Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Efficacy and safety of sodium cantharidinate and vitamin B6 injection for the treatment of digestive system neoplasms: a meta-analysis of randomized controlled trials

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Objective: To systematically evaluate the efficacy and safety of sodium cantharidinate and vitamin B6 (SC/B6) combined with conventional medical treatment (CMT) for the treatment of patients with advanced digestive system neoplasms (DSNs).

Methods: The Cochrane Library, Embase, PubMed, Web of Science, Chinese Scientific Journal Database (VIP), China National Knowledge Infrastructure, and Wanfang databases were searched for clinical trials using SC/B6 for DSNs. Outcome measures, including therapeutic efficacy, quality of life (QoL), and adverse events, were extracted and systematically evaluated.

Results: Data from 24 trials including 1,825 advanced DSN patients were included. Compared with CMT alone, its combination with SC/B6 significantly improved the patients' overall response rate (OR =2.25, 95% CI =1.83–2.76, $P<0.00001$), disease control rate (OR =2.41, 95% CI =1.85–3.15, $P<0.00001$), and QoL improvement rate (OR =2.75, 95% CI =2.13–3.55, $P<0.00001$). Moreover, adverse events caused by chemotherapy, including leukopenia, nausea and vomiting, gastrointestinal side effects, hepatotoxicity, diarrhea, transaminase disorder, myelosuppression, anorexia, and anemia, were significantly alleviated ($P<0.05$) when SC/B6 was applied to DSN patients. Nephrotoxicity, thrombocytopenia, hand-foot syndrome, and oral mucositis were not significantly alleviated in patients receiving combination therapy ($P>0.05$).

Conclusion: The combination of SC/B6 and CMT is more effective in treating DSNs than CMT alone. This combination alleviates the adverse effects associated with chemotherapy and improves the QoL of DSN patients, and its application in the clinic is worth promoting.

Keywords: sodium cantharidinate and vitamin B6, conventional medical treatment, digestive system neoplasms, meta-analysis

Introduction

Digestive system neoplasms (DSNs) are the leading cause of cancer-related death worldwide, and cause 3,056,412 deaths in 2018, which accounts for 32% of all cancer deaths worldwide.[1–3] This category comprises colorectal cancer, gastric cancer, liver cancer, esophageal cancer, and pancreatic cancer, which are the fourth, sixth, seventh, ninth, and fourteenth most common cancers, respectively.[1] Despite improvements in diagnostic and therapeutic methods in the past decades,[4] the prognosis of DSNs is still poor, because they are mostly diagnosed at advanced stages, which may be accompanied by extensive invasion and distant metastasis.[4–6] Therefore, effective therapeutic approaches should be developed.

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In recent years, traditional Chinese medicine has been more widely used as auxiliary treatment in tumor therapy and has shown promising therapeutic effects in many clinical studies.[7–9] Sodium cantharidinate/vitamin B6 (SC/B6) is a combination of sodium cantharidinate (SC) and vitamin B6, and has the pharmacologic characteristics of both.[7,8] SC is a derivative of cantharidin, which is extracted from the body of meloidae insects such as *Mylabris phalerata pallas* and *Mylabris cichorii linnaeus*.[10] SC preserves the unique anticancer activity of cantharidin and has lower toxicity and fewer adverse effects.[7,10] Its combination with vitamin B6 can even further lower the side effects.[7] In recent years, SC has been used as a safe auxiliary antitumor drug for malignancies such as gastric cancer, liver cancer, and non-small-cell lung cancer.[7–9,11] Tao et al[12] indicated that SC induces HepG2 cells to undergo apoptosis through the LC3 autophagy pathway. Liang et al[13] showed that SC can inhibit tumor growth by downregulating vascular endothelial growth factor expression and blocking tumor angiogenesis. In addition, SC can also have an anticancer effect by blocking progression through the cell cycle, inhibiting invasion/metastasis, and improving the immunity of cancer patients.[14–18]

Several clinical studies[8,19–41] have revealed the prominent therapeutic effects of SC/B6 and conventional medical treatment (CMT, including chemotherapy, symptomatic, and supporting therapy) for advanced DSNs but clinical efficacy and safety have not been systematically evaluated. In this study, we performed a meta-analysis to evaluate the efficacy and safety of SC/B6 for DSN treatment, with a comparison between SC/B6 and CMT combined therapy and CMT alone, in order to provide scientific reference for the design of future clinical trials.

Materials and methods

Search strategy and selection criteria

Publications were searched across the Cochrane Library, Embase, Pubmed, Web of Science, Chinese Scientific Journal Database (VIP), China National Knowledge Infrastructure, and Wanfang databases, using the search terms "sodium cantharidinate" or "disodium cantharidinate" and "vitamin B6" combined with "gastric cancer" or "colorectal cancer" or "gastrointestinal cancer" or "liver cancer" or "esophageal cancer" or "pancreatic cancer" or "digestive system neoplasms" without restriction on the language. The retrieval was initiated in May 2018 and updated in August 2018.

All of the clinical trials brought into this analysis were randomized controlled trials with reference to advanced DSNs, in which patients in the experimental groups were treated by SC/B6 and CMT combined therapy, and patients in the control groups were treated by CMT alone.

Data extraction and quality assessment

Literature screening and data extraction were carried out by two independent investigators (Meirong Liu and Chunhong Xu) and verified by a third reviewer (Yingying Sun). All included studies were summarized as follows: first author name, year of publication, study location, Karnofsky Performance Score (KPS), number of cases, patient ages, study parameter type, treatment regimen and enrollment period, and administration route and dosage of SC/B6. The quality of the included trials was evaluated as described in the Cochrane Handbook.[42]

Outcome definition

Clinical responses, including therapeutic effects, quality of life (QoL), and adverse events, were analyzed. Therapeutic effects were evaluated by overall survival (OS) rate, complete response (CR) rate, partial response (PR) rate, stable disease (SD) rate, progressive disease (PD) rate, overall response rate (ORR, ORR = CR + PR), and disease control rate (DCR = CR + PR + SD). OS was defined as the length of time from the start of treatment to death from any cause; QoL was assessed using KPS scales and the European Organization for Research and Treatment of Cancer core quality-of-life questionnaire. The QoL improvement rate (QIR) was defined as the improvement in QoL after treatment. Adverse events, including leukopenia, nausea and vomiting, gastrointestinal side effects, hepatotoxicity, nephrotoxicity, diarrhea, thrombocytopenia, transaminase disorder, myelosuppression, hand-foot syndrome, oral mucositis, anorexia, and anemia, were also assessed.

Statistical analysis

Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 13.0 (Stata Corp., College Station, TX, USA) were the main statistical analysis tools in this study. $P<0.05$ indicated statistically significant differences. Cochran's Q test was used to determine heterogeneity among studies,[43] and publication bias was analyzed by Begg's and Egger's regression asymmetry tests and presented by funnel plots.[44] $I^2<50\%$ or $P>0.1$ indicated study homogeneity. Therapeutic effects were mainly represented by HRs and ORs presented with 95% CIs. HRs were collected for survival data. If HRs can neither be collected directly nor calculated, survival curve plots were extracted by Engauge Digitizer software and then transformed by specialized form.[45–47]

Pooled analysis with publication bias determined that the trim-and-fill method would be applied to coordinate the estimates of unpublished studies, and the adjusted results were compared with the original pooled OR.[48] Sensitivity analysis (subgroup analyses) was conducted to evaluate the impact of different cancer types, SC/B6 dosages, therapeutic regimens, sample sizes, and study types on clinical efficacy.

Results

Search results

A total of 974 articles were identified with the initial search, and 602 papers were excluded due to duplication. After title and abstract review, 269 articles were further excluded because they did not include clinical trials (n=209), were reviews or meta-analyses (n=6), were unrelated studies (n=43), or were case reports (n=11), leaving 103 studies as potentially relevant. After detailed assessment of full texts, articles without a control group (n=11), studies with inappropriate criteria in the experimental or control group (n=16), studies with insufficient data (n=5), and studies including patients with non-digestive system tumors (n=47) were excluded. Finally, data from 24 trials[8,19–41] (gastric cancer, n=7; colorectal cancer, n=5; gastrointestinal cancer, n=3; liver cancer, n=7; esophageal cancer, n=1; and pancreatic cancer, n=1) including 1,825 advanced DSN patients were included in the present analysis (Figure 1).

Patient characteristics

All studies involved in this analysis were carried out in different hospitals in China. These trials include 1,825 patients with advanced DSNs; of these, 933 were treated by combined SC/B6 and CMT, and 892 were treated by CMT alone. Detailed information on the included trials and patients is presented in Tables 1 and 2.

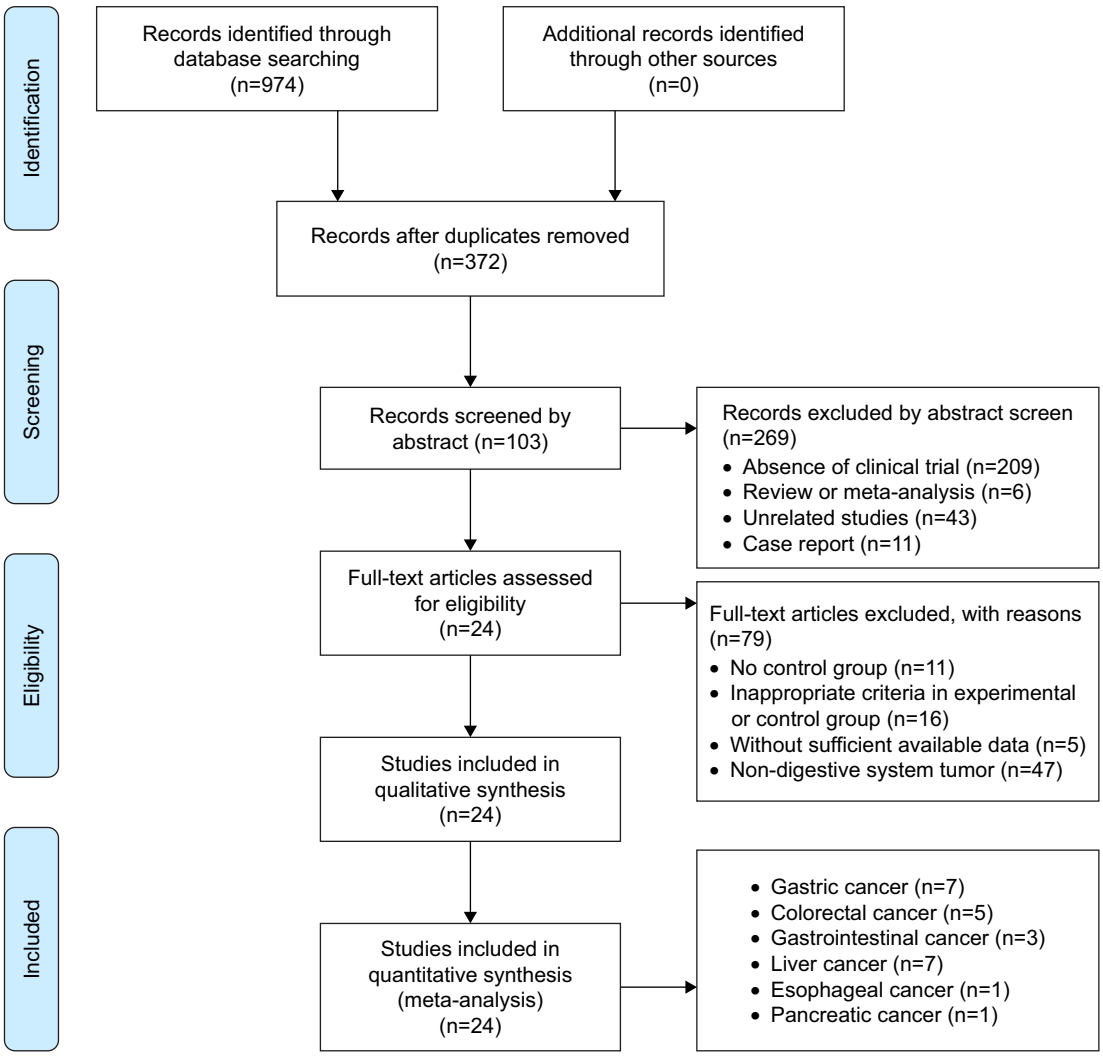

Figure 1 Flow diagram of the selection process.

