Ganglioside-monosialic acid (GM1) for prevention of chemotherapy-induced peripheral neuropathy: a meta-analysis with trial sequential analysis

Shaoyong Wu
Sun Yat-Sen University Cancer Center
Xiaohui Bai
Sun Yat-sen Memorial Hospital
Caixia Guo
Zengcheng District People's Hospital
Zhimei Huang
Sun Yat-sen University Cancer Center
Handong Ouyang
Sun Yat-Sen University Cancer Center
Jingxiu Huang
Sun Yat-Sen University Cancer Center
Weian Zeng (zengwa@mail.sysu.edu.cn)
Sun Yat-Sen University Cancer Center

Research Article

Keywords: Ganglioside-monosialic acid, chemotherapy, neuropathy, meta-analysis

Posted Date: May 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-431559/v1

Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting side effect that largely remains an unresolved clinical issue, leading to long-term morbidity. This meta-analysis aimed to evaluate the efficacy and safety of Ganglioside-monosialic acid (GM1) in preventing CIPN.

Methods: Systematic literature searches of Embase, Web of Science, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were performed to identify randomized controlled trials and cohort studies that evaluated the efficacy of GM1 for preventing CIPN. A

meta-analysis was conducted to calculate odds ratios (ORs) and 95% confidential intervals (CIs) using a random-effects model. Trial sequential analyses (TSA) also were conducted to control for random errors.

Results: A total of five studies involving 868 participants were included. The results showed that GM1 did not reduce the overall incidence of grade ≥2 CIPN when the common terminology criteria for adverse events (CTCAE) was used (OR 0.34, 95% CI 0.34-1.11). Subgroup analyses showed that GM1 could not reduce the risk of CTCAE grade ≥2 CIPN (OR 0.63, 95% CI 0.35-1.13) and neurotoxicity criteria of Debiopharm (DEB-NTC) grade ≥2 CIPN (OR 0.25, 95% CI 0.01-7.10) in oxaliplatin-treated patients, although GM1 might reduce the risk of CTCAE grade

≥2 CIPN in the taxane subgroup in one study (OR 0.003, 95% CI 0.00-0.05). Besides, TSA suggested that the results in the taxane subgroup were robust, while that of the oxaliplatin subgroup were inconclusive. Furthermore, GM1 did not influence the rate of response to chemotherapy and CTCAE grade ≥2 adverse events such as fatigue, nausea, diarrhea, and rash.

Conclusions: GM1 was not associated with a lower risk of oxaliplatin-induced peripheral neuropathy nor could improve the response or safety to chemotherapy; however, it might be able to prevent taxane-induced peripheral neuropathy. Higher-quality trials are required to clarify the preventive effect of GM1 in oxaliplatin-treated patients.

Background

The incidence of cancer is still alarming globally [1] and despite breakthroughs in cancer treatment, chemotherapy is still an important cornerstone in cancer treatment [2]. Chemotherapy-induced peripheral neuropathy (CIPN) is a troubling adverse effect for many cancer patients treated with chemotherapeutic agents, such as microtubule disruptors (taxanes, vinca alkaloids), platinum-based agents (cisplatin, oxaliplatin), epothilones (ixabepilone), and proteasome inhibitors (bortezomib) [3, 4]. It is believed to affect around 68% and 30% of patients treated using neurotoxic chemotherapy in the short and long term, respectively [5]. CIPN compromises the quality of daily life of these patients by impairing their sensory, motor, and autonomic functions [6], often causing chemotherapy dose reductions and discontinuations. Unfortunately, the pathogenetic mechanisms of CIPN genesis remain poorly understood. Available treatment options for CIPN are limited, often ineffective, or associated with undesirable side effects. To date, no agents were recommended for the prevention of CIPN [7]. For these reasons, the identification of novel analgesics of prevention CIPN is urgent and highly demanded in clinical practice.

Ganglioside-monosialic acid (GM1) is a monosialoglycosphingolipid mainly found in neurons and belongs to the family of gangliosides which are unique acidic glycolipids comprising of sphingosine, fatty acid, and sialic acid [8]. GM1 has been found to perform essential functions in the processes of signal transduction, cell recognition, neurogenesis, and nerve development and differentiation [9, 10]. Intravenous injection of gangliosides has been employed in many countries to treat neuropathies due to their neuroprotective effect and potential to promote nerve repair by enhancing nerve sprouting [11]. As early as in the 1980s, ganglioside treatment was found to be useful in the mitigation of vincristine-associated neuropathy, both in rabbit models and cancer patients [12, 13]. Preclinical animal models suggested that porcine GM1 could be effective in the prevention and treatment of paclitaxel-induced neuropathy [14]. Recently more and more researchers have started to focus on the possible efficacy of GM1 in preventing CIPN. A retrospective study showed that GM1 could significantly reduce the incidence of oxaliplatin-induced neuropathy [15]. However, the findings from two recent clinical trials regarding the efficacity of GM1 have shown inconsistent results [16, 17]. Therefore, we performed this meta-analysis to evaluate the efficacy and safety of GM1 treatment for preventing CIPN.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [19].

Search strategy

Electronic databases including Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were systematically searched from inception through February 28th, 2021. The search terms included *ganglioside-monosialic acid*, *GM1*, *ganglioside*, *monosialoganglioside*, and *chemotherapy-induced neuropathy*. Additionally, we checked the reference and citation lists of relevant publications for any unidentified studies. Details of our search strategy are presented in Supplementary Table S1. Retrieved study authors were contacted via e-mail or telephone for additional information when necessary.

Inclusion and exclusion criteria

Studies were considered eligible if they were randomized controlled trials (RCTs), nonrandomized clinical studies, or observational cohort studies that compared GM1 with controls to prevent CIPN in cancer patients treated with neurotoxic chemotherapy. Control drugs were defined as no intervention, a

placebo, or any drugs currently known not to relieve or prevent CIPN symptoms. Editorials, review articles, case reports, letters, and animal experimental studies were excluded.

