
H	NR	41.67	65.11	36.67	48.00	NR	NR	53.00
I	NR	66.00	69.44	85.00	NR	62.50	63.29	NR
J	NR	NR	NR	NR	81.00	NR	46.57	NR

Notes: SUCRA = surface under the cumulative ranking curves; NR = not report; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel.

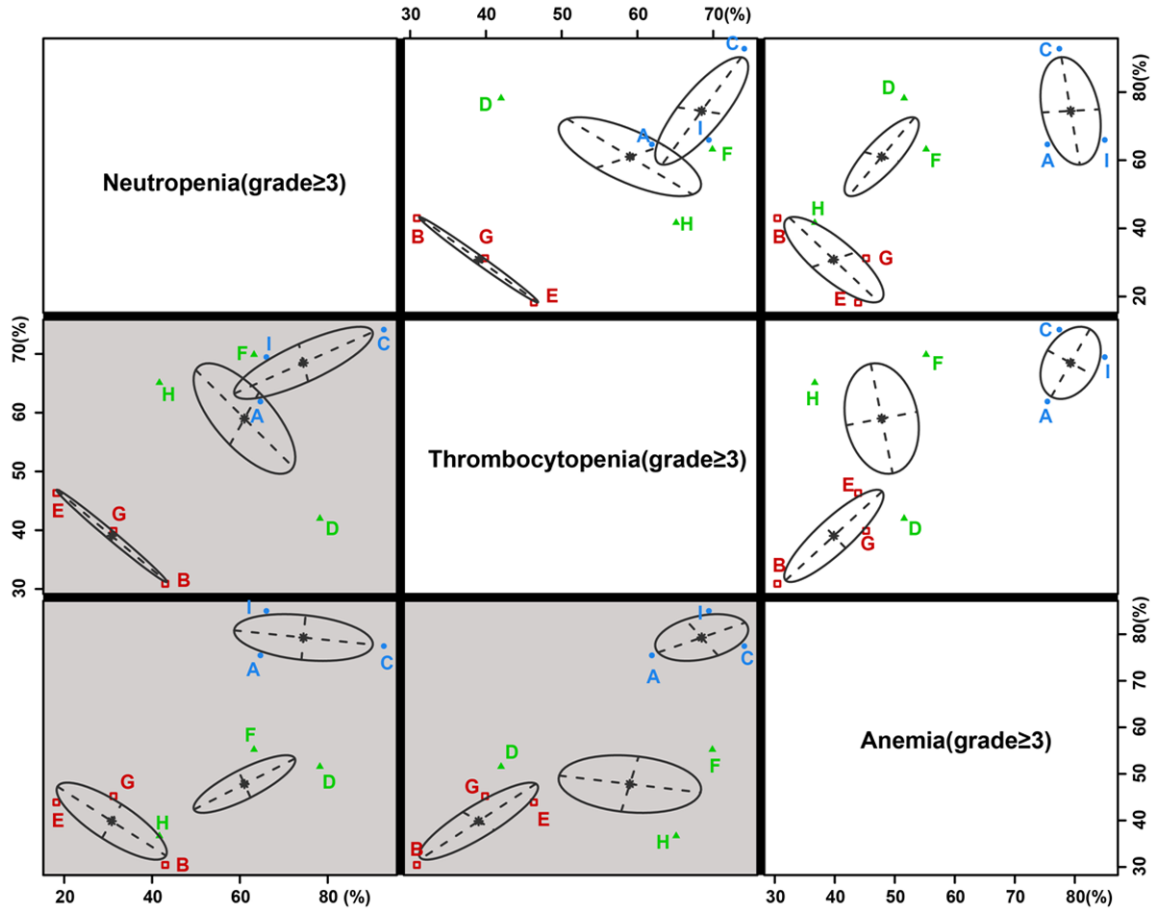

Figure 4. Clustered ranking plots based on SUCRA values of the incidences of neutropenia, thrombocytopenia and anemia of ten first-line chemotherapy regimens for stage III/IV NSCLC. Notes: A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel.