Table 1 Clinical information from the eligible trials in the meta-analysis

Included studies	Nation	KPS	Patients Con/Exp	Age (years)		Parameter types
				Con	Exp	
Chen Y 2016[19]	China	ND	25/25	61.27±1.46 (mean)	61.25±1.44 (mean)	ORR, DCR, QIR, AE
Fan LJ 2009[20]	China	KPS ≥60	42/42	51.5 (mean)	52.3 (mean)	ORR, DCR
Fan QL 2013[21]	China	KPS >60	19/23	ND	ND	ORR, DCR, QIR, AE
Fang XH 2016[22]	China	KPS >50	37/37	64.3±10.3 (mean)	66.3±9.3 (mean)	ORR, DCR
Guan LY 2015[23]	China	KPS >60	27/27	ND	ND	ORR, DCR, QIR, AE
Jia JM 2013[24]	China	KPS ≥60	18/18	ND	ND	ORR, DCR, QIR, AE
Li GP 2010[25]	China	KPS >60	25/25	40–58	42–65	AE
Liu GW 2017[26]	China	KPS ≥60	20/20	35–76 (mean)	37–74 (mean)	ORR, DCR, QIR, AE
Liu SH 2008[27]	China	60–90 (KPS)	32/32	54.7 (mean)	52.2 (mean)	ORR, DCR, QIR, AE
Mao WD 2016[28]	China	KPS ≥70	32/33	56.3±15.5 (mean)	55.7±17.2 (mean)	ORR, DCR, AE
Shao H 2014[8]	China	ND	41/63	41.71±8.55 (mean)	38.74±11.06 (mean)	ORR, DCR
Shi XY 2017[29]	China	KPS >60	48/48	62.14±11.23 (mean)	61.59±11.02 (mean)	ORR, DCR, QIR, AE
Tian XL 2006[30]	China	KPS ≥70	36/36	52.5±9.6 (mean)	53.4±10.5 (mean)	ORR, DCR, QIR, AE
Wang JH 2010[31]	China	50–90 (KPS)	26/26	51.79 (mean)	53.26 (mean)	ORR, DCR, QIR, AE
Wang YW 2017[32]	China	KPS ≥70	42/42	62.1±10.2 (mean)	61.2±9.7 (mean)	ORR, DCR, QIR, AE
Wei YF 2015[33]	China	KPS >70	44/48	ND	ND	ORR, DCR, AE
Wu ZM 2013[34]	China	ND	32/32	ND	ND	ORR, DCR, AE
Xie ZX 2016[35]	China	ND	32/32	58.1±3.2 (mean)	57.3±2.8 (mean)	ORR, DCR, QIR, AE
You ZY 2015[36]	China	KPS ≥60	85/85	ND	ND	ORR, DCR, QIR
Zeng L 2009[37]	China	60–80 (KPS)	63/63	ND	ND	ORR, DCR, QIR
Zhang MJ 2011[38]	China	KPS ≥60	38/38	55.0±2.2 (mean)	54.0±2.4 (mean)	ORR, DCR, QIR, AE
Zhang W 2012[39]	China	KPS ≥70	42/42	61.2 (mean)	62.1 (mean)	ORR, DCR
Zhang W 2015[40]	China	KPS ≥70	36/48	59.6 (median)	54.2 (median)	ORR, DCR, QIR, AE
Zhu WQ 2014[41]	China	ND	50/48	ND	ND	ORR, DCR, AE

Abbreviations: AE, adverse events; CMT, conventional medical treatment; Con, control group (CMT alone group); DCR, disease control rate; Exp, experimental group (SC/B6 plus CMT combined group); KPS, Karnofsky Performance Score; ND, nondetermined; ORR, overall response rate; QIR, quality-of-life improved rate; SC/B6, sodium cantharidinate and vitamin B6 injection.

Quality assessment

The evaluation of bias risk is presented in Figure 2. Twenty-two studies had low risk, and the other two articles did not have a clear description of the randomization process. None of the included trials provided a clear description of the performance and detection risks. Two studies were regarded as high-risk due to the absence of follow-up and seven trials were considered as unclear risk owing to selective reporting.

Therapeutic efficacy assessments

As shown in Figures 3 and 4, Table 3, and Figure S1, patients who underwent combined therapy had a significantly improved CR rate (OR =2.06, 95% CI =1.41–3.00, P=0.0002), PR rate (OR =1.85, 95% CI =1.50–2.29, P<0.00001), ORR (OR =2.25, 95% CI =1.83–2.76, P<0.00001), and DCR (OR =2.41, 95% CI =1.85–3.15, P<0.00001), and significantly decreased SD and PD rates (SD, OR =0.77, 95% CI =0.63–0.93, P=0.009; PD, OR =0.45, 95% CI =0.35–0.59, P<0.00001) compared to patients receiving CMT alone. The OS rates of patients who received combination treatment (HR =0.74, 95% CI =0.47–1.17, P=0.20) did not differ significantly from those in patients who received CMT alone.

QoL assessment

QoL evaluation demonstrated that SC/B6 and CMT combined therapy-treated DSN patients had improved QoL compared to those treated by CMT alone (Figure 5A, OR =2.75, 95% CI =2.13–3.55, P<0.00001).

Adverse events assessment

As shown in Table 4 and Figure S2, patients treated by SC/B6 and CMT combined therapy had lower incidences

Table 2 Information of SC/B6 combined with conventional medical treatment

Included studies	Therapeutic regimen		Enrollment period	Dosage of apatinib
	Experimental group	Control group		
Chen Y 2016[19]	CMT + SC/B6	CMT (raltitrexed, oxaliplatin)	2,013.4–2,016.4	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Fan LJ 2009[20]	CMT + SC/B6	CMT (calcium folinate, 5-Fu)	2,005.2–2,009.7	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Fan QL 2013[21]	CMT + SC/B6	CMT (S-1)	ND	20 mL/time (0.1 mg/10 mL, IV), 1 time/day
Fang XH 2016[22]	CMT + SC/B6	CMT (ND)	2,012.1–2,014.8	40 mL/time (0.1 mg/10 mL, IV), 1 time/day
Guan LY 2015[23]	CMT + SC/B6	CMT (S-1)	2,012.10–2,014.10	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Jia JM 2013[24]	CMT + SC/B6	CMT (oxaliplatin, paclitaxel)	2,011.1–2,012.10	20 mL/time (0.1 mg/10 mL, IV), 1 time/day
Li GP 2010[25]	CMT + SC/B6	CMT (FOLFOX4)	2,008.3–2,009.9	40 mL/time (0.1 mg/10 mL, IV), 1 time/day
Liu GW 2017[26]	CMT + SC/B6	CMT (capecitabine)	2,014.1–2,016.1	40 mL/time (0.1 mg/10 mL, IV), 1 time/day
Liu SH 2008[27]	CMT + SC/B6	CMT (leucovorin, oxaliplatin)	2,005.1–2,007.1	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Mao WD 2016[28]	CMT + SC/B6	CMT (capecitabine)	2,012.6–2,013.12	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Shao H 2014[8]	CMT + SC/B6	CMT (ND)	2,011.1–2,012.11	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Shi XY 2017[29]	CMT + SC/B6	CMT (XELOX)	2,013.12–2,015.12	20 mL/time (0.1 mg/10 mL, IV), 1 time/day
Tian XL 2006[30]	CMT + SC/B6	CMT (mitomycin, adriamycin/5-Fu, cisplatin)	2,001.9–2,003.9	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Wang JH 2010[31]	CMT + SC/B6	CMT (FOLFOX4)	2,008.1–2,009.10	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Wang YW 2017[32]	CMT + SC/B6	CMT (capecitabine)	2,016.6–2,017.6	20 mL/time (0.1 mg/10 mL, IV), 1 time/day
Wei YF 2015[33]	CMT + SC/B6	CMT (5-Fu, epirubicin, mitomycin)	2,010.1–2,011.9	80 mL/time (0.1 mg/10 mL, IV), 1 time/day
Wu ZM 2013[34]	CMT + SC/B6	CMT (FOLFIRI)	2,008.5–2,011.1	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Xie ZX 2016[35]	CMT + SC/B6	CMT (oxaliplatin, S-1)	2,013.4–2,015.4	40 mL/time (0.1 mg/10 mL, IV), 1 time/day
You ZY 2015[36]	CMT + SC/B6	CMT (cisplatin, 5-Fu)	2,010.4–2,012.6	ND
Zeng Li 2009[37]	CMT + SC/B6	CMT (ND)	2,005.3–2,008.6	30–50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Zhang MJ 2011[38]	CMT + SC/B6	CMT (mitomycin, adriamycin)	ND	50 mL/time (0.1 mg/10 mL, IV), 1 time/day
Zhang W 2012[39]	CMT + SC/B6	CMT (capecitabine)	2,007.2–2,011.7	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Zhang W 2015[40]	CMT + SC/B6	CMT (XELOX)	2,012.3–2,014.12	30 mL/time (0.1 mg/10 mL, IV), 1 time/day
Zhu WQ 2014[41]	CMT + SC/B6	CMT (ND)	2,008.3–2,012.3	50 mL/time (0.1 mg/10 mL, IV), 1 time/day

Abbreviations: 5-Fu, 5-fluorouracil; CMT, conventional medical treatment; Con, control group (CMT alone group); Exp, experimental group (SC/B6 plus CMT combined group); FOLFOX, oxaliplatin + calcium folinate + 5-fluorouracil; FOLFIRI, calcium folinate + irinotecan + 5-fluorouracil; IV, intravenous; S-1, gimeracil and oteracil porassium capsules; ND, nondetermined; SC/B6, sodium cantharidinate and vitamin B6 injection; XELOX, oxaliplatin + capecitabine.