Data extraction and study endpoints

Two authors (SYW, XHB) independently extracted data from the eligible studies. Disagreements among authors were discussed and finally confirmed by a third reviewer (WAZ). The extracted data included general study characteristics (the first author's name, publication year, study sites, study design, trial registry numbers, study duration); baseline patient demographics (age, sample size, types of malignancy, chemotherapy regimen); interventions (dose of GM1, controls); and endpoints of interest. Our primary endpoints were the incidence of CIPN measured with the common terminology criteria for adverse events (CTCAE) version 4.0 and neurotoxicity criteria of Debiopharm (DEB-NTC). Our secondary endpoints were the following: (1) response rate to chemotherapy [Response Evaluation Criteria in Solid Tumors (RECIST)], (2) adverse events related to GM1, and (3) proportion of patients that drop out of chemotherapy.

Quality assessment for the included studies

Two authors (SYW, CXG) independently evaluated the risk of bias in each study. Disagreements were resolved by consulting the author WAZ. The quality of RCTs was assessed using the Cochrane risk-of-bias assessment tool [20]. RCTs without a high risk of bias in any category were considered as good quality studies; RCTs with one high risk or two unclear risks were considered as fair quality studies; and the rest were considered to be poor quality studies [21]. The quality of each nonrandomized and observational study was evaluated using the Newcastle-Ottawa Scale, which evaluates three factors: patient selection (0-4 stars), comparability of the study groups (0-2 stars), and assessment of outcome (0-3 stars) [22]. An aggregated score of 7-9 stars demarcates good quality and 0-6 indicates poor quality.

Statistical analysis

All statistical methods followed the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions [23]. All data were combined as pooled odds ratios (ORs) with 95 % confidence intervals (CIs) using the Mantel-Haenszel statistical method. Random-effects models were used to pool the data across all outcomes to produce more conservative estimates [24]. Heterogeneity was evaluated using I^2 statistics (>75 % indicating high heterogeneity) and Q statistics (with a significance level set at $P = 0.10$) [25]. Subgroup analyses were conducted for the primary outcome with consideration of potential treatment effect modifiers. To decrease a potential type 1 error, a trial sequential analysis was performed on our primary outcome using the TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark, 2011) [26]. All meta-analyses were conducted using Stata SE version 12.0 (Stata Corp., College Station, TX, USA). All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant, except otherwise noted.

Results

Study selection

The systematic literature search yielded 404 records (Supplementary Table S1). After the titles, abstracts, and duplicates were screened, 15 articles were considered potentially relevant. Of these, ten articles were excluded because of non-extractable data (n = 3), lacked assessment on the prevention of CIPN (n = 3), absence of appropriate treatment group (n = 2), a review article (n = 1), and a piece of scientific news (n = 1). Thus, four RCTs [16, 17, 27, 28] and one retrospective cohort study [15] were included after full-text review for further analysis. The flowchart of the search strategy and study selection is illustrated in Fig. 1.

Characteristics and quality assessment of included studies

The general characteristics of all included studies are summarized in Table 1. These five studies involved 868 patients (413 patients in the GM1 group and 455 patients in the control group). All of them were conducted in China, and published between 2012 and 2020. Sample size, types of cancer, follow-up duration were well-balanced and comparable in each study between the intervention and control group (Table 1). Among the four included RCTs, two [16, 17] were of good quality, one [27] was of poor quality, and one [28] was of fair quality (Fig. 2A); the quality of the retrospective study [15] included in our analysis was assessed as good (Fig. 2B).

Primary endpoints

Incidence of CIPN (CTCAE)

Four studies [15-17, 28] provided data regarding the incidence of grade ≥2 CIPN using the CTCAE. Of the four studies, three studies [15, 16, 28] used the oxaliplatin regimen, only one study [17] used the taxanes regimen. Pooled data showed a tendency to reduce the risk of grade ≥2 CIPN (CTCAE), but not statistically significantly (OR 0.34, 95% CI 0.11 - 1.11, $P = 0.07$; Fig. 3), and there was substantial heterogeneity ($I^2 = 88.1\%$, $P < 0.0001$; Fig. 3).

Incidence of CIPN (DEB-NTC)

Two studies [16, 27] reported the data on the incidence of grade ≥2 CIPN measured with the Neurotoxicity criteria of Debiopharm (DEB-NTC), which was an oxaliplatin-specific neuropathy grading scale [29]. Pooled data showed that GM1 was not associated with a lower incidence of grade ≥2 CIPN (OR 0.25, 95% CI 0.01 - 7.10, $P = 0.42$) when compared with controls. Heterogeneity was substantial ($I^2 = 89.3\%$, $P = 0.002$; Fig. 4).

Secondary endpoints

Objective response rates to chemotherapy (RECIST)

Pooled data from three studies [15, 27, 28] that assessed the objective response rates to chemotherapy, including complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR), disease control rate (DCR), showed that GM1 did not influence any response rate parameter (including CR, PR, SD, PD, ORR, and DCR), indicating that GM1 could not affect the antineoplastic property of chemotherapeutic agents. The heterogeneity was relatively low (Fig. 5).

Incidence of adverse events (CTCAE)

The incidence of adverse events was investigated using the CTCAE. Two studies [16, 17] reported the data on the risk of grade ≥2 fatigue, nausea, and diarrhea, and these data were pooled for meta-analysis. GM1 did not influence the incidence of grade ≥2 fatigue (OR 0.19, 95% CI 0.00 - 11.15, $P = 0.42$), the risk of grade ≥2 nausea (OR 0.67, 95% CI 0.08 - 5.37, $P = 0.71$), or the risk of grade ≥2 diarrhea (OR 0.70, 95% CI 0.35 - 1.38, $P = 0.30$). There was low heterogeneity in grade ≥2 diarrhea ($I^2 = 0.0\%$, $P = 0.64$); however, the heterogeneity in grade ≥2 fatigue was high ($I^2 = 95.2\%$, $P < 0.001$), and the heterogeneity in grade ≥2 nausea was moderate ($I^2 = 54.3\%$, $P = 0.14$, Fig. 5). Only one study [17] reported on the incidence of rash associated taxane and no statistically significant differences were observed in grade ≥2 rash (OR 4.04, 95% CI 0.44 - 36.82, $P = 0.22$, Fig. 5).