Further analysis of the results of SUCRA revealed that Cisplatin + Gemcitabine regimen has the lowest incidences of leukopenia, thrombocytopenia and anemia, while the incidences of neutropenia and thrombocytopenia of Paclitaxel + Gemcitabine regimen ranked the highest; meanwhile Carboplatin + Paclitaxel regimen ranked the highest incidences of constipation and nausea/vomiting. A previous study has found that carboplatin was associated with a greater risk of thrombocytopenia and anemia compared with non-platinum based therapy, but there was no difference in the risk of nausea and/or vomiting [38]. Due to there were some differences between previous studies and the present study, the toxicity of different first-line chemotherapy regimens for stage III/IV NSCLC requires further study.

In conclusion, this network meta-analysis suggests that Paclitaxel + Gemcitabine and Docetaxel + Gemcitabine regimens may have lower incidence of hematologic toxicity in the treatment of stage III/IV NSCLC, while that of Carboplatin + Paclitaxel and Cisplatin + Gemcitabine + Vinorelbine regimens was relatively higher. These findings have a certain guiding significance for the clinical use and treatment of stage III/IV NSCLC. However, there still exist some limitations. For example, there were differences in the number of studies on the direct-paired comparison between different first-line chemotherapy regimens for stage III/IV NSCLC. And because there were relatively few studies on non-hematologic toxicity, the cluster analysis could not be carried out, which might have a certain impact on the results of the study. We would like to have more in the number of studies to focus on the direct-paired comparison and non-hematologic toxicity between different first-line chemotherapy regimens for stage III/IV NSCLC.

Acknowledgements

We thank for the person who gave assistance and helpful discussions for our manuscript.

Disclosure of conflict of interest

None.

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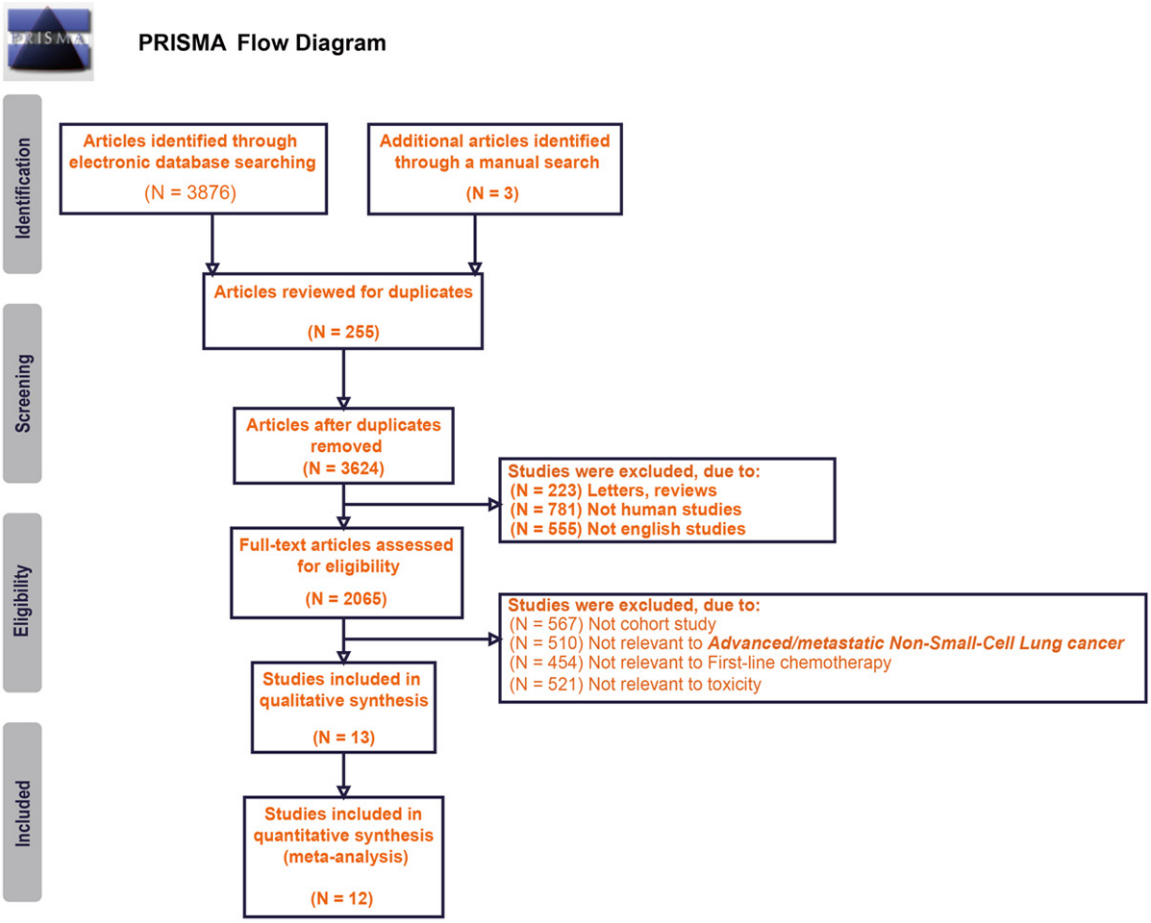

