RESEARCH ARTICLE

Cantharidin Combined with Chemotherapy for Chinese Patients with Metastatic Colorectal Cancer

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Abstract

Background: This systematic analysis was conducted to evaluate the efficacy and safety of cantharidin combined with chemotherapy in treating Chinese patients with metastatic colorectal cancer. Methods: Clinical studies evaluating the efficacy and safety of cantharidin combined with chemotherapy on response and safety for Chinese patients with colorectal cancer were identified using a predefined search strategy. Pooled response rate (RR) of treatment were calculated.Results: When cantharidin combined with chemotherapy, 4 clinical studies which included 155 patients with advanced colorectal cancer were considered eligible for inclusion. The systematic analysis suggested that, in all patients, pooled RR was 46.5% (72/155) in cantharidin combined regimens. Major adverse effects were neutropenia, leukopenia, fatigue, and anemia with cantharidin combined treatment; no treatment related deaths occurred. Conclusion: This systematic analysis suggests that cantharidin combined regimens are associated with high response rate and accepted toxicity in treating Chinese patients with metastatic colorectal cancer suggesting that randomized clinical trials are now warranted.

Keywords: Cantharidin - colorectal cancer - chemotherapy combination - response rate - toxicity

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Introduction

Colorectal cancer is the third most commonly cancer in the world, with over 1.2 million new cancer cases and 608, 700 deaths estimated to occurred in 2008 (Jemal et al., 2011). Approximately half of all patients will develop metastatic cancer (Parkin et al., 2005). On many occasions, disease is too advanced and only palliative therapy could be considered. Doublets such as irinotecan plus infusional 5-FU/LV (FOLFIRI) or oxaliplatin plus infusional 5-FU/LV (FOLFOX) prolonged median survival to more than 20 months (De Gramont et al., 2000; Douillard et al., 2000; Goldberg et al., 2004; Kohne et al., 2005). Nevertheless, many patients still failed to treatment due to tumor recurrence and metastasis, and 5-year survival rate still less than 10%.

Cantharidin is a sesquiterpene derivatives extracted from the Mylabris body (Verma et al., 2012). Cantharidin sodium is a semi-synthetic derivative of cantharidin. By reducing the cancer cells to the uptake of amino acids, inhibit protein synthesis, stimulating macrophages, lymphocytes, polymorphonuclear cells produce interleukin, and finally to improve immunity and enhance anticancer efficacy (Bajsa et al., 2011; Hsieh et al., 2011).

Cantharidin sodium injection has been developed and manufactured by Guizhou magic Pharmaceutical Co., Ltd in China. Studies have shown that the main active ingredient is cantharidin, which has characteristics of anti-cancer without causing myelosuppression, and it can promote hematopoietic stem cells to accomplish differentiation into myelomonocytic in order to increase the leukocyte (Liu et al., 2009). So, our hypothesis is that the combination of Chemotherapy and cantharidinate sodium could be superior to chemotherapy alone regarding the efficacy and toxicity when treating patients with colorectal cancer.

Materials and Methods

Search strategy

We searched http: //www.cnki.net/ (a website for Chinese research), by using the following search term: (cantharidin) and (colorectal cancer). All clinical studies evaluating the impact of cantharidin on the response or survival and side effects for colorectal cancer published in Chinese prior to October 1st of 2014 were identified. If samples of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (a) clinical studies, with cantharidin; (b) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the

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World Medical Association. Eligibility criteria included histologically verified with colorectal cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age 18 years. Studies were excluded if one of the following existed: (a) duplicate data; (b) No sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 122 papers relevant to the search words on 1st of October, 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Chen and Wu 2004; Fan, 2009; Fan and Wang, 2013; He and Fan, 2014) when cantharidin was used in chemotherapy. All these studies had been carried out in China. The following outcomes were presented in all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities.

Characteristics of cantharidin as a component of chemotherapy, studies included in this study are presented as short-term outcomes: the response rate of He and Fan was 50%, of Fan and Wang was 56.5%, 39.5% for Chen and Wu, 42.9% for Fan. Totally, 155 patients were enrolled and 72 patients achieved CR or PR, the pooled response rate thus was 46.5% (72/155).

Observation on toxicities: Nausea and vomiting, were exceedingly common. Grade 3/4 toxicities included neutropenia, thrombocytopenia, and anemia (graded according to the World Health Organization grading system). No treatment related death occurred in cantharidin based treatment.