Chemotherapy dropout

Pooled data from two studies [15, 16] that assessed chemotherapy dropout suggested that GM1 did not influence the risk of chemotherapy dropout (OR 0.85, 95% CI 0.33 - 2.18, $P = 0.74$) with moderate heterogeneity ($I^2 = 72.8\%$, $P = 0.06$; Fig. 5).

Subgroup analyses

Because no significant effect was observed on the overall incidence of CTCAE grade ≥2 CIPN in the primary analysis, we further conducted subgroup analysis to explore the effect of the type of chemotherapy drugs on the results. It showed that for the endpoint of CTCAE grade ≥2 CIPN, GM1 was associated with a lower risk of taxane-induced peripheral neuropathy (OR 0.003, 95% CI 0.00 - 0.05) but not reduced risk of oxaliplatin-induced peripheral neuropathy (OR 0.63, 95% CI 0.35 - 1.13) (Fig. 2); indicating that GM1 might be more useful in preventing taxane-based peripheral neuropathy, and GM1 could not prevent oxaliplatin-induced neurotoxicity. Moreover, subgroup analyses stratified by other factors such as age, gender were not conducted because no sufficient data were available.

Trial sequential analysis (TSA) for the incidence of CIPN

To assess whether the results of taxanes and oxaliplatin in our meta-analysis were conclusive, TSA was conducted. The calculations were based on a 5% α with a two-tailed test. We used a random-effects model to construct the cumulative Z curve. The incidence in the control arm was set empirically at 40%, and heterogeneity correction was model variance-based. We used an anticipated relative risk reduction (RRR) of 25.0% with a power of 80% to calculate the required information size (RIS) to detect or reject an intervention effect. The TSA findings showed that the results of the taxane subgroup were robust, while those of the oxaliplatin subgroup were inconclusive (Fig. 6).

Discussion

This meta-analysis included four RCTs and one retrospective cohort study, with a total of 868 patients, and evaluated the efficacy and safety of GM1 in preventing CIPN caused by the two most prominent types of neurotoxic antineoplastic agents, taxanes and oxaliplatin. CIPNs related to these two types of drugs share several similarities, such as numbness, tingling, and pain[30]. Our analysis suggests that despite the overall incidence of CIPN was not reduced by GM1, GM1 might have different effects on different chemotherapy drugs. For oxaliplatin, no significant difference was found in the risk of grade ≥2 CIPN measured by CTCAE, as well as DEB-NTC. TSA further showed an absence of evidence to support the use of GM1 to treat oxaliplatin-induced neurotoxicity. For taxanes, GM1 was associated with a reduced incidence of CIPN in one RCT. TSA further confirmed that the efficacy of GM1 in the prevention of taxane-induced neurotoxicity was robust. Also, GM1 was well-tolerated and did not influence the anti-tumor activity of chemotherapeutic agents (Fig. 5).

In this study, the efficacy of GM1 on CIPN prevention was assessed using two tools - the CTCAE and DEB-NTC. The CTCAE is a common tool for assessing CIPN symptoms and other chemotherapy-related adverse events, consisting of 5 grades (grade 1-5); in contrast, the DEB-NTC is a specific tool for oxaliplatin-induced neurotoxicity assessment, consisting of 3 grades (grade 1-3)(Supplementary Table S2). Both CTCAE and DEB-NTC are physician-reported toxicity tools. Patient-reported outcome (PRO) tools such as European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy Induced Peripheral Neuropathy 20 (EORTC QLQ CIPN-20) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) were not used in our analysis because of lack of sufficient data. Clinicians often use a combination of patient symptom reports and physical examination to assess CIPN, and PRO tools are not routinely used in clinical practice [31]. Although there is some discrepancy in the explanation of PRO tools and physician-reported toxicity tools, Jennifer *et al.* [32] found that the association between QLQ CIPN-20 scores and CTCAE grades was strong. Of note, the QLQ CIPN-20 score was not significantly different for oxaliplatin-induced neuropathy between GM1 and the control group in the study by Wang *et al.* [16], which was consistent with the results of our meta-analysis measured by CTCAE and DEB-NTC. Similarly, both FACT-Ntx scores and CTCAE confirmed the efficacy of GM1 in preventing neurotoxicity of taxanes in the study of Su *et al.* [17]. Thus, we believe that our results are robust despite the lack of PRO tools used in our analysis.

Our study provided different results about the efficacy of GM1 on the incidence of neurotoxicity of taxanes and oxaliplatin in the subgroup analyses. There are two potential explanations for these results. First, the toxicity profile differs among different drugs. Pachman *et al.* [33] found that oxaliplatin-induced neurotoxicity deteriorated after the completion of treatment and began to improve three months after the treatment; unlike, paclitaxel-induced neuropathy

began improving immediately after chemotherapy cessation. This means that oxaliplatin-induced neuropathy might be more severe and refractory to conventional treatment than taxanes. Second, the underlying mechanism of GM1 and the reason why GM1 is more useful in taxane-induced neurotoxicity remains to be fully elucidated. Each anti-cancer agent induces CIPN through different mechanisms; for example, taxanes damage neuronal axons by causing stabilization of microtubules, while platinum derivatives accumulate in the cell bodies of sensory nerves, react with DNA to form both intrastrand and interstrand cross-links [34]. The mechanism of action of GM1 may vary based on the chemotherapeutic agent used.

The latest clinical guideline for prevention and management of CIPN did not recommend any agents for preventing CIPN [30]. In this guideline update [30], the evidence for the efficacy of GM1 was deemed as preliminary because the taxane-induced neuropathy in the study by Su *et al*. [17] was almost totally resolved three months after the completion of taxane therapy, which was faster than other trials [35]. Despite the compelling effect of GM1 in taxane-associated neuropathy prevention confirmed by our meta-analysis via TSA, more trials are still needed to cover individuals from western nationalities.

