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Original article

Efficacy of Traditional Chinese Medicines in Preventing Oxaliplatin-induced Peripheral Neurotoxicity in Cancer Patients: A Network Meta-analysis

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ABSTRACT

Objective Oxaliplatin-induced peripheral neurotoxicity (OIPN) is the main limitation for its continuation in cancer patients. Traditional Chinese medicines (TCMs) have been used to prevent OIPN in China and have been demonstrated to be effective. However, due to the lack of direct comparison among TCMs, it remains unclear that which TCM is the best for OIPN prevention. Consequently, the present study aimed to compare the relative efficacies of TCMs to find out the best TCM by applying a network meta-analysis. **Methods** Studies were identified by searching PubMed, EMbase, Cochrane Libraries, CNKI, WanFang, and WeiPu database from January 1990 to May 2016. Randomized controlled trials (RCTs) that evaluated the efficacy of TCMs in preventing OIPN in cancer patients were included. Statistical analysis was performed with ADDIS 1.16.6. **Results** Twenty-five RCTs (1572 patients) involving five TCMs were included. The results of network meta-analyses showed that compared with oxaliplatin-based chemotherapy alone, the combination with Huangqi Injection (HQI), Shenmai Injection (SMI), Shenfu Injection (SFI), Buyang Huanwu Decoction (BHD), and Huangqi Guizhi Wuwu Decoction (HGWD) could decrease the overall OIPN incidence and the severe OIPN incidence in cancer patients. In addition, probability ranking results showed the order of efficacy in preventing overall OIPN incidence was HQI > HGWD > SFI = SMI > BHD, while the order of efficacy in preventing severe OIPN incidence was HQI > HGWD > BHD > SFI = SMI. **Conclusion** All five TCMs are effective neuroprotective agents against OIPN. Among these TCMs, HQI and HGWD were superior to others in clinical efficacy. Moreover, *Astragalus membranaceus* might be a more promising herb for the OIPN prevention. However, more direct head-to-head RCTs with high quality and large sample size are still needed to further confirm the conclusion.

Key words

network meta-analysis; oxaliplatin; peripheral neurotoxicity; prevention; traditional Chinese medicines

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1. Introduction

Oxaliplatin is a third-generation organoplatinum with antineoplastic effect through producing inter- and intra-strand platinum DNA crosslinks and inhibiting DNA replication and transcription (Salehi and Roayaei, 2015). Oxaliplatin becomes the principle chemotherapeutic agent used against colorectal cancer in both adjuvant and palliative therapy when combined with 5-fiuorouracil/leucovorin (André et al, 1999; 2004; de Gramont et al, 2000). In addition to colorectal cancer, oxaliplatin has shown promising activity against other malignancies such as esophageal (Khushalani et al, 2002), gastric (Bang et al, 2012), pancreatic (Assaf et al, 2011), hepatocellular (Sun et al, 2011), and non-small cell lung (Trédaniel et al, 2009) cancers. However, peripheral neurotoxicity is one of the most important limitations of oxaliplatin use. Oxaliplatin typically induces two clinically distinct forms of peripheral neurotoxicity: transient, acute syndrome which usually occurs during or within hours of infusion and chronic, and cumulative peripheral neuropathy that generally persists between cycles. Whereas acute form is not dosis dependent, high cumulative doses of oxaliplatin are strongly associated with occurrence of chronic peripheral nerve damage (Sereno et al, 2014).

The Food and Drug Administration reported oxaliplatin to be responsible for more than 70% of symptomatic neurotoxicity with any severity. In other studies, approximately 80% of colorectal cancer patients treated with oxaliplatin alone or in combination with other chemotherapeutics experienced neurotoxicity (Avan et al, 2015). This complication may reduce dosage and duration of oxaliplatin administration, even lead to treatment discontinuation, affect survival, and impair patients' quality of life (Salehi and Roayaei, 2015). Moreover, once neurotoxicity is established, impairment may be permanent and irreversible and there are no options to reverse the damage. Therefore, significant interest in the preventative or neuroprotective investigation against OIPN seems reasonable. Although there are several drugs to reduce OIPN, such as amifostine, calcium/magnesium infusion, glutathione, vitamin E, carbamazepine, and oxcarbazepine (Sereno et al, 2014), no well-accepted therapy to prevent OIPN has been identified (Hoff et al, 2012; Grothey, 2005). Hence, an alternative or novel approach is required to prevent OIPN.

Traditional Chinese medicine (TCM) is an essential part of the healthcare system in several Asian countries, and is considered a complementary or alternative medical system in most Western countries. Traditional Chinese medicines (TCMs) are an essential part of TCM (Hu et al, 2011). Due to their multilevel, multitarget, and coordinated intervention effects, TCMs seem to be a promising and viable choice for OIPN prevention (Cheng et al, 2015). Based on recent literatures, five TCMs exhibiting promising effects on OIPN or a putative influence on mechanisms of OIPN have been identified. However, there are no direct head-to-head evidences to declare which is the best TCM in preventing OIPN. As such, it is difficult to determine the superiority of a treatment using pairwise comparison meta-analysis. Network meta-analysis is an extension of traditional meta-analysis and is a method that can combine both direct and indirect evidence from multiple trials using a Bayesian approach and Markov chain Monte Carlo methods to determine the relative efficacies of five TCMs for OIPN prevention (Lu and Ades, 2004; Gupta and Paquet, 2013). Therefore, the objective of the present study is to compare the clinical efficacy of five TCMs by performing a network meta-analysis, in order to put forward the best TCM in preventing OIPN in cancer patients.

2. Materials and methods

2.1 Literature search

A systematic literature search was performed using the following electronic databases (from January 1990 to May 2016): PubMed, Embase, Cochrane Central Registry of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wanfang Database, and Weipu Database (without collecting unpublished studies). The searched literature included the following terms and/or combination in their titles, abstracts, or keyword lists: randomized controlled trials (RCTs), chemotherapy, peripheral neurotoxicity, peripheral neuropathy, prophylaxis, prevention, TCMs, and oxaliplatin. No date or language limits were applied. References of included studies and previous relevant reviews were scanned for potentially relevant studies that had been missed in literature searching.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows. (1) Types of studies: RCTs with a parallel design; (2) Types of participants: cancer patients with oxaliplatin-based chemotherapy; (3) Types of interventions: TCMs combined with chemotherapy compared with chemotherapy alone; (4) Types of outcome measures: overall OIPN incidence and severe OIPN incidence ($\geq$ 2 grade).

The exclusion criteria were as follows. (1) Non-RCTs, case reports, reviews, animal experiments, and duplicates; (2) Patients suffered from nervous system diseases; (3) Patients taking other medicines that may cause neurological disturbances; (4) OIPN not as the outcome measure; (5) The datum cannot be extracted from the study.

2.3 Data extraction

Two authors (Xiao-chen Wei and Li-qin Zhu) independently extracted the data (patient characteristics, treatment details, and clinical outcomes) and assessed the methodological quality of included trials. The full-text versions of selected studies were then assessed by the two authors to determine whether the inclusion criteria were satisfied. Differences in opinion were resolved by discussion until consensus was reached.