Figure S1. Flow chart showing literature search and study selection. Twelve randomized controlled trials that met the inclusion criteria were included in this network meta-analysis.

Table S1A. Estimated OR and 95% CI from pairwise meta-analysis in terms of hematologic toxicity

Included studies	Comparisons	Toxicity events		Pairwise meta-analysis
		Treatment 1	Treatment 2	OR (95% CI)
Hematologic toxicity (grade ≥3)				
Leukopenia				
1 study	A VS. B	1/26	4/28	0.24 (0.03; 2.30)
2 studies	A VS. D	23/199	62/190	0.39 (0.06; 2.57)
1 study	C VS. D	17/213	41/212	0.36 (0.20; 0.66)
Neutropenia				
1 study	A VS. I	4/52	4/54	1.04 (0.25; 4.40)
1 study	A VS. B	1/26	3/28	0.33 (0.03; 3.43)
1 study	A VS. D	13/30	9/31	1.87 (0.65; 5.39)
1 study	F VS. H	48/213	78/221	0.53 (0.35; 0.81)
1 study	C VS. D	38/212	62/211	0.52 (0.33; 0.83)
1 study	B VS. E	16/47	30/51	0.36 (0.16; 0.82)
1 study	B VS. G	24/76	26/74	0.85 (0.43; 1.68)
2 studies	F VS. G	27/100	50/100	0.37 (0.20; 0.66)
1 study	E VS. F	18/83	7/82	2.97 (1.17; 7.55)
Thrombocytopenia				
1 study	A VS. I	2/52	0/54	5.40 (0.25; 115.13)
1 study	A VS. B	1/26	6/28	0.15 (0.02; 1.31)
2 studies	A VS. D	8/199	76/190	0.30 (0.00; 26.25)
1 study	F VS. H	7/213	9/221	0.80 (0.29; 2.19)
1 study	C VS. D	5/212	54/211	0.07 (0.03; 0.18)
1 study	B VS. E	18/47	6/51	4.66 (1.65; 13.11)
1 study	B VS. G	4/76	4/74	0.97 (0.23; 4.04)
2 studies	F VS. G	1/100	10/100	0.13 (0.02; 0.75)
1 study	E VS. F	8/83	1/82	8.64 (1.06; 70.73)
Anemia				
1 study	A VS. I	2/52	1/54	2.12 (0.19; 24.11)
1 study	A VS. B	0/26	5/28	0.08 (0.00; 1.54)
2 studies	A VS. D	7/199	14/190	0.46 (0.18; 1.22)
1 study	F VS. H	3/213	6/221	0.51 (0.13; 2.07)
1 study	C VS. D	11/212	28/212	0.36 (0.17; 0.74)
1 study	B VS. E	6/47	5/51	1.35 (0.38; 4.74)
1 study	B VS. G	5/76	3/74	1.67 (0.38; 7.24)
2 studies	F VS. G	7/100	9/100	0.76 (0.27; 2.13)
1 study	E VS. F	1/83	0/82	3.00 (0.12; 74.72)

Notes: OR = Odds ratio; 95% CI = 95% confidence intervals; NA = not available; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine.