Notably, GM1 has the possibility of developing human autoimmune neuropathy in rare cases, leading to ganglioside-associated Guillain-Barré syndrome (GBS) [36], a serious complication of gangliosides use, which usually manifests as limb weakness and presents with rapidly progressive paralysis; often needing artificial ventilation [37]. Most countries, except China, withdrew gangliosides from the therapeutic market because of a possible epidemiological connection with the development of GBS [38]. There are also some case reports about the incidence of ganglioside-associated GBS in China [39]. Besides, the molecular pathogenesis of this syndrome was clarified by Yuki [40], who established a disease model for GBS by sensitization with GM1 and confirmed the relationship between anti-GM1 antibody and GBS. Although there are no reports about the cases of ganglioside-associated GBS in the studies included in our meta-analysis, the use of GM1 should be prudent only when necessary.

There were some limitations in this review worth mentioning. First, all the included studies were conducted in China, so the results may be influenced by patient selection factors such as Chinese ethnicity. Given the exciting data in the taxane subgroup, more studies should be replicated in different ethnic populations. Second, due to the limited number of studies included in each analysis, publication bias was not assessed, and sensitivity analysis was not conducted. Moreover, the preventive effect of GM1 in oxaliplatin-induced neurotoxicity was not significant, and the cumulative Z curve crossed neither the TSA boundary nor the RIS, meaning that the results in the oxaliplatin subgroup were inconclusive.

Conclusions

In summary, this meta-analysis indicates that the use of GM1 can lead to reduced incidence of taxane-induced peripheral neuropathy, but might not reduce the incidence of oxaliplatin-induced peripheral neuropathy. Further well-designed studies are warranted to evaluate the effectiveness of GM1 in oxaliplatin-treated patients.

Abbreviations

CENTRAL, the Cochrane Central Register of Controlled Trials; CI, confidential interval; CIPN, Chemotherapy-induced peripheral neuropathy; CR, complete response; CTCAE, common terminology criteria for adverse events; DCR, disease control rate; DEB-NTC, Neurotoxicity criteria of Debiopharm; GBS, Guillain-Barré syndrome; GM1, Ganglioside-monosialic acid; NA, not applicable; OR, odds ratio; ORR, overall response rate; PD, progressive disease; PR, partial response; RCT, randomized control trial; RECIST, response evaluation criteria in solid tumors; RIS, required information size; SD, stable disease; TSA, Trial sequential analysis.

Declarations

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 81971057).

Conflict of interest

All authors declared no potential conflict of interest.

Acknowledgements

Not applicable.

Authors' contributions

Shaoyong Wu, Xiaohui Bai, and Caixia Guo conceived and designed the study. Shaoyong Wu, Xiaohui Bai, and Caixia Guo carried out the literature search, abstract screening, and data extraction. Shaoyong Wu, Zhimei Huang, and Handong Ouyang analyzed the data and drafted the manuscript. Jingxiu Huang revised the manuscript. All authors read and approved the final manuscript.

References

1. Cao M, Li H, Sun D, Chen W: **Cancer burden of major cancers in China: A need for sustainable actions**. *Cancer communications (London, England)* 2020, **40**(5):205-210.

2. Borcoman E, Kanjanapan Y, Champiat S, Kato S, Servois V, Kurzrock R, Goel S, Bedard P, Le Tourneau C: **Novel patterns of response under immunotherapy**. *Annals of Oncology* 2019, **30**(3):385-396.
3. Lehmann HC, Staff NP, Hoke A: **Modeling chemotherapy induced peripheral neuropathy (CIPN) in vitro: Prospects and limitations**. *Exp Neurol* 2019:113140.
4. Argyriou AA, Bruna J, Park SB, Cavaletti G: **Emerging pharmacological strategies for the management of chemotherapy-induced peripheral neurotoxicity (CIPN), based on novel CIPN mechanisms**. *Expert review of neurotherapeutics* 2020.
5. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M: **Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis**. *Pain* 2014, **155**(12):2461-2470.
6. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L: **Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review**. *Supportive Care in Cancer* 2014, **22**(8):2261-2269.
7. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB *et al*: **Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014, **32**(18):1941-1967.
8. Aureli M, Mauri L, Ciampa MG, Prinetti A, Toffano G, Secchieri C, Sonnino S: **GM1 Ganglioside: Past Studies and Future Potential**. *Molecular neurobiology* 2016, **53**(3):1824-1842.
9. Fishman PH, Brady RO: **Biosynthesis and function of gangliosides**. *Science* 1976, **194**(4268):906-915.
10. Schwarz S, Lehmbecker A, Tongtako W, Hahn K, Wang Y, Felmy F, Zdora I, Brogden G, Branitzki-Heinemann K, von Kockritz-Blickwede M *et al*: **Neurotrophic effects of GM1 ganglioside, NGF, and FGF2 on canine dorsal root ganglia neurons in vitro**. *Scientific reports* 2020, **10**(1):5380.
11. Roisen F, Bartfeld H, Nagele R, Yorke G: **Ganglioside stimulation of axonal sprouting in vitro**. *Science* 1981, **214**(4520):577-578.
12. Hellmann K, Hutchinson GE, Henry K: **Reduction of vincristine toxicity by Cronassial**. *Cancer Chemotherapy and Pharmacology* 1987, **20**(1):21-25.
13. Favaro G, Di Gregorio F, Panozzo C, Fiori MG: **Ganglioside treatment of vincristine-induced neuropathy. An electrophysiologic study**. *Toxicology* 1988, **49**(2-3):325-329.
14. Chentanez V, Thanomsridejchai N, Duangmardphon N, Agthong S, Kaewsema A, Huanmanop T, Maneesri S: **Ganglioside GM1 (porcine) ameliorates paclitaxel-induced neuropathy in rats**. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 2009, **92**(1):50-57.
15. Chen XF, Wang R, Yin YM, Røe OD, Li J, Zhu LJ, Guo RH, Wu T, Shu YQ: **The effect of monosialotetrahexosylganglioside (GM1) in prevention of oxaliplatin induced neurotoxicity: A retrospective study**. *Biomedicine and Pharmacotherapy* 2012, **66**(4):279-284.
16. Wang DS, Wang ZQ, Chen G, Peng JW, Wang W, Deng YH, Wang FH, Zhang JW, Liang HL, Feng F *et al*: **Phase III randomized, placebo-controlled, double-blind study of monosialotetrahexosylganglioside for the prevention of oxaliplatin-induced peripheral neurotoxicity in stage II/III colorectal cancer**. *Cancer Med* 2020, **9**(1):151-159.
17. Su Y, Huang J, Wang S, Unger JM, Arias-Fuenzalida J, Shi Y, Li J, Gao Y, Shi W, Wang X *et al*: **The Effects of Ganglioside-Monosialic Acid in Taxane-Induced Peripheral Neurotoxicity in Patients with Breast Cancer: A Randomized Trial**. *JNCI Journal of the National Cancer Institute* 2020, **112**(1):55-62.
18. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *Annals of internal medicine* 2009, **151**(4):264-269, w264.
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: **Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group**. *JAMA* 2000, **283**(15):2008-2012.
20. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *BMJ* 2011, **343**:d5928.
21. Song SY, Ko YB, Kim H, Lee GW, Yang JB, Chang HK, Kwak SM, Jung J, Lee S, Lee SY *et al*: **Effect of serotonin-norepinephrine reuptake inhibitors for patients with chemotherapy-induced painful peripheral neuropathy: A meta-analysis**. *Medicine* 2020, **99**(1):e18653.
22. Stang A: **Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses**. *European Journal of Epidemiology* 2010, **25**(9):603-605.
23. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, VA W (editors). **Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021)**. Cochrane, 2021. Available from www.training.cochrane.org/handbook.
24. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, Bosch J, O'Donnell MJ, Canavan M: **Association of Blood Pressure Lowering With Incident Dementia or Cognitive Impairment: A Systematic Review and Meta-analysis**. *JAMA* 2020, **323**(19):1934-1944.
25. Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ: **Scales to assess the quality of randomized controlled trials: a systematic review**. *Physical therapy* 2008, **88**(2):156-175.
26. Wetterslev J, Jakobsen JC, Gluud C: **Trial Sequential Analysis in systematic reviews with meta-analysis**. *BMC medical research methodology* 2017, **17**(1):39.
27. Cao M, Hua H, Qin S: **Protective Effects of Monosialoganglioside on Oxaliplatin-induced Chronic Sensory Neurotoxicity**. *Cancer Research on Prevention and Treatment* 2014, **41**(4):387-390.
28. Zhu Y, Yang J, Jiao S, Ji T: **Ganglioside-monosialic acid (GM1) prevents oxaliplatin-induced peripheral neurotoxicity in patients with gastrointestinal tumors**. *World Journal of Surgical Oncology* 2013, **11**(1):19.
29. Lévi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, Chollet P, Garufi C, Itzhaki M, Dogliotti L *et al*: **Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial**. *JNCI Journal of the National Cancer Institute* 1994, **86**(21):1608-1617.