Discussion

Colorectal cancer, the second leading cause of cancer death in the USA, has increased in frequency in China in recent years. Based on a registry in Shanghai, a city with a population of 23 million, colorectal cancer has become the third most prevalent malignancy (Shanghai, 2007). Approximately 50-60% of patients diagnosed with colorectal cancer will develop metastases (Van Cutsem et al., 2006; Yoo et al., 2006), for whom systematic chemotherapy is the standard treatment. Irinotecan combined with continuous infusion of 5-fluorouracil (5-FU) and folinic acid (the FOLFIRI regimen) is an established option for first- and/or second-line treatment of metastatic colorectal cancer. Capecitabine, an oral fluoropyrimidine that mimics continuous 5-FU infusion by generating 5-FU preferentially in the tumor tissues (Miwa et al., 1998), has been shown to have comparable efficacy to 5-FU/folinic acid as first-line treatment of metastatic colorectal cancer, with an additional benefit of convenient administration without hospitalization (Va n Cutsem et al., 2000). The combination of irinotecan and capecitabine (XELIRI) has been assessed, but the associated gastrointestinal toxicity, especially the incidence of severe diarrhea, affected the feasibility of this regimen (Fuchs et al., 2007; Kohne et al., 2008). The incidence of grade 3/4 diarrhea was higher (17-36% vs 12-15%) with a 3-week XELIRI regimen than with the FOLFIRI regimen (Bajetta et al., 2004; Borner et al., 2005; Cartwright et al., 2005; Patt et al., 2007), and nonsuperior time to progression (TTP; 6-9 months vs 6.7-8.5 months) and overall survival (OS; 13-20 months vs 14.8-17.4 months) were observed (Andre et al., 1999; Douillard et al., 2000; Saltz et al., 2000). Toxicity-induced dose reduction and treatment delay weakened the efficacy of the XELIRI regimen. To reduce the side effect of diarrhea, a 2-week XELIRI regimen was tried recently. The 2-week regimen (irinotecan on day 1, capecitabine on days 2-8 or days 1-5 and 8-12) exhibited promising activity (TTP, 8-10 months, OS, 15-19 months) with improved tolerability (grade 3/4 diarrhea, 8.1-15.0%) (Garcia-Alfonso et al., 2009), but an increased rate of severe diarrhea was noted in elderly patients, which resulted in dose reduction (Garcia-Alfonso et al., 2009). So, in this field no standard regimen is available. How to increase efficacy and decrease toxicities of chemotherapy remains a focus in this area. It is a distinguishing feature of traditional Chinese medicine to contribute in this area (Xu et al., 2012).

Cantharidin is a sesquiterpene derivatives extracted from the Mylabris body (Verma et al., 2012). Cantharidin sodium is a semi-synthetic derivative of cantharidin. By reducing the cancer cells to the uptake of amino acids, inhibit protein synthesis, stimulating macrophages, lymphocytes, polymorphonuclear cells produce interleukin, and finally to improve immunity and enhance anticancer efficacy (Bajsa et al., 2011; Hsieh et al., 2011).

Our current clinical study evaluated the efficacy and safety of cantharidin combined with chemotherapy on response and safety for Chinese patients with colorectal cancer Our results demonstrate that in all patients, pooled RR was 46.5% (72/155) in cantharidin combined regimens. Major adverse effects were neutropenia, leukopenia, fatigue, and anemia in cantharidin combined treatment; No treatment related death occurred in cantharidin combined regimens. In conclusion, this systemic analysis suggests that cantharidin combined regimens are associated with high response rate and accepted toxicities in treating Chinese patients with metastatic colorectal cancer, however, this result should be confirmed by randomized clinical trials.

References

Andre T, Louvet C, Maindrault-Goebel F, et al (1999). CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. *Eur J Cancer*, **35**, 1343-7.

Bajetta E, Di Bartolomeo M, Mariani L, et al (2004). Randomized

multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. *Cancer*, **100**, 279-87.

Bajsa J, Pan Z, Duke SO (2011). Transcriptional responses to cantharidin, a protein phosphatase inhibitor, in Arabidopsis thaliana reveal the involvement of multiple signal transduction pathways. *Physiol Plant*, **143**, 188-205.

Borner MM, Bernhard J, Dietrich D, et al (2005). A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. *Ann Oncol*, **16**, 282-8.