Table S1B. Estimated OR and 95% CI from pairwise meta-analysis in terms of non-hematologic toxicity

Included studies	Comparisons	Toxicity events		Pairwise meta-analysis
		Treatment 1	Treatment 2	OR (95% CI)
Non-hematologic toxicity (grade ≥3)				
Constipation				
1 study	E VS. J	1/118	0/118	3.03 (0.12; 75.03)
1 study	F VS. H	13/213	9/221	1.53 (0.64; 3.66)
1 study	E VS. F	1/83	14/82	0.06 (0.01; 0.46)
Diarrhea				
1 study	A VS. I	2/52	1/54	2.12 (0.19; 24.11)
1 study	A VS. B	0/26	5/28	0.08 (0.00; 1.54)
2 studies	A VS. D	7/199	14/190	0.46 (0.18; 1.22)
Fatigue				
1 study	A VS. I	3/52	3/54	1.04 (0.20; 5.41)
1 study	E VS. J	1/118	1/118	1.00 (0.06; 16.18)
1 study	A VS. B	1/26	3/28	0.33 (0.03; 3.43)
1 study	A VS. D	2/30	1/31	2.14 (0.18; 24.96)
1 study	C VS. D	4/219	3/219	1.34 (0.30; 6.06)
1 study	B VS. E	10/47	7/51	1.70 (0.59; 4.90)
Nausea/Vomiting				
1 study	F VS. H	8/213	26/221	0.29 (0.13; 0.66)
1 study	B VS. E	11/47	3/51	4.89 (1.27; 18.82)
1 study	B VS. G	12/76	12/74	0.97 (0.40; 2.32)
1 study	F VS. G	1/57	8/57	0.11 (0.01; 0.91)
1 study	E VS. F	24/83	27/82	0.83 (0.43; 1.61)

Notes: OR = Odds ratio; 95% CI = 95% confidence intervals; NA = not available; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel.

Table S2. Odds ratio and 95% confidence intervals of ten drug regimens in the treatment of stage III/IV non-small cell lung cancer