30. Loprinzi CL, Lacchetti C, Bleeker J, Cavaletti G, Chauhan C, Hertz DL, Kelley MR, Lavino A, Lustberg MB, Paice JA *et al*: **Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update**. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2020, **38**(28):3325-3348.
31. Curcio KR: **Instruments for Assessing Chemotherapy-Induced Peripheral Neuropathy: A Review of the Literature**. *Clinical journal of oncology nursing* 2016, **20**(2):144-151.
32. Le-Rademacher J, Kanwar R, Seisler D, Pachman DR, Qin R, Abyzov A, Ruddy KJ, Banck MS, Lavoie Smith EM, Dorsey SG *et al*: **Patient-Reported (EORTC QLQ-CIPN20) Versus Physician-Reported (CTCAE) Quantification of Oxaliplatin- and Paclitaxel/Carboplatin-Induced Peripheral Neuropathy in NCCTG/Alliance Clinical Trials**. *Supportive Care in Cancer* 2017, **25**(11):3537-3544.
33. Pachman DR, Qin R, Seisler D, Smith EM, Kaggal S, Novotny P, Ruddy KJ, Lafky JM, Ta LE, Beutler AS *et al*: **Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505)**. *Supportive Care in Cancer* 2016, **24**(12):5059-5068.
34. Eldridge S, Guo L, Hamre J, 3rd: **A Comparative Review of Chemotherapy-Induced Peripheral Neuropathy in In Vivo and In Vitro Models**. *Toxicologic pathology* 2020, **48**(1):190-201.
35. Loprinzi CL, Hershman DL, Staff N: **Neuronal Protection for Chemotherapy Neuropathy Prevention?** *JNCI Journal of the National Cancer Institute* 2020, **112**(1):3-4.
36. Illa I, Ortiz N, Gallard E, Juarez C, Grau JM, Dalakas MC: **Acute axonal Guillain-Barré syndrome with IgG antibodies against motor axons following parenteral gangliosides**. *Annals of Neurology* 1995, **38**(2):218-224.
37. Willison HJ, Jacobs BC, van Doorn PA: **Guillain-Barré syndrome**. *Lancet (London, England)* 2016, **388**(10045):717-727.
38. Goodfellow JA, Willison HJ: **Gangliosides and Autoimmune Peripheral Nerve Diseases**. *Progress in molecular biology and translational science* 2018, **156**:355-382.
39. Wu X, Wu W, Wang Z, Shen D, Pan W, Wang Y, Wu L, Wu X, Feng J, Liu K *et al*: **More severe manifestations and poorer short-term prognosis of ganglioside-associated Guillain-Barré syndrome in Northeast China**. *PLoS One* 2014, **9**(8):e104074.
40. Yuki N: **Guillain-Barré syndrome and anti-ganglioside antibodies: a clinician-scientist's journey**. *Proceedings of the Japan Academy Series B, Physical and biological sciences* 2012, **88**(7):299-326.