Cartwright T, Lopez T, Vukelja SJ, et al (2005). Results of a phase II open-label study of capecitabine in combination with irinotecan as first-line treatment for metastatic colorectal cancer. *Clin Colorectal Cancer*, **5**, 50-6.

Chen HJ, Wu AG (2004). A clinical study on cantharidin combined with 5-Fu/CF in treating patients with advanced colorectal cancer. *J Chinese Doctor***.**

De Gramont A, Figer A, Seymour M, et al (2000). Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol,* **18**, 2938-47.

De Gramont A, Kindler HL (2002). Pemetrexed in patients with gastrointestinal carcinoma. *Semin Oncol*, **29**, 42-9.

Douillard JY, Cunningham D, Roth AD, et al (2000). Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*, **355**, 1041-7.

Douillard JY, Cunningham D, Roth AD, et al (2000). Irinotecan combined with fluorouracil compared with fluorouracil alone. As first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*, 25, 1041-7.

Fan LJ (2009). A clinical observation on Cantharidin B6 5-Fu and CF in treating patients with advanced colorectal cancer. *Mod Med J China*, **11**, 64-5

Fan QL, Wang Y (2013). A clinical study on Cantharidin B6 and S-1 in treating patients with advanced gastrointestinal cancer. *Guang Ming Chin Med,* **28**, 4.

Fuchs CS, Marshall J, Mitchell E, et al (2007). Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol*, **25**, 4779-86.

Garcia-Alfonso P, Munoz-Martin A, Mendez-Urena M, et al (2009). Capecitabine in combination with irinotecan (XELIRI), administered as a 2-weekly schedule, as first-line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group. *Br J Cancer*, **101**, 1039-43.

He F, Fan T (2014). Cantharidin and mFOLFOX6 in treating patients with colorectal cancer. *J Med Sci Central South China*, **3**, 311-3

Hsieh CH, Huang YC, Tsai TH, et al (2011). Cantharidin modulates development of human monocyte-derived dendritic cells. *Toxicol In Vitro,* **25**, 1740-7.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90

Kohne CH, De Greve J, Hartmann JT, et al (2008). Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. *Ann Oncol*, **19**, 920-6.

Kohne CH, Van Cutsem E, Wils J, et al (2005). Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol,* **23**, 4856-65.

Liu D, Chen Z (2009). The effects of cantharidin and cantharidin derivates on tumour cells. *Anticancer Agents Med Chem*, **9**, 392-6.

Miwa M, Ura M, Nishida M, et al (1998). Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer*, **34**, 1274-81.

Parkin DM, Bray F, Ferlay J, Pisani P (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.

Patt YZ, Lee FC, Liebmann JE, et al (2007). Capecitabine plus 3-weekly irinotecan (XELIRI regimen) as first-line chemotherapy for metastatic colorectal cancer: phase II trial results. *Am J Clin Oncol*, **30**, 350-7.

Saltz LB, Cox JV, Blanke C, et al (2000). Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *New Engl J Med*, 343, 905-14.

Shanghai municipal center for disease control and prevention: Shanghai Cancer Report 2007.

Van Cutsem E, Findlay M, Osterwalder B, et al (2000). Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. *J Clin Oncol*, **18**, 1337-45.

Van Cutsem E, Nordlinger B, Adam R, et al (2006). Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer*, **42**, 2212-21.

Verma AK, Prasad SB (2012). Bioactive component, cantharidin from Mylabris cichorii and its antitumor activity against Ehrlich ascites carcinoma. *Cell Biol Toxicol*, **28**, 133-47.

Wang L, Huang XE, Cao J (2014). Clinical study on safety of cantharidin sodium and shenmai injection combined with chemotherapy in treating patients with breast cancer postoperatively. *Asian Pac J Cancer Prev*, **15**, 5597-600

Xu Y, Zhao AG, Li ZY (2012). Survival benefit of traditional chinese herbal medicine (a herbal formula for invigorating spleen) for patients with advanced gastric cancer. *Integr Cancer Ther*, **9**, 9.

Yoo PS, Lopez-Soler RI, Longo WE, et al (2006). Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. *Clin Colorectal Cancer*, **6**, 202-7.

Zhan YP, Huang XE, Cao J (2012). Clinical study on safety and efficacy of Qinin® (cantharidin sodium) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pacific J Cancer Prev*, **13**, 4773-6