OR (95% CI)								
Leukopenia								
A	5.69 (0.18, 304.38)	1.00 (0.04, 23.04)	2.79 (0.39, 18.89)					
0.18 (0.00, 5.71)	B	0.17 (0.00, 19.02)	0.49 (0.01, 25.62)					
1.00 (0.04, 26.17)	6.00 (0.05, 1074.04)	C	2.82 (0.21, 38.67)					
0.36 (0.05, 2.55)	2.06 (0.04, 171.24)	0.35 (0.03, 4.84)	D					
Thrombocytopenia								
A	10.78 (0.06, 2308.60)	0.26 (0.00, 75.76)	4.01 (0.10, 112.74)	4.01 (0.01, 3216.13)	0.59 (0.00, 575.53)	5.78 (0.01, 5141.15)	0.71 (0.00, 3300.92)	0.38 (0.00, 80.49)
0.09 (0.00, 16.14)	B	0.02 (0.00, 51.93)	0.38 (0.00, 170.05)	0.36 (0.01, 21.44)	0.06 (0.00, 4.44)	0.53 (0.01, 32.95)	0.07 (0.00, 43.64)	0.03 (0.00, 73.25)
3.78 (0.01, 1720.39)	41.96 (0.02, 117567.08)	C	15.21 (0.14, 1892.65)	15.69 (0.00, 115189.26)	2.33 (0.00, 20073.72)	22.97 (0.00, 157914.42)	2.76 (0.00, 75946.34)	1.39 (0.00, 5008.38)
0.25 (0.01, 10.23)	2.61 (0.01, 1978.74)	0.07 (0.00, 6.99)	D	0.98 (0.00, 2204.36)	0.15 (0.00, 385.21)	1.44 (0.00, 3115.70)	0.18 (0.00, 1778.66)	0.09 (0.00, 57.84)
0.25 (0.00, 184.47)	2.76 (0.05, 144.70)	0.06 (0.00, 385.96)	1.02 (0.00, 1548.70)	E	0.15 (0.00, 10.52)	1.45 (0.01, 143.06)	0.18 (0.00, 102.18)	0.09 (0.00, 548.43)
1.69 (0.00, 1654.39)	17.95 (0.23, 1787.15)	0.43 (0.00, 3298.24)	6.76 (0.00, 13656.55)	6.59 (0.10, 541.80)	F	9.85 (0.33, 306.15)	1.23 (0.01, 119.16)	0.58 (0.00, 5280.55)
0.17 (0.00, 130.79)	1.87 (0.03, 115.12)	0.04 (0.00, 242.78)	0.69 (0.00, 932.09)	0.69 (0.01, 76.85)	0.10 (0.00, 3.05)	G	0.12 (0.00, 41.16)	0.06 (0.00, 426.77)
1.42 (0.00, 6306.78)	15.07 (0.02, 11501.59)	0.36 (0.00, 7634.65)	5.56 (0.00, 46453.72)	5.44 (0.01, 3805.19)	0.81 (0.01, 103.27)	8.25 (0.02, 2668.65)	H	0.51 (0.00, 11647.52)
2.64 (0.01, 726.92)	30.99 (0.01, 58197.10)	0.72 (0.00, 2002.52)	10.82 (0.02, 6533.07)	11.30 (0.00, 65206.73)	1.73 (0.00, 9053.91)	16.17 (0.00, 75510.55)	1.96 (0.00, 36159.99)	I
Anemia								
A	6.66 (0.45, 442.41)	0.82 (0.11, 6.14)	2.27 (0.58, 9.09)	4.45 (0.25, 388.89)	3.14 (0.13, 207.64)	4.06 (0.15, 262.10)	6.72 (0.10, 760.28)	0.40 (0.01, 6.07)
0.15 (0.00, 2.22)	B	0.12 (0.00, 4.02)	0.33 (0.00, 8.85)	0.67 (0.13, 3.74)	0.46 (0.06, 3.57)	0.59 (0.10, 3.75)	0.92 (0.06, 20.23)	0.05 (0.00, 2.59)
1.22 (0.16, 9.35)	8.61 (0.25, 800.01)	C	2.76 (0.62, 13.17)	5.85 (0.15, 659.05)	4.19 (0.07, 433.51)	5.26 (0.09, 520.05)	8.82 (0.06, 1636.37)	0.47 (0.01, 15.49)
0.44 (0.11, 1.73)	3.03 (0.11, 231.76)	0.36 (0.08, 1.62)	D	2.12 (0.07, 219.47)	1.50 (0.03, 110.75)	1.84 (0.04, 133.90)	3.22 (0.03, 433.80)	0.17 (0.00, 3.60)
0.22 (0.00, 4.03)	1.49 (0.27, 7.82)	0.17 (0.00, 6.86)	0.47 (0.00, 14.55)	E	0.67 (0.07, 6.97)	0.87 (0.10, 7.98)	1.41 (0.07, 31.99)	0.07 (0.00, 4.28)
0.32 (0.00, 7.80)	2.18 (0.28, 16.16)	0.24 (0.00, 13.35)	0.67 (0.01, 30.10)	1.50 (0.14, 13.82)	F	1.26 (0.36, 4.83)	2.07 (0.31, 16.32)	0.10 (0.00, 8.31)
0.25 (0.00, 6.71)	1.69 (0.27, 9.97)	0.19 (0.00, 11.62)	0.54 (0.01, 26.88)	1.14 (0.13, 9.56)	0.79 (0.21, 2.78)	G	1.56 (0.16, 19.56)	0.08 (0.00, 7.52)
0.15 (0.00, 9.54)	1.09 (0.05, 17.48)	0.11 (0.00, 16.41)	0.31 (0.00, 38.72)	0.71 (0.03, 13.49)	0.48 (0.06, 3.19)	0.64 (0.05, 6.16)	H	0.05 (0.00, 10.68)
2.52 (0.16, 132.15)	19.49 (0.39, 3462.34)	2.12 (0.06, 176.33)	5.72 (0.28, 349.63)	13.67 (0.23, 3023.80)	9.84 (0.12, 2430.54)	12.57 (0.13, 2649.54)	20.06 (0.09, 10519.60)	I
Constipation								
E	28.35 (0.79, 1781.19)	19.71 (0.17, 2641.63)	0.90 (0.01, 100.20)					
0.04 (0.00, 1.27)	F	0.67 (0.03, 14.56)	0.03 (0.00, 9.95)					
0.05 (0.00, 5.91)	1.49 (0.07, 36.18)	H	0.05 (0.00, 33.52)					
1.11 (0.01, 107.22)	31.02 (0.10, 13635.96)	20.61 (0.03, 15205.55)	J					
Diarrhea								
A	0.82 (0.02, 20.71)	0.58 (0.06, 3.55)	0.80 (0.02, 20.15)					
1.22 (0.05, 40.08)	B	0.69 (0.01, 32.82)	0.91 (0.01, 115.77)					
1.74 (0.28, 15.60)	1.45 (0.03, 69.88)	D	1.53 (0.02, 70.10)					