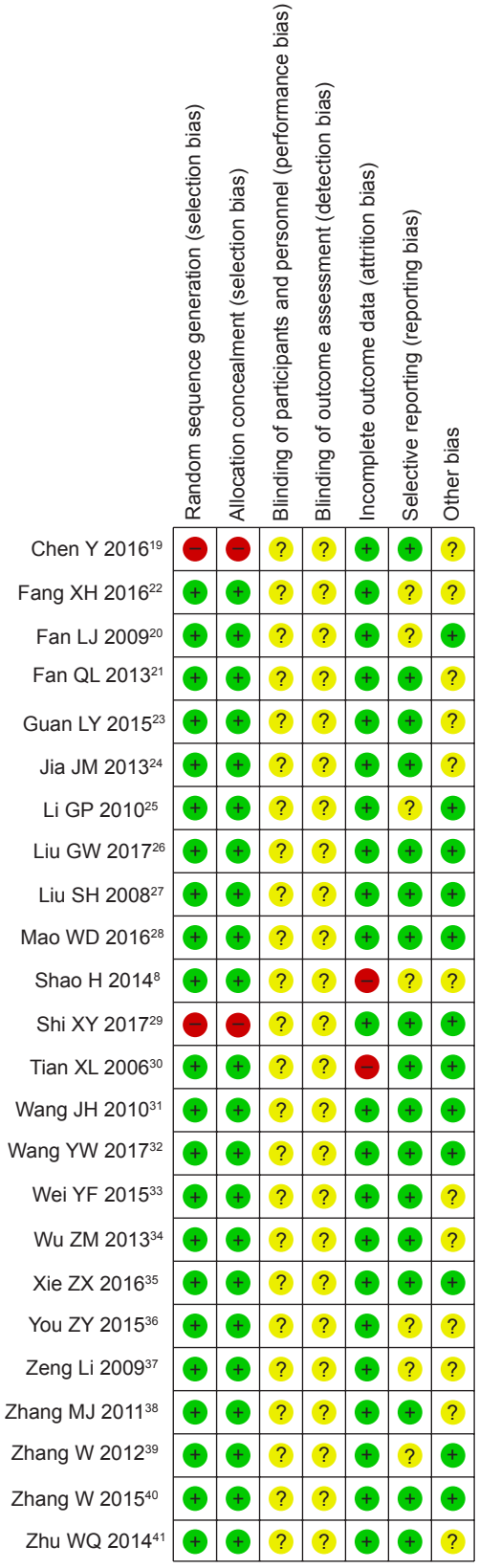

Figure 2 Risk of bias summary: review of authors' judgments about each risk of bias item for included studies.
Note: Each color represents a different level of bias: red for high risk, green for low risk, and yellow for unclear risk of bias.

of leukopenia, nausea and vomiting, gastrointestinal side effects, hepatotoxicity, diarrhea, transaminase disorder, myelosuppression, anorexia, and anemia than those treated with CMT alone (leukopenia: OR =0.29, 95% CI =0.21–0.39, $P<0.00001$; nausea and vomiting: OR =0.30, 95% CI =0.22–0.40, $P<0.00001$; gastrointestinal side effects: OR =0.42, 95% CI =0.29–0.62, $P<0.00001$; hepatotoxicity: OR =0.49, 95% CI =0.30–0.78, $P=0.003$; diarrhea: OR =0.37, 95% CI =0.23–0.60, $P<0.0001$; transaminase disorder: OR =0.23, 95% CI =0.09–0.62, $P=0.003$; myelosuppression: OR =0.33, 95% CI =0.18–0.60, $P=0.0003$; anorexia: OR =0.37, 95% CI =0.20–0.68, $P=0.001$; anemia: OR =0.54, 95% CI =0.32–0.91, $P=0.02$). No significant difference was found in the occurrence of nephrotoxicity, thrombocytopenia, hand-foot syndrome, and oral mucositis (nephrotoxicity: OR =0.70, 95% CI =0.38–1.30, $P=0.26$; thrombocytopenia: OR =0.77, 95% CI =0.31–1.92, $P=0.57$; hand-foot syndrome: OR =0.75, 95% CI =0.40–1.40, $P=0.36$; oral mucositis: OR =0.45, 95% CI =0.13–1.62, $P=0.22$) between patients receiving combination treatment and those receiving CMT alone.

Publication bias

Publication bias of primary outcomes (CR, PR, SD, PD, ORR, DCR, QIR, and adverse events) was evaluated and presented by funnel plots. All plots were approximately symmetrical, indicating generally controlled publication bias (Figures 6 and S3).

We also assessed the publication bias by Begg's and Egger's regression asymmetry tests, and SD and leukopenia were found to have bias (SD, Egger: 0.024, Begg: 0.039; leukopenia, Egger: 0.041, Begg: 0.080; Table 5). To determine whether the bias affected the pooled risk, we conducted trim-and-fill analysis. The adjusted OR indicated the same trend as the primary analysis (SD, before: $P=0.010$, after: $P<0.0001$; leukopenia, before: $P<0.0001$, after: $P<0.0001$), reflecting the reliability of our primary conclusions, except those based on a small number of trials.

Sensitivity analysis

Subgroup analysis was performed for ORR and DCR heterogeneity assessment concerning cancer types, SC/B6 dosages, therapeutic regimens, sample sizes, and study types of involved trials. No significant difference was observed in the sample sizes, study types, or SC/B6 dosages (Table 6). SC/B6 combined with CMT was more effective in treating gastric cancer, colorectal cancer, and liver cancer. Moreover, SC/B6

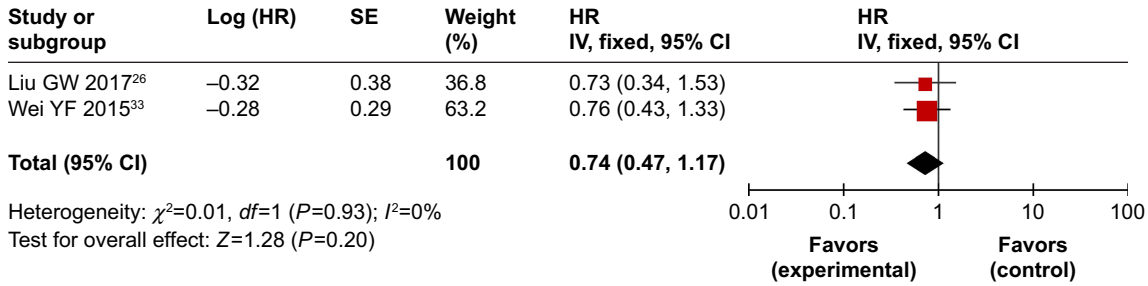

Figure 3 Forest plot of the comparison of overall survival between the experimental and control groups.
Notes: Control group, CMT-alone group; Experimental group, sodium cantharidinate and vitamin B6 injection (SC/B6) + CMT. The fixed-effects meta-analysis model (inverse variance method) was used.
Abbreviations: CMT, conventional medical treatment; IV, intravenous.

combined with oxaliplatin and capecitabine (XELOX) or capecitabine regimens was more effective for DSN treatment.

Discussion

The chemotherapeutic regimens commonly used to treat DSNs cause serious side effects, such as myelosuppression, hepatotoxicity, and gastrointestinal side effects, which severely affect the QoL of DSN patients.[7,9] Therefore, seeking a therapy that can improve treatment outcomes and decrease the adverse effects of chemotherapy is a major direction in the development of tumor treatment. Traditional Chinese medicine plays a unique role in improving host immunity and lowering the toxic effects of chemotherapy.[7,9,49–52] In recent decades, SC/B6 has been clinically applied as an adjuvant therapy for malignancies and has been beneficial for advanced DSN patients in several trials.[7–9,11] Despite the published reports on clinical trials using SC/B6, its therapeutic effects have not been systematically demonstrated.

A

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[19]	11	25	4	25	1.8	4.13 (1.09, 15.59)
Fan LJ 2009[20]	18	42	9	42	4.2	2.75 (1.06, 7.16)
Fan QL 2013[21]	13	23	7	19	2.7	2.23 (0.64, 7.74)
Fang XH 2016[22]	23	37	17	37	5.2	1.93 (0.76, 4.88)
Guan LY 2015[23]	3	27	2	27	1.5	1.56 (0.24, 10.19)
Jia JM 2013[24]	9	18	6	18	2.4	2.00 (0.52, 7.69)
Liu GW 2017[26]	18	20	13	20	1.1	4.85 (0.86, 27.22)
Liu SH 2008[27]	23	32	21	32	4.8	1.34 (0.46, 3.87)
Mao WD 2016[28]	17	33	9	32	3.6	2.72 (0.97, 7.60)
Shao H 2014[8]	7	45	0	17	0.5	6.82 (0.37, 126.16)
Shi XY 2017[29]	18	48	12	48	6.1	1.80 (0.75, 4.32)
Tian XL 2006[30]	16	35	12	33	5.5	1.47 (0.56, 3.90)
Wang JH 2010[31]	12	26	7	26	3.1	2.33 (0.73, 7.42)
Wang YW 2017[32]	18	42	9	42	4.2	2.75 (1.06, 7.16)
Wei YF 2015[33]	30	48	22	44	7.0	1.67 (0.73, 3.83)
Wu ZM 2013[34]	13	32	14	32	6.8	0.88 (0.33, 2.37)
Xie ZX 2016[35]	19	32	14	32	4.6	1.88 (0.70, 5.07)
You ZY 2015[36]	59	85	41	85	10.2	2.44 (1.30, 4.56)
Zeng Li 2009[37]	32	63	6	63	2.4	9.81 (3.70, 26.01)
Zhang MJ 2011[38]	15	38	14	38	6.9	1.12 (0.44, 2.82)
Zhang W 2012[39]	18	42	9	42	4.2	2.75 (1.06, 7.16)
Zhang W 2015[40]	20	48	10	36	5.4	1.86 (0.73, 4.70)
Zhu WQ 2014[41]	32	48	21	50	5.6	2.76 (1.21, 6.28)
Total (95% CI)		**889**		**840**	**100**	**2.25 (1.83, 2.76)**
Total events	444		279			

Heterogeneity: χ^2=20.39, *df*=22 (*P*=0.56); I^2=0%
Test for overall effect: *Z*=7.71 (*P*<0.00001)

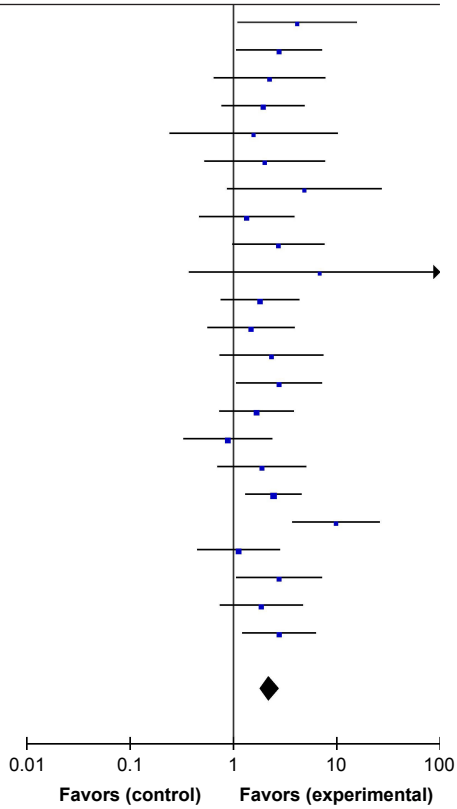

Figure 4 (*Continued*)