Table

Table 1 Characteristics of included studies

Study	study design	Type of malignancy	Chemotherapy regimen	Participants				GM1 regimen	Controls	Mean cumulative dose of chemotherapy (GM1 vs. control)	E
				age, yr (mean/median)	age range	GM1	Control				
Chen et al, 2012	retrospective	colorectal cancer	mFOLFOX6, FOLFOX4, XELOX	53.5 (median)	36-75	114	164	40mg*4/cycle	None	oxaliplatin, 1120 vs. 960 mg/m^2	C (C R C
Zhu et al, 2013	RCT	gastrointestinal cancer	FOLFOX4, XELOX	54.96 (mean)	21-74	60	60	100mg*3/cycle	None	oxaliplatin, 692.08 vs. 740.83 mg/m^2	C (C R
Cao et al, 2014	RCT	gastrointestinal cancer	FOLFOX6, XELOX	56 (median)	31-72	38	30	40mg*3/cycle	Vitamin B12	NR	C (D N R A
Su et al, 2020	RCT (multicenter)	breast cancer	EC-P, EC-D, DC	44.5 (median)	23-74	103	103	80mg*3/cycle	Placebo	paclitaxel, 942.67 vs. 954.29 mg/m^2; Docetaxel, 525.31 vs. 501.81 mg/m^2	C (C A
Wang et al, 2020	RCT (multicenter)	colorectal cancer	mFOLFOX6, XELOX	52.6 (mean)	> 18	98	98	80mg*5/cycle	Placebo	NR	C (C D N A

Abbreviations: AEs, adverse events; CD, chemotherapy dropout; CIPN, chemotherapy-induced peripheral neuropathy; CTCAE, common termino events; DC, docetaxel and cyclophosphamide; DEB-NTC, neurotoxicity criteria of Debiopharm; EC-P, epirubicin and cyclophosphamide followed epirubicin and cyclophosphamide followed by docetaxel; mFOLFOX6, modified FOLFOX6; NR, not reported; RCT, randomized controlled trial; R evaluation criteria in solid tumors.

Figures

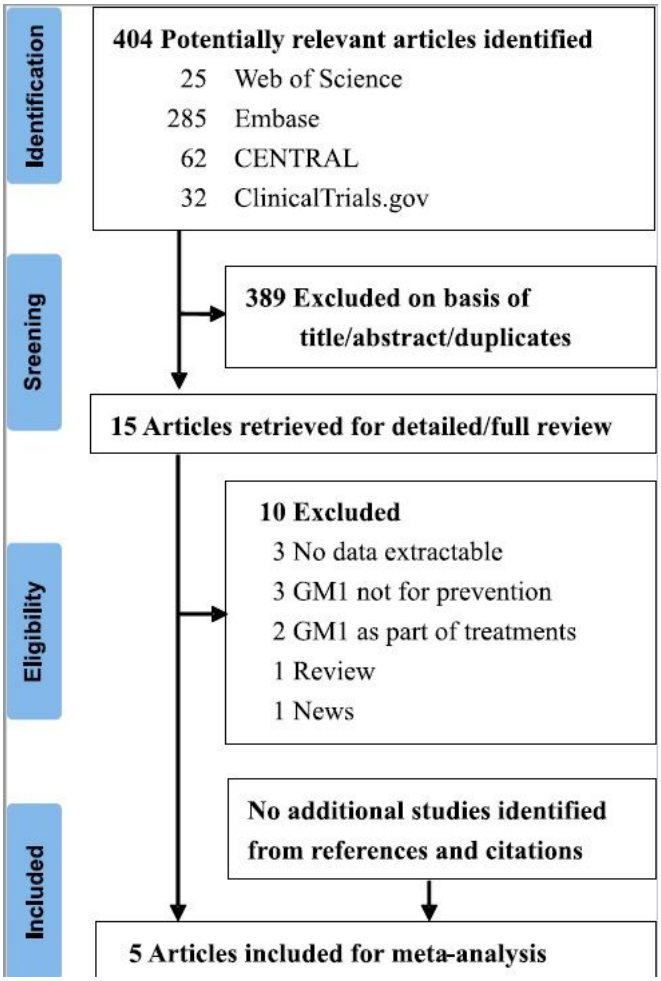


Figure 1

Flowchart of the literature search and study selection.