1.25 (0.05, 64.56)	1.10 (0.01, 129.69)	0.65 (0.01, 54.89)	I			
Fatigue						
A	4.36 (0.31, 115.26)	0.54 (0.01, 15.46)	0.41 (0.01, 6.38)	2.62 (0.13, 83.90)	0.96 (0.11, 6.64)	3.07 (0.03, 277.88)
0.23 (0.01, 3.22)	B	0.13 (0.00, 8.76)	0.10 (0.00, 4.35)	0.60 (0.13, 2.42)	0.22 (0.01, 6.26)	0.63 (0.02, 29.94)
1.84 (0.06, 92.14)	7.62 (0.11, 1255.68)	C	0.76 (0.11, 4.58)	4.47 (0.05, 890.45)	1.65 (0.03, 141.75)	5.82 (0.02, 2556.15)
2.42 (0.16, 90.56)	10.03 (0.23, 1553.97)	1.31 (0.22, 8.96)	D	6.03 (0.10, 1029.18)	2.29 (0.07, 140.18)	7.77 (0.03, 3170.79)
0.38 (0.01, 7.61)	1.67 (0.41, 7.41)	0.22 (0.00, 20.77)	0.17 (0.00, 10.28)	E	0.32 (0.01, 12.65)	1.10 (0.04, 38.68)
1.04 (0.15, 9.07)	4.49 (0.16, 174.74)	0.61 (0.01, 30.53)	0.44 (0.01, 14.52)	3.09 (0.08, 124.67)	I	3.37 (0.02, 481.80)
0.33 (0.00, 33.43)	1.58 (0.03, 61.27)	0.17 (0.00, 57.73)	0.13 (0.00, 30.35)	0.91 (0.03, 27.52)	0.30 (0.00, 50.71)	J
Nausea/Vomiting						
B	0.14 (0.02, 1.19)	0.15 (0.01, 1.54)	1.19 (0.18, 9.70)	0.52 (0.02, 12.85)		
6.91 (0.84, 62.38)	E	1.06 (0.14, 6.78)	8.12 (0.84, 101.89)	3.71 (0.21, 61.74)		
6.58 (0.65, 79.21)	0.94 (0.15, 6.96)	F	7.82 (0.94, 91.76)	3.45 (0.41, 31.73)		
0.84 (0.10, 5.51)	0.12 (0.01, 1.19)	0.13 (0.01, 1.06)	G	0.45 (0.02, 9.01)		
1.92 (0.08, 53.01)	0.27 (0.02, 4.80)	0.29 (0.03, 2.43)	2.24 (0.11, 59.92)	H		

Notes: OR = Odds ratio; 95% CI = confidence intervals; A = Gemcitabine; B = Cisplatin + Gemcitabine; C = Paclitaxel + Gemcitabine; D = Carboplatin + Gemcitabine; E = Carboplatin + Paclitaxel; F = Vinorelbine + Gemcitabine; G = Cisplatin + Gemcitabine + Vinorelbine; H = Vinorelbine + Carboplatin; I = Docetaxel + Gemcitabine; J = Dicycloplatin + Paclitaxel.