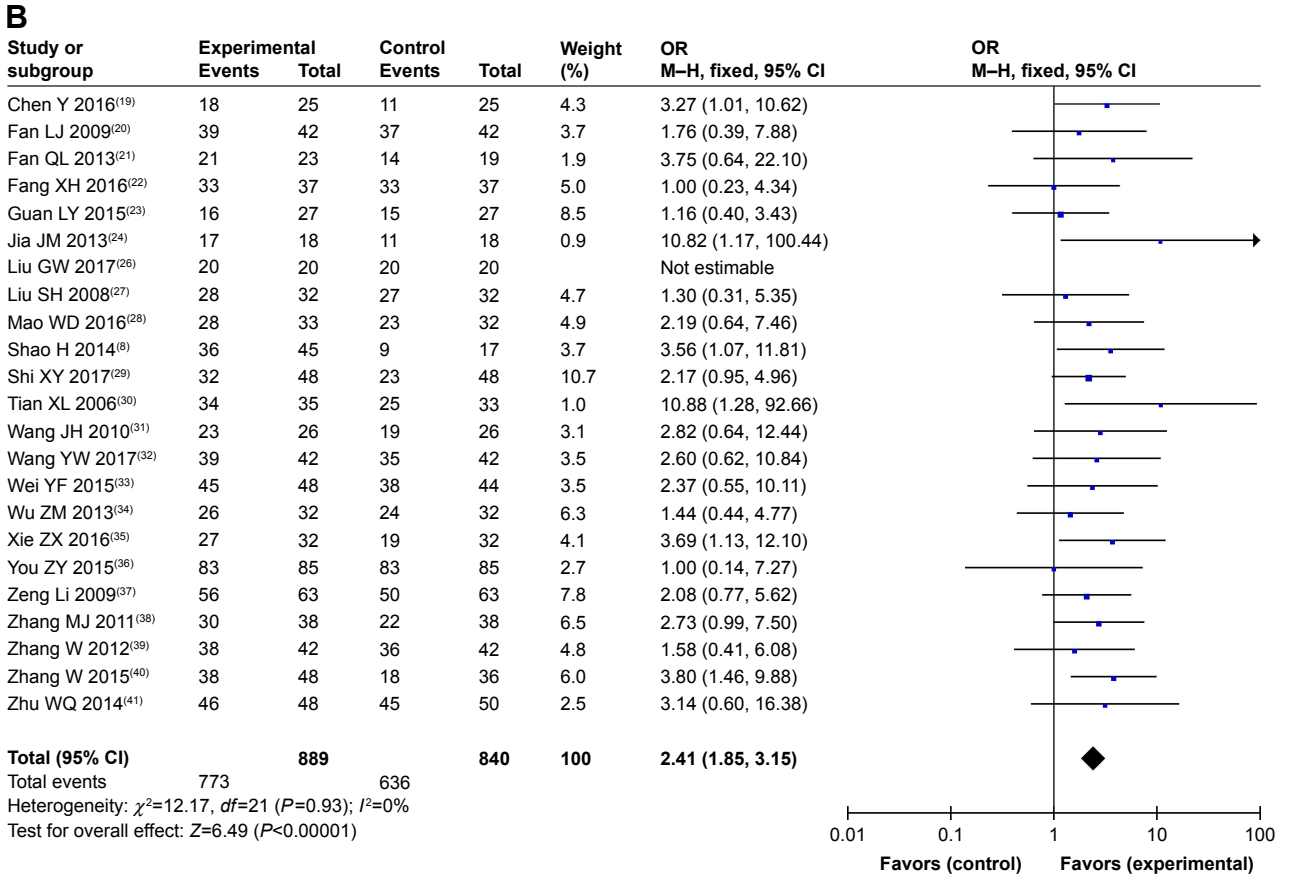

Figure 4 Forest plot of the comparison of overall response rate (**A**) and disease control rate (**B**) between the experimental and control groups.
Notes: Control group, CMT-alone group; Experimental group, sodium cantharidinate and vitamin B6 injection (SC/B6) + CMT. The fixed-effects meta-analysis model (M–H method) was used.
Abbreviations: CMT, conventional medical treatment; M–H, Mantel–Haenszel.

In the present study, we performed an extensive literature search followed by rigorous contrasting and combining data analysis for categorization to provide clear and systematic conclusions.

Our meta-analysis revealed that SC/B6 and CMT combined therapy for DSN patients achieved more beneficial effects than CMT alone. Combined therapy-treated patients exhibited markedly improved ORR and DCR ($P<0.05$ for all) and also significantly improved QoL. These results indicated that intravenous infusion of SC/B6 improved the curative effects of CMT for advanced DSNs.

Our analysis indicates that most of the adverse events caused by chemotherapy, including leukopenia, nausea and vomiting, gastrointestinal side effects, and hepatotoxicity,

Table 3 Comparison of CR, PR, SD, PD, ORR, and DCR between the SC/B6 + CMT and SC/B6 group

Parameter	SC/B6 + CMT group	CMT group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
	No of patients (n)	No of patients (n)		I^2 (%)	*P*-value			
CR	889	840	Fixed	0	0.99	2.06	1.41–3.00	0.0002
PR	889	840	Fixed	0	0.89	1.85	1.50–2.29	<0.00001
SD	889	840	Fixed	43	0.01	0.77	0.63–0.93	0.009
PD	889	840	Fixed	0	0.91	0.45	0.35–0.59	<0.00001
ORR	889	840	Fixed	0	0.56	2.25	1.83–2.76	<0.00001
DCR	889	840	Fixed	0	0.93	2.41	1.85–3.15	<0.00001

Abbreviations: CMT, conventional medical treatment; CR, complete response rates; DCR, disease control rate; ORR, overall response rate; PD, progressive disease rates; PR, partial response rates; SC/B6, sodium cantharidinate and vitamin B6 injection; SD, stable disease rates.

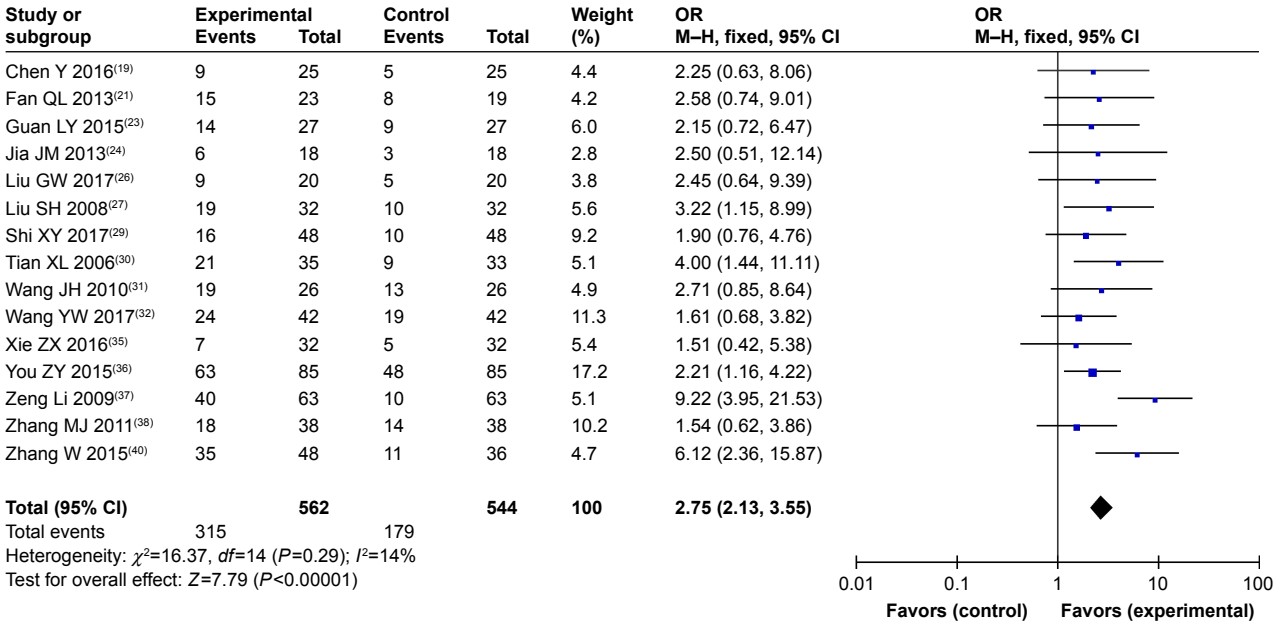

Figure 5 Forest plot of the comparison of quality-of-life improved rate between the experimental and control groups.
Notes: Control group, CMT-alone group; Experimental group, SC/B6 + CMT. The fixed-effects meta-analysis model (M–H method) was used.
Abbreviations: CMT, conventional medical treatment; M–H, Mantel–Haenszel; SC/B6, sodium cantharidinate and vitamin B6 injection.

Table 4 Comparison of adverse events between the SC/B6 + CMT and SC/B6 group

Adverse events	SC/B6 + CMT group	CMT group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
	No patients (n)	No patients (n)		I^2 (%)	*P*-value			
Leucopenia	449	427	Fixed	0	0.72	0.29	0.21–0.39	<0.00001
Leucopenia I + II	364	344	Fixed	0	0.92	0.39	0.28–0.54	<0.00001
Leucopenia III + IV	399	377	Fixed	0	0.99	0.36	0.21–0.63	0.0003
Nausea, vomiting	407	393	Fixed	0	0.93	0.30	0.22–0.40	<0.00001
Nausea, vomiting I + II	242	226	Fixed	0	0.97	0.28	0.19–0.43	<0.00001
Nausea, vomiting III + IV	242	226	Fixed	0	1.00	0.59	0.23–1.51	0.27
Gastrointestinal side effects	278	271	Fixed	0	0.97	0.42	0.29–0.62	<0.00001
Gastrointestinal side effects I + II	167	162	Fixed	0	0.81	0.49	0.30–0.80	0.004
Gastrointestinal side effects III + IV	190	182	Fixed	0	0.54	0.37	0.17–0.79	0.01
Hepatotoxicity	262	257	Fixed	0	0.67	0.49	0.30–0.78	0.003
Hypertension I + II	206	201	Fixed	0	0.69	0.54	0.31–0.94	0.03
Hypertension III + IV	206	201	Fixed	0	0.79	0.44	0.12–1.61	0.22
Nephrotoxicity	277	272	Fixed	0	0.95	0.70	0.38–1.30	0.26
Nephrotoxicity I + II	154	149	Fixed	0	1.00	0.89	0.39–2.08	0.80
Nephrotoxicity III + IV	154	149	Fixed	Not applicable		1.00	0.14–7.40	1.00
Diarrhea	192	176	Fixed	0	0.61	0.37	0.23–0.60	<0.0001
Diarrhea I + II	192	176	Fixed	0	0.74	0.38	0.23–0.62	<0.0001
Diarrhea III + IV	192	176	Fixed	0	0.81	0.58	0.15–2.30	0.44
Thrombocytopenia	143	169	Random	63	0.03	0.77	0.31–1.92	0.57
Thrombocytopenia I + II	141	137	Fixed	0	0.69	0.50	0.27–0.92	0.03
Thrombocytopenia III + IV	141	137	Fixed	0	0.98	0.43	0.09–1.95	0.27

(*Continued*)

Table 4 (*Continued*)

Adverse events	SC/B6 + CMT group	CMT group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
	No patients (n)	No patients (n)		I^2 (%)	*P*-value			
Transaminase disorder	149	145	Random	55	0.07	0.23	0.09–0.62	0.003
Transaminase disorder I + II	117	113	Fixed	0	0.40	0.33	0.15–0.69	0.004
Transaminase disorder III + IV	117	113	Fixed	0	0.80	0.46	0.08–2.57	0.38
Myelosuppression	151	152	Fixed	0	0.90	0.33	0.18–0.60	0.0003
Myelosuppression I + II	151	152	Random	79	0.003	0.70	0.23–2.08	0.52
Myelosuppression III + IV	113	114	Random	0	0.81	0.28	0.11–0.73	0.009
Hand-foot syndrome	116	104	Fixed	0	0.39	0.75	0.40–1.40	0.36
Hand-foot syndrome I + II	116	104	Fixed	0	0.70	0.83	0.44–1.57	0.56
Hand-foot syndrome III + IV	116	104	Fixed	0	0.51	0.49	0.10–2.41	0.38
Oral mucositis	45	45	Fixed	0	0.98	0.45	0.13–1.62	0.22
Oral mucositis I + II	45	45	Fixed	0	0.63	0.34	0.07–1.59	0.17
Oral mucositis III + IV	45	45	Fixed	Not applicable		1.00	0.13–7.72	1.00
Anorexia	92	88	Fixed	39	0.20	0.37	0.20–0.68	0.001
Anorexia I + II	92	88	Fixed	39	0.20	0.37	0.20–0.68	0.001
Anorexia III + IV	92	88	Fixed	Not applicable				
Anemia	162	162	Fixed	0	0.73	0.54	0.32–0.91	0.02
Anemia I + II	77	77	Fixed	0	0.49	0.60	0.31–1.16	0.13
Anemia III + IV	77	77	Fixed	0	0.84	0.41	0.06–2.90	0.37

Abbreviations: CMT, conventional medical treatment; SC/B6, sodium cantharidinate and vitamin B6 injection.