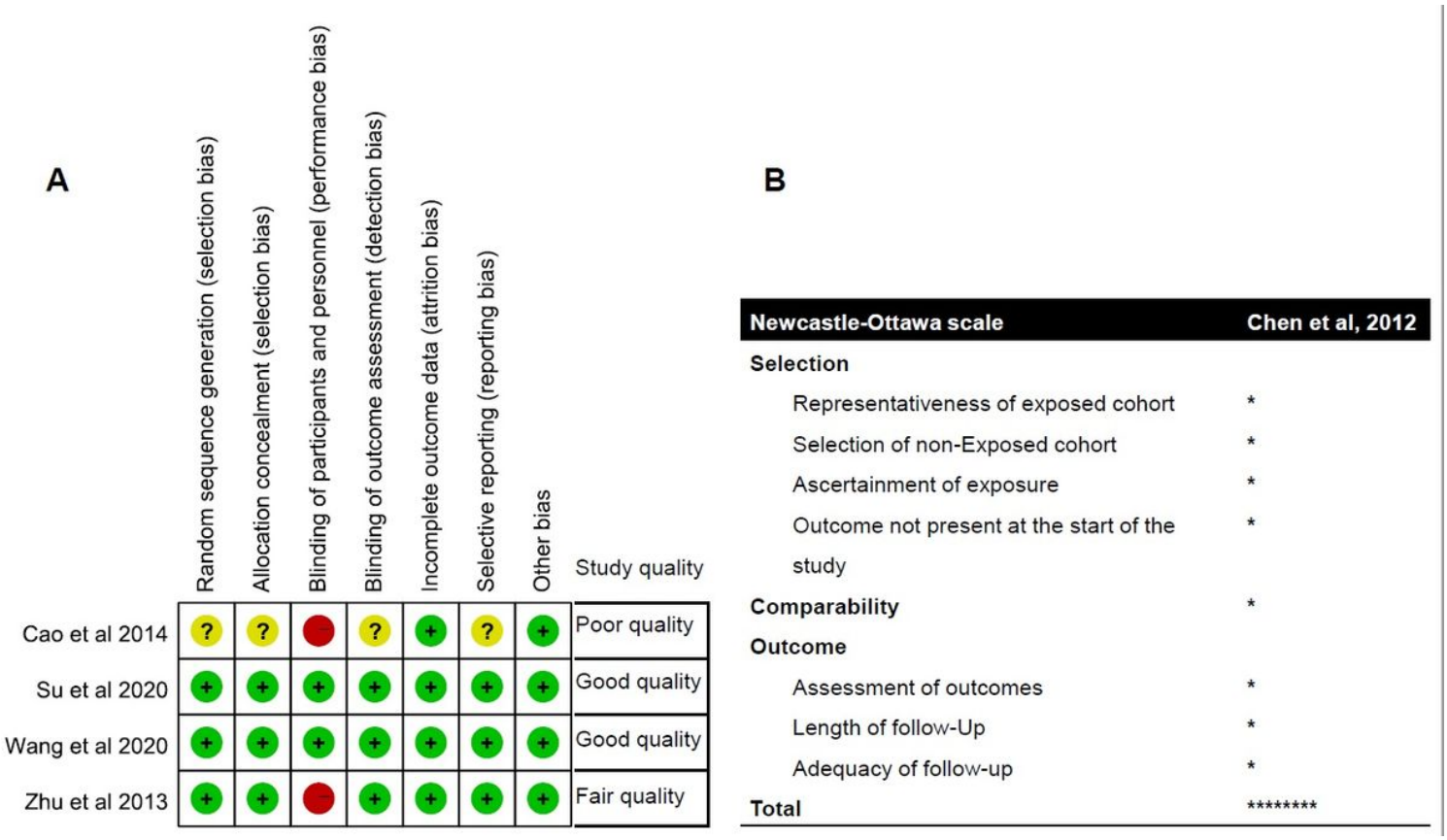
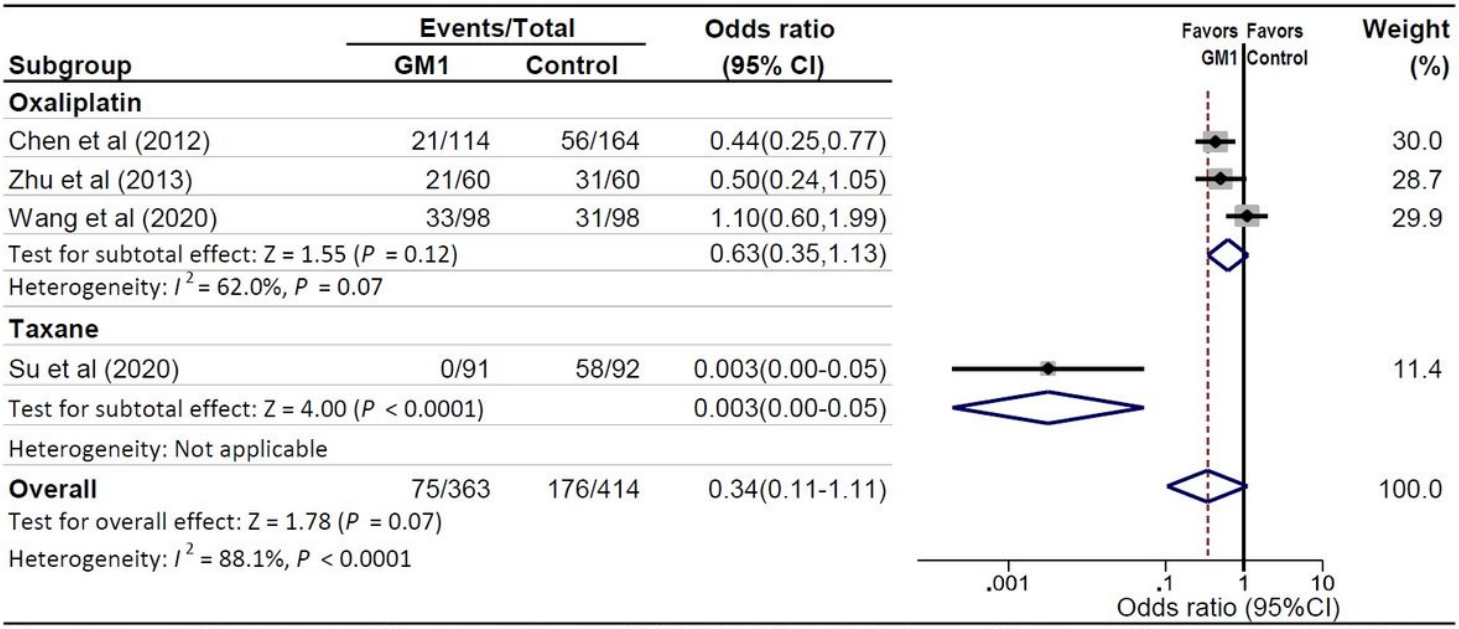


Figure 2

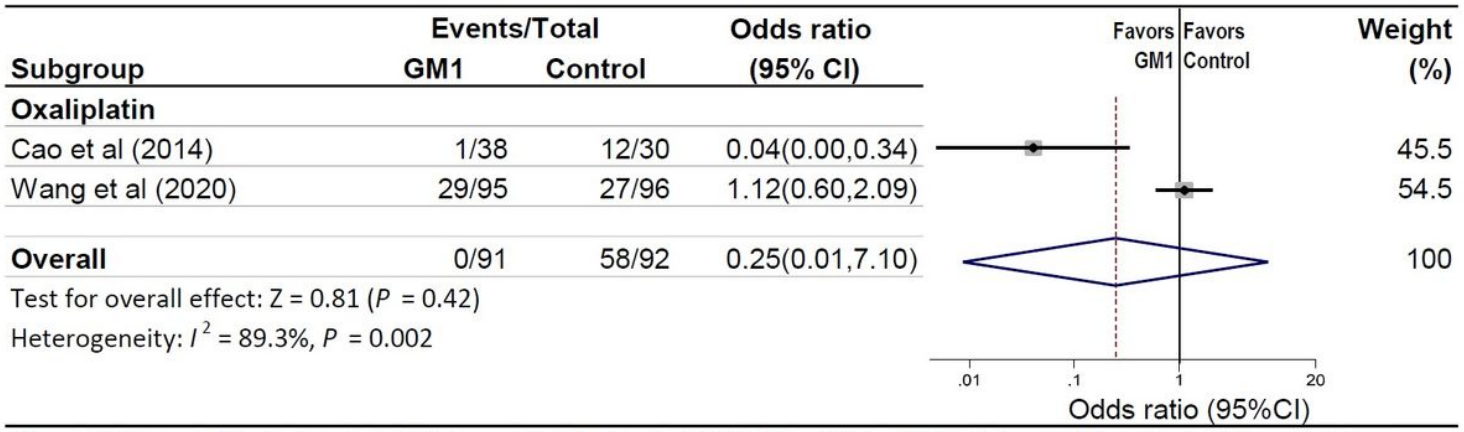
Risk-of-bias assessment of included RCTs using the Cochrane risk-of-bias assessment tool (A) and one cohort study using Newcastle-Ottawa Scale (B).