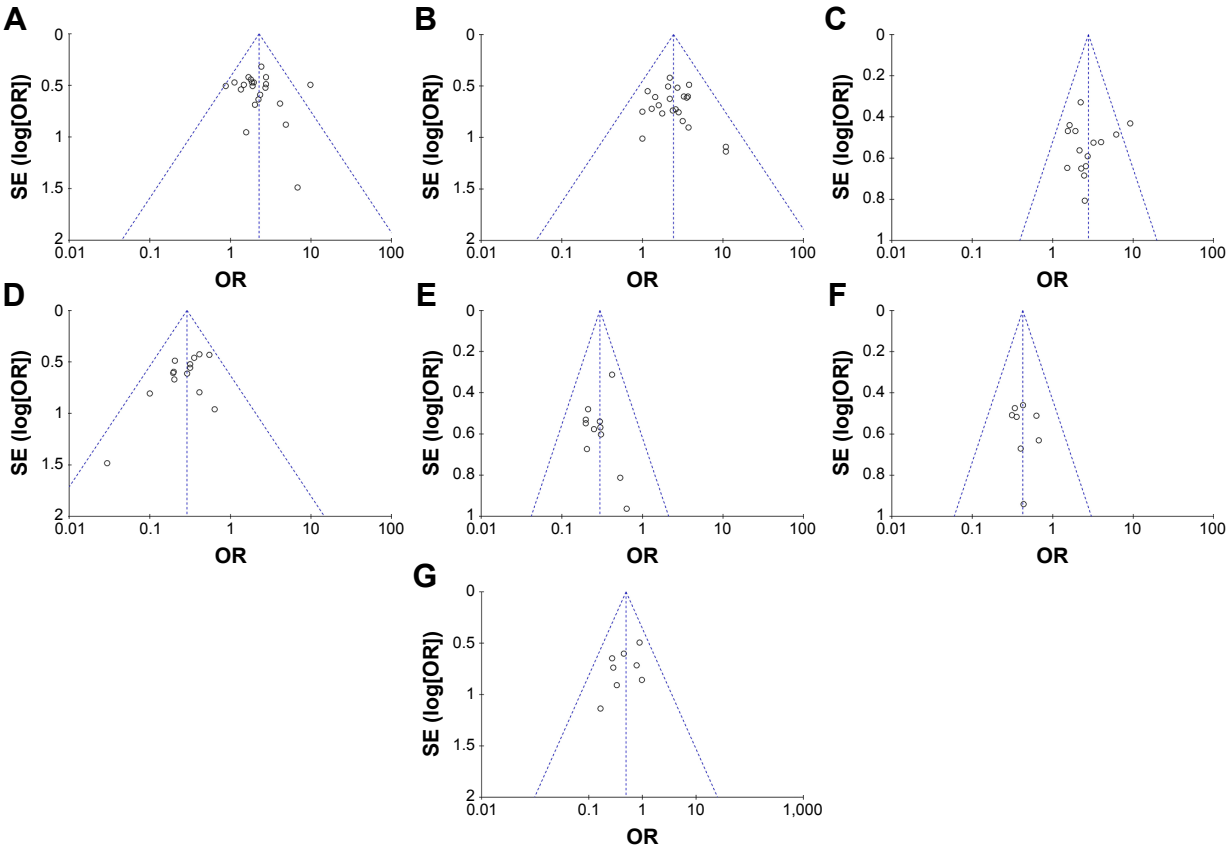

Figure 6 Funnel plot of percentage of overall response rate (**A**), disease control rate (**B**), quality-of-life improved rate (**C**), leukopenia (**D**), nausea and vomiting (**E**), gastrointestinal side effects (**F**), and hepatotoxicity (**G**).
Note: Parameters discussed in over eight papers were conducted bias analyses.

Table 5 Publication bias on therapeutic efficacy and adverse events

Publication bias	Therapeutic efficacy							Adverse events			
	CR	PR	SD	PD	ORR	DCR	QIR	Leukopenia	Nausea and vomiting	Hepatotoxicity	Gastrointestinal side effects
Begg	0.058	0.154	0.039	0.195	0.369	0.612	1.000	0.080	0.213	0.386	0.711
Egger	0.078	0.259	0.024	0.149	0.489	0.425	0.808	0.041	0.697	0.198	0.581

Note: Parameters discussed in over eight papers were conducted bias analyses.
Abbreviations: CR, complete response rates; DCR, disease control rate; ORR, overall response rate; PD, progressive disease rates; PR, partial response rates; QIR, quality-of-life improved rate; SD, stable disease rates.

Table 6 Subgroup analyses of ORR and DCR between the SC/B6 + CMT and SC/B6 groups

Parameter	Factors at study level	Exp group	Con group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
		No patients (n)	No patients (n)		I^2 (%)	*P*-value			
ORR	**Type of cancer**								
	Gastric cancer	219	206	Fixed	0	0.60	1.78	1.20–2.66	0.005
	Colorectal cancer	161	161	Fixed	0	0.79	2.60	1.59–4.26	0.0001
	Gastrointestinal cancer	150	146	Fixed	0	0.96	2.48	1.53–4.02	0.0002
	Liver cancer	314	282	Fixed	54	0.04	2.42	1.70–3.43	<0.00001
	Esophageal cancer	18	18	Fixed			2.00	0.52–7.69	0.31
	Pancreatic cancer	27	27	Fixed			1.56	0.24–10.19	0.64
	Dosage of SC/B6								
	20 mL/day	131	127	Fixed	0	0.93	2.16	1.28–3.66	0.004
	30 mL/day	222	209	Fixed	0	0.81	2.37	1.56–3.58	<0.0001
	40 mL/day	89	89	Fixed	0	0.61	2.19	1.17–4.09	0.01
	50 mL/day	251	223	Fixed	0	0.54	1.68	1.12–2.52	0.01
	Therapeutic regimen								
	SC/B6 + XELOX	96	84	Fixed	0	0.96	1.83	0.97–3.45	0.06
	SC/B6 + S-1	50	46	Fixed	0	0.76	2.00	0.71–5.63	0.19
	SC/B6 + capecitabine	137	136	Fixed	0	0.94	2.91	1.70–4.97	<0.0001
	Study sample size								
	>80	511	469	Fixed	10	0.35	2.70	2.04–3.57	<0.00001
	<80	378	371	Fixed	0	0.84	1.80	1.32–2.44	0.0002
	Type of control trials								
	RCT	816	767	Fixed	0	0.50	2.24	1.81–2.78	<0.00001
	Overall	889	840	Fixed	0	0.56	2.25	1.83–2.76	<0.00001
DCR	**Type of cancer**								
	Gastric cancer	219	206	Fixed	0	0.67	2.32	1.43–3.76	0.0006
	Colorectal cancer	161	161	Fixed	0	0.91	2.41	1.37–4.26	0.002
	Gastrointestinal cancer	150	146	Fixed	0	0.61	2.32	0.90–6.02	0.08
	Liver cancer	314	282	Fixed	0	0.69	2.65	1.64–4.27	<0.0001
	Esophageal cancer	18	18	Fixed			10.82	1.17–100.44	0.04
	Pancreatic cancer	27	27	Fixed			1.16	0.40–3.43	0.78
	Dosage of SC/B6								
	20 mL/day	131	127	Fixed	0	0.59	2.87	1.54–5.35	0.0009
	30 mL/day	222	209	Fixed	0	0.79	2.39	1.45–3.93	0.0006
	40 mL/day	89	89	Fixed	46	0.17	2.22	0.91–5.45	0.08
	50 mL/day	251	223	Fixed	0	0.55	2.45	1.53–3.93	0.0002

(*Continued*)

Table 6 (*Continued*)

Parameter	Factors at study level	Exp group	Con group	Analysis method	Heterogeneity		OR	95% CI	*P*-value
		No patients (n)	No patients (n)		I^2 (%)	*P*-value			
	Therapeutic regimen								
	SC/B6 + XELOX	96	84	Fixed	0	0.39	2.76	1.48–5.14	0.001
	SC/B6 + S-1	50	46	Fixed	18	0.27	1.63	0.66–4.01	0.29
	SC/B6 + capecitabine	137	136	Fixed	0	0.88	2.08	0.97–4.45	0.06
	Study sample size								
	>80	511	469	Fixed	0	0.97	2.40	1.64–3.51	<0.00001
	<80	378	371	Fixed	0	0.59	2.42	1.67–3.52	<0.00001
	Type of control trials								
	RCT	816	767	Fixed	0	0.89	2.40	1.80–3.20	<0.00001
	Overall	889	840	Fixed	0	0.93	2.41	1.85–3.15	<0.00001

Abbreviations: CMT, conventional medical treatment; Con, control group (CMT alone group); DCR, disease control rate; Exp, experimental group (SC/B6 plus CMT combined group); RCT, randomized controlled trial; ORR, overall response rate; S-1, gimeracil and oteracil porassium capsules; SC/B6, sodium cantharidinate and vitamin B6 injection; XELOX, oxaliplatin + capecitabine.

were alleviated with SC/B6 combination therapy ($P<0.05$). Therefore, SC/B6 is a safe auxiliary antitumor medicine for DSN and can effectively alleviate the adverse events associated with chemotherapy.

The analysis of therapeutic effects may be influenced by several factors. In our study, no difference was found between sample sizes, study types, and SC/B6 dosages. SC/B6 combined with CMT was more effective in treating gastric cancer, colorectal cancer, and liver cancer than it was in treating esophageal cancer and pancreatic cancer. Moreover, our subgroup analysis showed that SC/B6 combined with XELOX/capecitabine was more effective for DSN treatment. However, recent studies on the impact of these factors on the curative effect of SC/B6 adjuvant therapy remain insufficient, and further investigations should be performed.

There are some limitations in our analysis. First, the follow-up durations of the included studies were not long enough. Second, as a traditional medicine, SC/B6 was mainly applied in China, which may bring an unavoidable regional bias and subsequently influence the clinical application of SC/B6 worldwide. Furthermore, treatment/medical history is very important for evaluating the efficacy of SC/B6-mediated therapy. However, our data were extracted from published papers rather than from the original patient records; therefore, analytical bias may possibly exist. More original data would be valuable to achieve a higher reliability of statistical analysis on SC/B6 for DSN treatment.

In summary, this meta-analysis indicated that SC/B6 and CMT combined therapy was effective in treating advanced DSNs. Intravenous infusion of SC/B6 not only greatly improved the therapeutic effects of CMT but also effectively alleviated the toxicity and most of the side effects associated with chemotherapy. Therefore, SC/B6 has potential for development as a new adjuvant therapy for the treatment of DSN.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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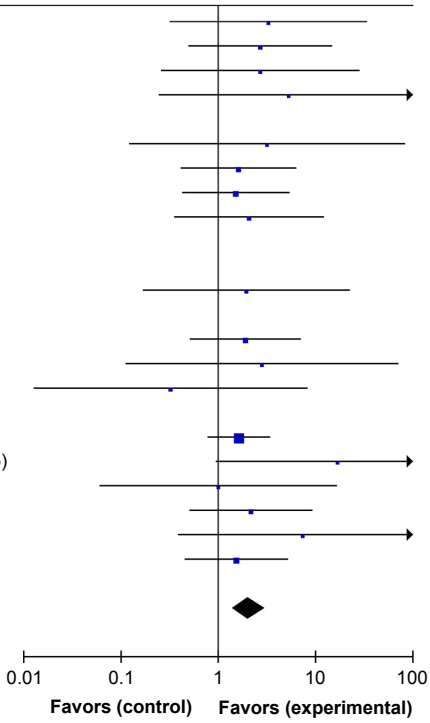
Supplementary materials

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	3	25	1	25	2.2	3.27 (0.32, 33.84)
Fan LJ 2009[2]	5	42	2	42	4.5	2.70 (0.49, 14.79)
Fan QL 2013[3]	3	23	1	19	2.4	2.70 (0.26, 28.34)
Fang XH 2016[4]	2	37	0	37	1.2	5.28 (0.24, 113.87)
Guan LY 2015[5]	0	27	0	27		Not estimable
Jia JM 2013[6]	1	18	0	18	1.2	3.17 (0.12, 83.17)
Liu GW 2017[7]	7	20	5	20	8.2	1.62 (0.41, 6.34)
Liu SH 2008[8]	7	32	5	32	9.9	1.51 (0.42, 5.38)
Mao WD 2016[9]	4	33	2	32	4.5	2.07 (0.35, 12.18)
Shao H 2014[10]	0	45	0	17		Not estimable
Shi XY 2017[11]	0	48	0	48		Not estimable
Tian XL 2006[12]	2	35	1	33	2.5	1.94 (0.17, 22.46)
Wang JH 2010[13]	0	26	0	26		Not estimable
Wang YW 2017[14]	7	42	4	42	8.4	1.90 (0.51, 7.05)
Wei YF 2015[15]	1	48	0	44	1.3	2.81 (0.11, 70.81)
Wu ZM 2013[16]	0	32	1	32	3.7	0.32 (0.01, 8.23)
Xie ZX 2016[17]	0	32	0	32		Not estimable
You ZY 2015[18]	22	85	15	85	28.1	1.63 (0.78, 3.41)
Zeng Li 2009[19]	7	63	0	63	1.1	16.86 (0.94, 301.85)
Zhang MJ 2011[20]	1	38	1	38	2.5	1.00 (0.06, 16.59)
Zhang W 2012[21]	6	42	3	42	6.5	2.17 (0.50, 9.31)
Zhang W 2015[22]	4	48	0	36	1.3	7.38 (0.38, 141.65)
Zhu WQ 2014[23]	7	48	5	50	10.6	1.54 (0.45, 5.22)
Total (95% CI)		**889**		**840**	**100**	**2.06 (1.41, 3.00)**
Total events	89		46			

Heterogeneity: χ^2=6.01, *df*=17 (*P*=0.99); I^2=0%
Test for overall effect: *Z*=3.77 (*P*=0.0002)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	8	25	3	25	1.6	3.45 (0.79, 15.01)
Fan LJ 2009[2]	13	42	7	42	3.7	2.24 (0.79, 6.36)
Fan QL 2013[3]	10	23	6	19	2.9	1.67 (0.47, 5.94)
Fang XH 2016[4]	21	37	17	37	5.7	1.54 (0.62, 3.86)
Guan LY 2015[5]	3	27	2	27	1.4	1.56 (0.24, 10.19)
Jia JM 2013[6]	8	18	6	18	2.6	1.60 (0.41, 6.18)
Liu GW 2017[7]	11	20	8	20	2.8	1.83 (0.52, 6.43)
Liu SH 2008[8]	16	32	16	32	6.2	1.00 (0.38, 2.66)
Mao WD 2016[9]	13	33	7	32	3.3	2.32 (0.78, 6.91)
Shao H 2014[10]	7	45	0	17	0.5	6.82 (0.37, 126.16)
Shi XY 2017[11]	18	48	12	48	5.8	1.80 (0.75, 4.32)
Tian XL 2006[12]	14	35	11	33	5.2	1.33 (0.50, 3.59)
Wang JH 2010[13]	12	26	7	26	2.9	2.33 (0.73, 7.42)
Wang YW 2017[14]	11	42	5	42	2.8	2.63 (0.82, 8.37)
Wei YF 2015[15]	29	48	22	44	7.0	1.53 (0.67, 3.49)
Wu ZM 2013[16]	13	32	13	32	5.9	1.00 (0.37, 2.71)
Xie ZX 2016[17]	19	32	14	32	4.4	1.88 (0.70, 5.07)
You ZY 2015[18]	37	85	26	85	11.3	1.75 (0.93, 3.28)
Zeng Li 2009[19]	25	63	6	63	2.8	6.25 (2.34, 16.67)
Zhang MJ 2011[20]	14	38	13	38	6.3	1.12 (0.44, 2.87)
Zhang W 2012[21]	12	42	6	42	3.3	2.40 (0.80, 7.16)
Zhang W 2015[22]	16	48	10	36	5.9	1.30 (0.51, 3.34)
Zhu WQ 2014[23]	25	48	16	50	5.8	2.31 (1.02, 5.25)
Total (95% CI)		**889**		**840**	**100**	**1.85 (1.50, 2.29)**
Total events	355		233			

Heterogeneity: χ^2=14.19, *df*=22 (*P*=0.89); I^2=0%
Test for overall effect: *Z*=5.77 (*P*<0.00001)

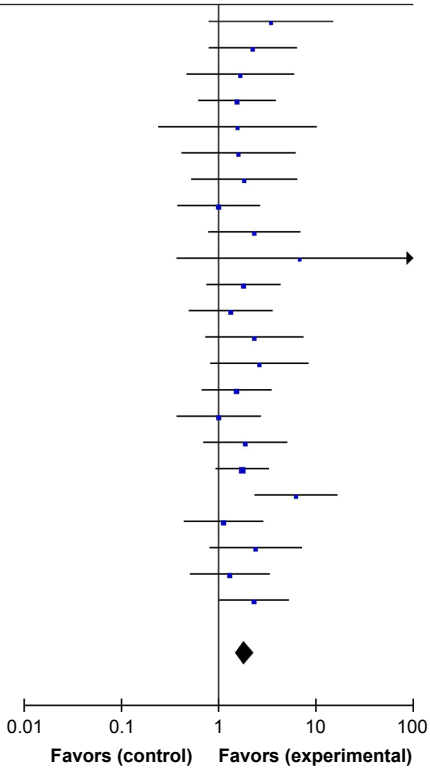
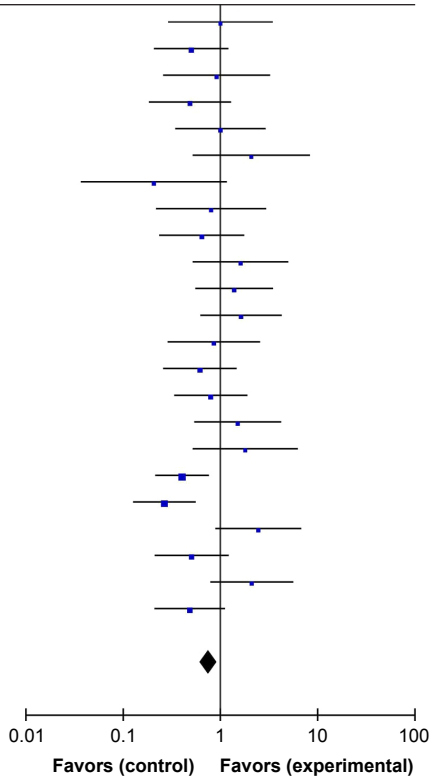


Figure S1 (*Continued*)

C

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	7	25	7	25	2.2	1.00 (0.29, 3.44)
Fan LJ 2009[2]	21	42	28	42	6.2	0.50 (0.21, 1.21)
Fan QL 2013[3]	8	23	7	19	2.2	0.91 (0.26, 3.25)
Fang XH 2016[4]	10	37	16	37	5.2	0.49 (0.18, 1.29)
Guan LY 2015[5]	13	27	13	27	3.0	1.00 (0.34, 2.91)
Jia JM 2013[6]	8	18	5	18	1.2	2.08 (0.52, 8.34)
Liu GW 2017[7]	2	20	7	20	2.8	0.21 (0.04, 1.16)
Liu SH 2008[8]	5	32	6	32	2.3	0.80 (0.22, 2.95)
Mao WD 2016[9]	11	33	14	32	4.2	0.64 (0.24, 1.76)
Shao H 2014[10]	29	45	9	17	2.1	1.61 (0.52, 4.99)
Shi XY 2017[11]	14	48	11	48	3.5	1.39 (0.55, 3.46)
Tian XL 2006[12]	18	35	13	33	2.9	1.63 (0.62, 4.27)
Wang JH 2010[13]	11	26	12	26	3.1	0.86 (0.29, 2.56)
Wang YW 2017[14]	21	42	26	42	5.8	0.62 (0.26, 1.47)
Wei YF 2015[15]	15	48	16	44	5.1	0.80 (0.33, 1.89)
Wu ZM 2013[16]	13	32	10	32	2.6	1.51 (0.54, 4.21)
Xie ZX 2016[17]	8	32	5	32	1.7	1.80 (0.52, 6.25)
You ZY 2015[18]	24	85	42	85	13.4	0.40 (0.21, 0.76)
Zeng Li 2009[19]	24	63	44	63	12.2	0.27 (0.13, 0.56)
Zhang MJ 2011[20]	15	38	8	38	2.2	2.45 (0.89, 6.75)
Zhang W 2012[21]	20	42	27	42	6.3	0.51 (0.21, 1.21)
Zhang W 2015[22]	18	48	8	36	2.5	2.10 (0.79, 5.59)
Zhu WQ 2014[23]	14	48	23	50	7.1	0.48 (0.21, 1.11)
Total (95% CI)		**889**		**840**	**100**	**0.77 (0.63, 0.93)**
Total events	329		357			

Heterogeneity: χ^2=38.86, *df*=22 (*P*=0.01); I^2=43%
Test for overall effect: *Z*=2.63 (*P*=0.009)



D

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	7	25	14	25	6.2	0.31 (0.09, 0.99)
Fan LJ 2009[2]	3	42	5	42	2.8	0.57 (0.13, 2.55)
Fan QL 2013[3]	2	23	5	19	3.1	0.27 (0.05, 1.57)
Fang XH 2016[4]	4	37	4	37	2.2	1.00 (0.23, 4.34)
Guan LY 2015[5]	11	27	12	27	4.3	0.86 (0.29, 2.53)
Jia JM 2013[6]	1	18	7	18	4.0	0.09 (0.01, 0.86)
Liu GW 2017[7]	0	20	0	20		Not estimable
Liu SH 2008[8]	4	32	5	32	2.7	0.77 (0.19, 3.18)
Mao WD 2016[9]	5	33	9	32	4.7	0.46 (0.13, 1.55)
Shao H 2014[10]	9	45	8	17	5.7	0.28 (0.08, 0.93)
Shi XY 2017[11]	16	48	25	48	10.2	0.46 (0.20, 1.05)
Tian XL 2006[12]	1	35	8	33	4.9	0.09 (0.01, 0.78)
Wang JH 2010[13]	3	26	7	26	3.8	0.35 (0.08, 1.56)
Wang YW 2017[14]	3	42	7	42	4.0	0.38 (0.09, 1.60)
Wei YF 2015[15]	3	48	6	44	3.6	0.42 (0.10, 1.80)
Wu ZM 2013[16]	6	32	8	32	4.0	0.69 (0.21, 2.29)
Xie ZX 2016[17]	5	32	13	32	6.7	0.27 (0.08, 0.89)
You ZY 2015[18]	2	85	2	85	1.2	1.00 (0.14, 7.27)
Zeng Li 2009[19]	7	63	13	63	7.1	0.48 (0.18, 1.30)
Zhang MJ 2011[20]	8	38	16	38	7.7	0.37 (0.13, 1.01)
Zhang W 2012[21]	4	42	6	42	3.3	0.63 (0.16, 2.42)
Zhang W 2015[22]	10	48	8	36	4.4	0.92 (0.32, 2.63)
Zhu WQ 2014[23]	2	48	6	50	3.4	0.32 (0.06, 1.66)
Total (95% CI)		**889**		**840**	**100**	**0.45 (0.35, 0.59)**
Total events	116		194			

Heterogeneity: χ^2=12.90, *df*=21 (*P*=0.91); I^2=0%
Test for overall effect: *Z*=5.83 (*P*<0.00001)

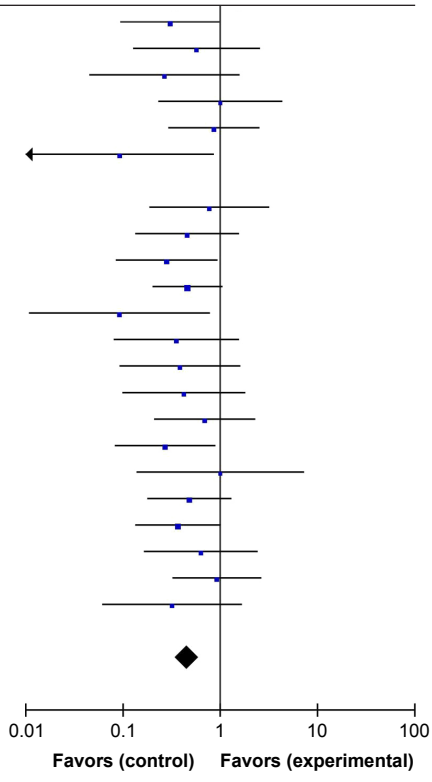


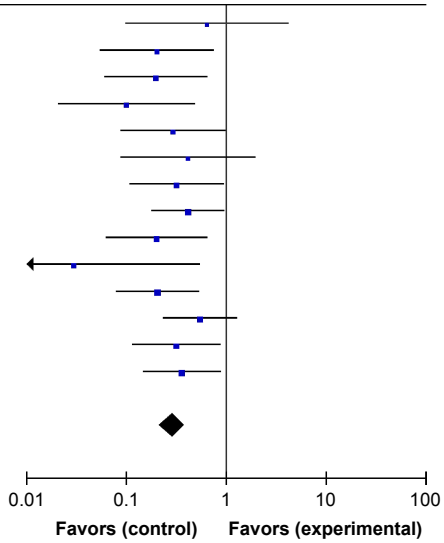
Figure S1 Forest plot of the comparison of complete response rates (**A**), partial response rates (**B**), stable disease rates (**C**), and progressive disease rates (**D**) between the experimental and control groups. Control group, CMT alone group; Experimental group, sodium cantharidinate and vitamin B6 injection (SC/B6) + CMT. The fixed-effects meta-analysis model (M–H method) was used.