The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. Diamonds represent the combined effects and the vertical solid line represents the line of no association.

Figure 3

Forest plot displaying a random-effects meta-analysis of the effect of GM1 on the incidence of grade ≥2 chemotherapy-induced peripheral neuropathy using the common terminology criteria for adverse events (CTCAE).

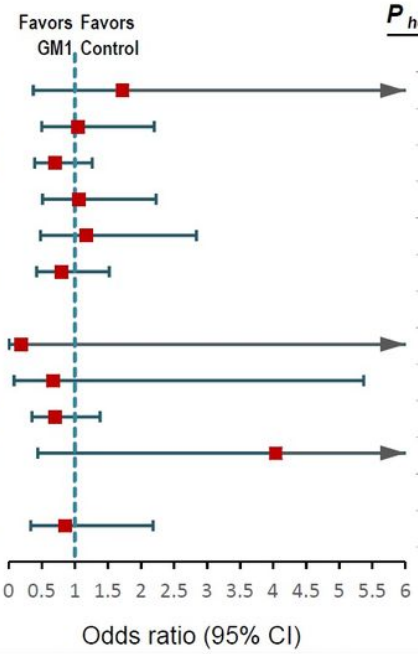


The squares and bars represent the mean values and 95% CIs of the effect sizes and the area of the squares reflects the weight of the studies. Diamonds represent the combined effects and the vertical solid line represents the line of no association.

Figure 4

Forest plot displaying a random-effects meta-analysis of the effect of GM1 on the incidence of grade ≥2 oxaliplatin-induced peripheral neuropathy using the Neurotoxicity criteria of Debiopharm (DEB-NTC).

Outcome	No. of studies	*n* events/total GM1	*n* events/total Control	*P* value	Odds ratio (95% CI)	$P_{heterogeneity}$	I^2(%)
RECIST							
CR	2	4/105	3/123	0.49	1.72 (0.37-7.98)	0.65	0.0
PR	3	30/143	38/153	0.89	1.05 (0.50-2.20)	0.31	15.0
SD	3	24/143	36/153	0.24	0.70 (0.39-1.26)	0.63	0.0
PD	3	16/143	17/153	0.87	1.06 (0.51-2.23)	0.62	0.0
ORR	2	31/105	39/123	0.73	1.17 (0.48-2.84)	0.21	36.9
DCR	2	49/105	68/123	0.49	0.80 (0.42-1.52)	0.42	0.0
Adverse events (CTCAE grade ≥2)							
Fatigue	2	11/198	51/196	0.42	0.19 (0.00-11.15)	<0.001	95.2
Nausea	2	19/198	18/196	0.71	0.67 (0.08-5.37)	0.14	54.3
Diarrhea	2	16/198	22/196	0.30	0.70 (0.35-1.38)	0.64	0.0
Rash	1	4/100	1/98	0.22	4.04 (0.44-36.82)	NA	NA
Chemotherapy Dropout	2	43/212	53/262	0.74	0.85 (0.33-2.18)	0.06	72.8



The squares with bars represent the mean values and 95% CIs of the effect sizes. The vertical dotted line represents the line of no association.

Figure 5

Summary of safety and RECIST data related to GM1.

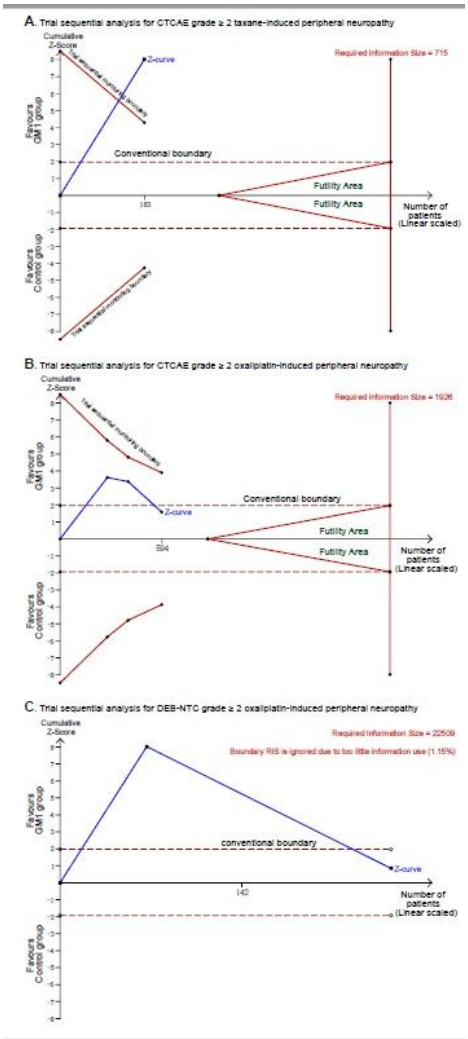


Figure 6

TSA for taxane-induced peripheral neuropathy showing that the cumulative Z curve (blue line) has crossed the TSA monitoring boundary (red line) for statistical significance (A). TSA for oxaliplatin-induced peripheral neuropathy showing that the cumulative Z curve (blue line) has crossed neither the TSA monitoring boundary curve (red line) for benefit nor the required information size (B, C). Of note, the result of the DEB-NTC scale shows that the cumulative sample size in the included studies (133+126=259) was far less than the required information size of 22509, indicating that the effect of GM1 on oxaliplatin-induced peripheral neuropathy is inconclusive.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1searchstrategyinthismetaanalysis.doc
- SupplementaryTableS2CriteriaofneurotoxicityaccordingtotheNCICTCAEver.4.0andDEBNTCscales.docx