Abbreviations: CMT, conventional medical treatment; M–H, Mantel–Haenszel.

A

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	2	25	3	25	1.7	0.64 (0.10, 4.19)
Fan QL 2013[3]	7	23	13	19	6.0	0.20 (0.05, 0.75)
Guan LY 2015[5]	11	27	21	27	7.6	0.20 (0.06, 0.64)
Jia JM 2013[6]	3	18	12	18	6.1	0.10 (0.02, 0.49)
Li GP 2010[24]	12	25	19	25	6.0	0.29 (0.09, 0.98)
Liu GW 2017[7]	3	20	6	20	3.1	0.41 (0.09, 1.95)
Liu SH 2008[8]	17	32	25	32	7.1	0.32 (0.11, 0.94)
Shi XY 2017[11]	14	48	24	48	10.3	0.41 (0.18, 0.95)
Tian XL 2006[12]	5	35	15	33	8.0	0.20 (0.06, 0.64)
Wang JH 2010[13]	16	26	26	26	6.3	0.03 (0.00, 0.54)
Wang YW 2017[14]	9	42	24	42	11.5	0.20 (0.08, 0.53)
Wei YF 2015[15]	15	48	20	44	8.7	0.55 (0.23, 1.28)
Xie ZX 2016[17]	12	32	21	32	8.0	0.31 (0.11, 0.87)
Zhang W 2015[22]	20	48	24	36	9.7	0.36 (0.15, 0.88)
Total (95% CI)		**449**		**427**	**100**	**0.29 (0.21, 0.39)**
Total events	146		253			

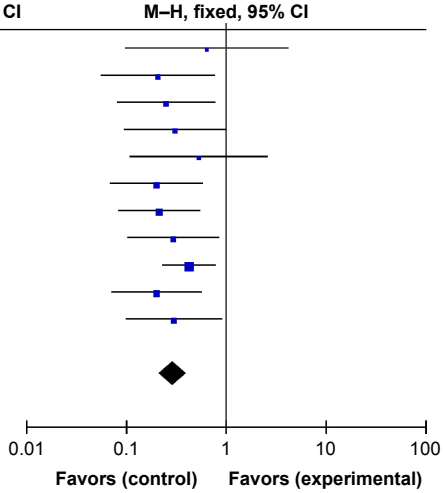
Heterogeneity: χ^2=9.65, *df*=13 (*P*=0.72); I^2=0%
Test for ovarall effect: *Z*=8.19 (*P*<0.00001)



B

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	2	25	3	25	1.9	0.64 (0.10, 4.19)
Fan QL 2013[3]	6	23	12	19	6.6	0.21 (0.06, 0.77)
Guan LY 2015[5]	9	27	18	27	8.2	0.25 (0.08, 0.78)
Li GP 2010[24]	11	25	18	25	6.9	0.31 (0.09, 0.99)
Liu GW 2017[7]	3	20	5	20	2.9	0.53 (0.11, 2.60)
Liu SH 2008[8]	8	32	20	32	10.3	0.20 (0.07, 0.59)
Wang YW 2017[14]	10	42	25	42	13.0	0.21 (0.08, 0.54)
Xie ZX 2016[17]	8	32	17	32	8.7	0.29 (0.10, 0.85)
You ZY 2015[18]	35	85	53	85	21.3	0.42 (0.23, 0.78)
Zhang W 2015[22]	24	48	30	36	11.7	0.20 (0.07, 0.57)
Zhu WQ 2014[23]	5	48	14	50	8.4	0.30 (0.10, 0.91)
Total (95% CI)		**407**		**393**	**100**	**0.30 (0.22, 0.40)**
Total events	121		215			

Heterogeneity: χ^2=4.35, *df*=10 (*P*=0.93); I^2=0%
Test for ovarall effect: *Z*=7.61 (*P*<0.00001)



C

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Jia JM 2013[6]	2	18	4	18	4.3	0.44 (0.07, 2.76)
Mao WD 2016[9]	18	33	21	32	11.6	0.63 (0.23, 1.71)
Shi XY 2017[11]	7	48	17	48	17.4	0.31 (0.11, 0.84)
Tian XL 2006[12]	4	35	8	33	8.8	0.40 (0.11, 1.50)
Wang JH 2010[13]	6	26	8	26	7.4	0.68 (0.20, 2.32)
Wei YF 2015[15]	11	48	18	44	17.4	0.43 (0.17, 1.06)
Wu ZM 2013[16]	13	32	21	32	15.0	0.36 (0.13, 0.99)
Zhang MJ 2011[20]	14	38	24	38	18.2	0.34 (0.13, 0.86)
Total (95% CI)		**278**		**271**	**100**	**0.42 (0.29, 0.62)**
Total events	75		121			

Heterogeneity: χ^2=1.83, *df*=7 (*P*=0.97); I^2=0%
Test for ovarall effect: *Z*=4.47 (*P*<0.00001)

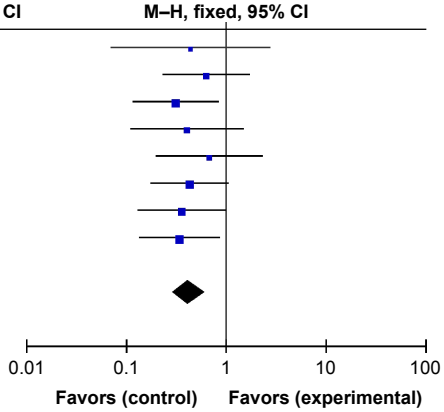
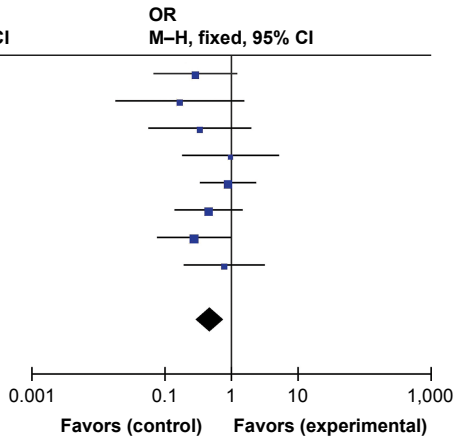


Figure S2 (*Continued*)

D

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Jia JM 2013[6]	4	18	9	18	13.9	0.29 (0.07, 1.21)
Li GP 2010[24]	1	25	5	25	9.5	0.17 (0.02, 1.55)
Liu GW 2017[7]	2	20	5	20	8.9	0.33 (0.06, 1.97)
Mao WD 2016[9]	3	33	3	32	5.5	0.97 (0.18, 5.19)
Shi XY 2017[11]	10	48	11	48	17.3	0.89 (0.34, 2.33)
Wei YF 2015[15]	5	48	9	44	16.7	0.45 (0.14, 1.47)
Xie ZX 2016[17]	4	32	11	32	19.1	0.27 (0.08, 0.98)
Zhang MJ 2011[20]	4	38	5	38	8.9	0.78 (0.19, 3.15)
Total (95% CI)		**262**		**257**	**100**	**0.49 (0.30, 0.78)**
Total events	33		58			

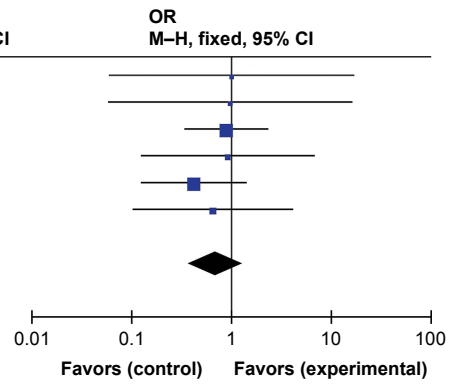
Heterogeneity: χ^2=4.92, *df*=7 (*P*=0.67); I^2=0%
Test for overall effect: *Z*=2.97 (*P*=0.003)



E

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Li GP 2010[24]	1	25	1	25	4.0	1.00 (0.06, 16.93)
Mao WD 2016[9]	1	33	1	32	4.1	0.97 (0.06, 16.18)
Shi XY 2017[11]	10	48	11	48	36.2	0.89 (0.34, 2.33)
Wei YF 2015[15]	2	48	2	44	8.3	0.91 (0.12, 6.77)
You ZY 2015[18]	4	85	9	85	35.6	0.42 (0.12, 1.41)
Zhang MJ 2011[20]	2	38	3	38	11.8	0.65 (0.10, 4.12)
Total (95% CI)		**277**		**272**	**100**	**0.70 (0.38, 1.30)**
Total events	20		27			

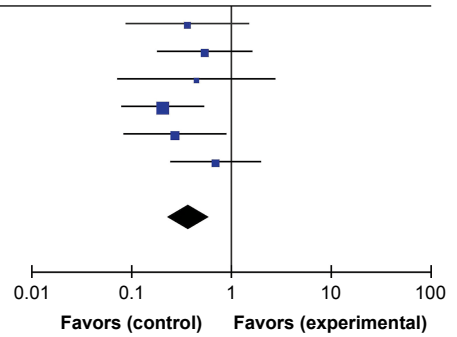
Heterogeneity: χ^2=1.11, *df*=5 (*P*=0.95); I^2=0%
Test for overall effect: *Z*=1.12 (*P*=0.26)



F

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Fan QL 2013[3]	4	23	7	19	11.2	0.36 (0.09, 1.50)
Guan LY 2015[5]	9	27	13	27	15.3	0.54 (0.18, 1.62)
Liu GW 2017[7]	2	20	4	20	6.3	0.44 (0.07, 2.76)
Wang YW 2017[14]	9	42	24	42	33.2	0.20 (0.08, 0.53)
Xie ZX 2015[17]	5	32	13	32	19.3	0.27 (0.08, 0.89)
Zhang W 2015[22]	9	48	9	36	14.7	0.69 (0.24, 1.97)
Total (95% CI)		**192**		**176**	**100**	**0.37 (0.23, 0.60)**
Total events	38		70			

Heterogeneity: χ^2=3.60, *df*=5 (*P*=0.61); I^2=0%
Test for overall effect: *Z*=4.09 (*P*<0.0001)



G

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, random, 95% CI
Li GP 2010[24]	4	25	7	25	18.6	0.49 (0.12, 1.95)
Liu GW 2017[7]	2	20	5	20	14.6	0.33 (0.06, 1.97)
Liu SH 2008[8]	11	32	10	32	22.7	1.15 (0.41, 3.27)
Shi XY 2017[11]	6	48	15	48	22.6	0.31 (0.11, 0.90)
Wei YF 2015[15]	10	18	12	44	21.5	3.33 (1.06, 10.44)
Total (95% CI)		**143**		**169**	**100**	**0.77 (0.31, 1.92)**
Total events	33		49			

Heterogeneity: τ^2=0.68; χ^2=10.92, *df*=4 (*P*=0.03); I^2=63%
Test for overall effect: *Z*=0.57 (*P*=0.57)

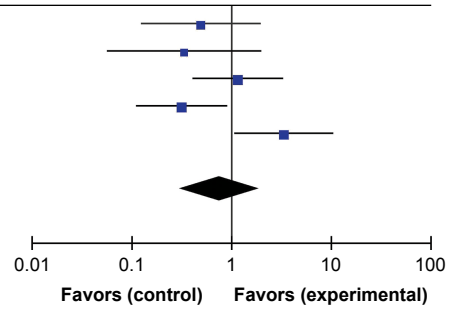
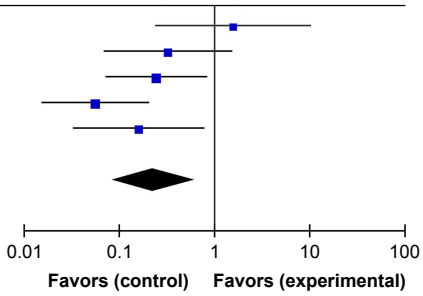


Figure S2 (*Continued*)

H

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, random, 95% CI
Chen Y 2016[1]	3	25	2	25	15.8	1.57 (0.24, 10.30)
Fan QL 2013[3]	3	23	6	19	19.3	0.33 (0.07, 1.53)
Guan LY 2015[5]	5	27	13	27	23.5	0.24 (0.07, 0.84)
Liu SH 2008[8]	4	32	23	32	22.5	0.06 (0.02, 0.21)
Wang YW 2017[14]	2	42	10	42	18.9	0.16 (0.03, 0.78)
Total (95% CI)		**149**		**145**	**100**	**0.23 (0.09, 0.62)**
Total events	17		54			

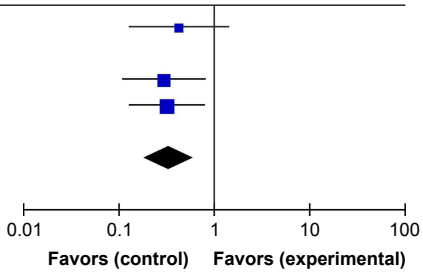
Heterogeneity: τ^2=0.69; χ^2=8.84, *df*=4 (*P*=0.07); I^2=55%
Test for overall effect: *Z*=2.92 (*P*=0.003)



I

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Mao WD 2016[9]	23	33	27	32	21.2	0.43 (0.13, 1.43)
Wu ZM 2013[16]	32	32	32	32		Not estimable
Zhang MJ 2011[20]	8	38	18	38	36.2	0.30 (0.11, 0.81)
Zhu WQ 2014[23]	9	48	21	50	42.6	0.32 (0.13, 0.80)
Total (95% CI)		**151**		**152**	**100**	**0.33 (0.18, 0.60)**
Total events	72		98			

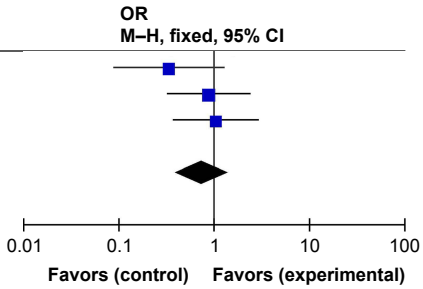
Heterogeneity: χ^2=0.22, *df*=2 (*P*=0.90); I^2=0%
Test for overall effect: *Z*=3.64 (*P*=0.0003)



J

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Liu GW 2017[7]	5	20	10	20	33.1	0.33 (0.09, 1.27)
Shi XY 2017[11]	9	48	10	48	35.8	0.88 (0.32, 2.40)
Zhang W 2015[22]	11	48	8	36	31.1	1.04 (0.37, 2.93)
Total (95% CI)		**116**		**104**	**100**	**0.75 (0.40, 1.40)**
Total events	25		28			

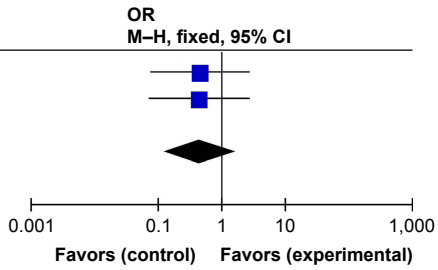
Heterogeneity: χ^2=1.89, *df*=2 (*P*=0.39); I^2=0%
Test for overall effect: *Z*=0.91 (*P*=0.36)



K

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Chen Y 2016[1]	2	25	4	25	50.5	0.46 (0.08, 2.75)
Liu GW 2017[7]	2	20	4	20	49.5	0.44 (0.07, 2.76)
Total (95% CI)		**45**		**45**	**100**	**0.45 (0.13, 1.62)**
Total events	4		8			

Heterogeneity: χ^2=0.00, *df*=1 (*P*=0.98), I^2=0%
Test for overall effect: *Z*=1.22 (*P*=0.22)



L

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Fan QL 2013[3]	10	23	11	19	19.5	0.56 (0.16, 1.91)
Guan LY 2015[5]	13	27	16	27	23.8	0.64 (0.22, 1.87)
Wang YW 2017[14]	10	42	26	42	56.7	0.19 (0.07, 0.49)
Total (95% CI)		**92**		**88**	**100**	**0.37 (0.20, 0.68)**
Total events	33		53			

Heterogeneity: χ^2=3.27, *df*=2 (*P*=0.20), I^2=39%
Test for overall effect: *Z*=3.23 (*P*=0.001)

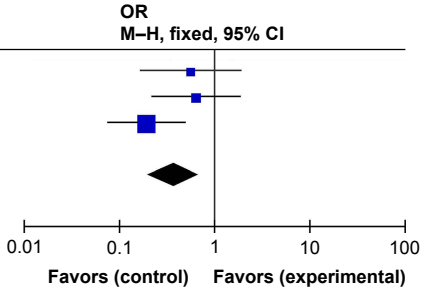


Figure S2 (*Continued*)

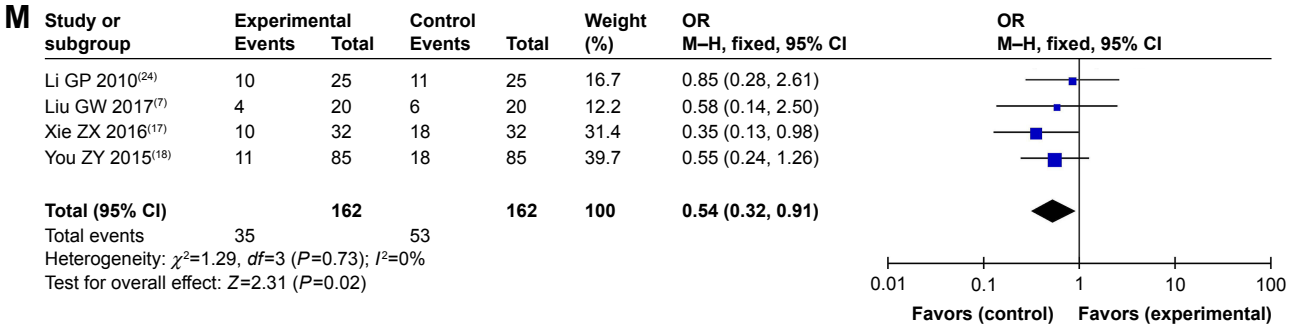


Figure S2 Forest plot of the comparison of adverse effects including leukopenia (**A**), nausea and vomiting (**B**), gastrointestinal side effects (**C**), hepatotoxicity (**D**), nephrotoxicity (**E**), diarrhea (**F**), thrombocytopenia (**G**), transaminase disorder (**H**), myelosuppression (**I**), hand foot syndrome (**J**), oral mucositis (**K**), anorexia (**L**), and anemia (**M**) between the experimental and control groups. Control group, CMT-alone group; Experimental group, sodium cantharidinate and vitamin B6 injection (SC/B6) + CMT.
Abbreviation: CMT, conventional medical treatment.

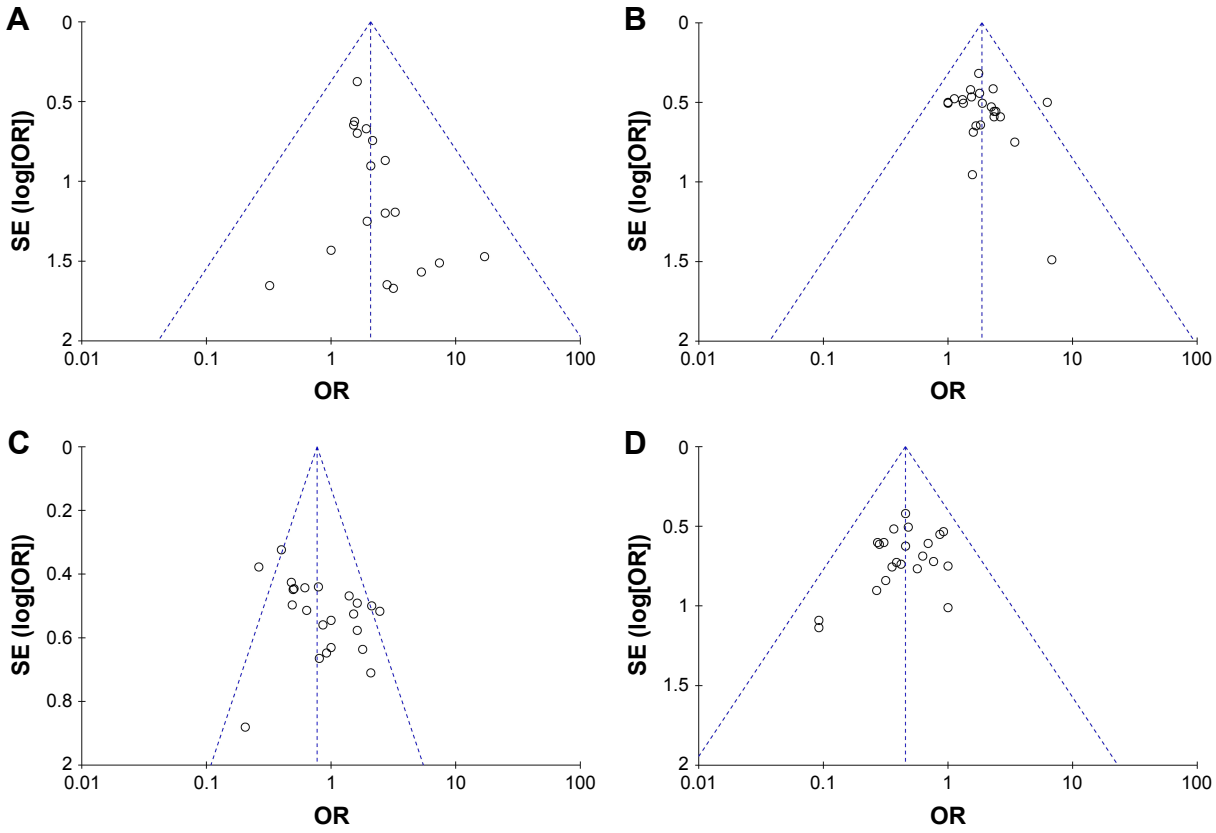


Figure S3 Funnel plot of percentage of complete response rates (**A**), partial response rates (**B**), stable disease rates (**C**), and progressive disease rates (**D**).

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