Endostar combined with chemotherapy compared with chemotherapy alone in the treatment of nonsmall lung carcinoma: A meta-analysis based on Chinese patients

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Abstract

INTRODUCTION: Lung cancer is the leading cause of cancer-associated death world-wide. And the lung cancer is generally divided into small cell lung carcinoma and non-small cell lung cancer. For advanced NSCLC, the chemotherapy and target therapy were the important treatment modality. This meta-analysis was to evaluate the clinical efficacy and toxicity between endostar combined chemotherapy and chemotherapy alone in Chinese patients. **MATERIALS AND METHODS:** We searched the PubMed, EMBASE, and CNKI databases to find the potential relevant articles reporting the endostar combined with chemotherapy regimen in the treatment of nonsmall cell lung cancer in Chinese patients. The tumor response and toxicity difference between the two groups were demonstrated by odds ratio (OR) and its 95% confidence interval (95% CI). All the data was pooled by Stata 11.0 (http://www.stata.com; Stata Corporation, College Station, TX) software. **RESULTS:** We included 14 studies published in Chinese or English studies. The pooled results showed adding endostar in the chemotherapy regimen can significant increase the objective response rate (OR = 2.42, 95% CI = 1.87–3.12, P = 0.00) and disease control rate (OR = 2.22, 95% CI = 1.68–2.94, P = 0.00). For toxicities, the pooled data showed no statistical difference for grade III-IV granulocytopenia risk (OR = 1.04, 95% CI = 0.74–1.44, P = 0.83). Nausea and vomiting (OR = 0.93 95% CI: 0.51–1.52, P = 0.78) and grade III-IV alopecia (OR = 0.99, 95% CI: 0.76–1.29, P = 0.95). The funnel plot showed no statistical publications. **CONCLUSION:** Combined treatment with endostar can improve the response rate for NSCLC patients without increasing the risk of developing severe adverse event.

Key Words: Chemotherapy, endostar, meta-analysis, nonsmall cell lung cancer, response, toxicity

Introduction

Endostar is a 20-kDa C-terminal fragment derived from type XVIII collagen. It is reported to serve as an antiangiogenic agent, similar to angiostatin and thrombospondin. Endostar is a broad-spectrum angiogenesis inhibitor and may interfere with the pro-angiogenic action of growth factors such as basic fibroblast growth factor/fibroblast growth factor-2 and vascular endothelial growth factor. Many studies have evaluated the efficacy of endostar combined with platinum-based chemotherapy versus chemotherapy alone for treating advanced nonsmall cell lung cancer (NSCLC).[1-3] Most of the studies showed that adding endostar to platinum-based chemotherapy regimen can improve the prognosis of nonsmall cell lung cancer patients. But other studies provide opposed results.[4] We made this current meta-analysis to quantify the response toxicities of endostar combined with platinum-based chemotherapy versus chemotherapy alone in treating advanced NSCLC.

Materials and Methods

Literature search and inclusion criteria

We searched the PubMed, EMBASE, and CNKI databases to find the potential relevant articles reporting the endostar combined with chemotherapy regimen in the treatment of nonsmall cell lung cancer. The searching procedure was performed by two authors independently. The following search items were used as free text word: "Nonsmall cell lung cancer," "NSCLC," "nonsmall cell lung cancer," "nonsmall cell lung carcinoma," "lung adenocarcinoma," "lung cancer," "lung squamous carcinoma," "rh-endostatin," "endostatin," "chemotherapy," "Endostar," and "recombinant human endostatin injection." The searching strategy was limited to human trials, with the language restriction of English and Chinese. The included criteria of the individual study of this meta-analysis were as follows: (1) The patients in each included study were nonsmall cell lung carcinoma with pathology confirmation. (2) Two arm treatments with, one is endostar combined with chemotherapy the other is chemotherapy alone. (3) The individual study provided the response rate of complete response (CR), partial response (PR), stable disease (SD) and progress disease (PD). (4) The studies are published in English or Chinese. The exclusion criteria were: (1) Review or case report publication. (2) The study does not provide enough data such as CR, PR, SD and PD. (3) Duplicate publications or data.

Statistical analysis

All of the data in this meta-analysis was analyzed by Stata 11.0 (http://www.stata.com; Stata Corporation, College Station, TX) software. The odds for objective response rate (ORR), disease control rate (DCR) and toxicity were demonstrated by odds ratio (OR) and its 95% confidence interval (CI). The statistical heterogeneity of OR for ORR, DCR and toxicity was evaluated by Chi-square test.[5] No statistical heterogeneity was existed among the studies if $P > 0.1$ for Chi-square test, and the OR was calculated by fixed effect model. Otherwise, the OR was pooled by random effect model. The publication bias was tested by Begg's funnel plot.

Results

Searching results

Through searching the Medline, and CNKI databases, 14 studies[1-4,6-15] related to endostar combined chemotherapy in the treatment of colorectal cancer were recruited in this meta-analysis. The detailed information of each included article is demonstrated in Table 1. Five studies compared the tumor response and toxicity between endostar combined NP

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Table 1: The general characteristics of the 14 studies

Study	Endostar+chemotherapy				Chemotherapy				Year
	Number	Age	Male/female	Regiment	Number	Age	Male/female	Regiment	
Wang *et al.*[6]	322	57	229/93	Endostar+NP	164	55	117/47	NP+placebo	2005
Song *et al.*[7]	9	NA	NA	Endostar+NP	11	NA	NA	GP	2007
Chen *et al.*[8]	24	58	18/6	Endostar+NP	26	57	19/7	NP	2008
Wang and Cai[9]	17	63	11/6	Endostar+NP	18	64	12/6	NP	2009
Han and Xing[10]	37	NA	22/15	Endostar+TP	31	NA	20/11	TP	2009
Xu and Wang[11]	25	NA	NA	Endostar+DP	26	NA	NA	DP	2009
Chen *et al.*[12]	33	NA	22/11	Endostar+NP	17	NA	9/8	NP	2009
Ning[2]	30	50	23/7	Endostar+GP	25	49	18/7	GP	2010
Fu *et al.*[13]	44	61	29/15	Endostar+TP	37	63	24/13	TP	2010
Peng[3]	27	NA	NA	Endostar+GP	33	NA	NA	GP	2010
Sun *et al.*[1]	18	NA	10/8	Endostar+TP	18	NA	11/7	TP	2010
Wei *et al.*[4]	16	NA	NA	Endostar+GP	16	NA	NA	GP	2010
Wang[14]	50	NA	NA	Endostar+GP	55	NA	NA	GP	2013
Han[15]	50	NA	NA	Endostar+NP/TP	50	NA	NA	NP/TP	2014

NA=Not available

chemotherapy with NP chemotherapy alone. Four articles compared the endostar combined GP chemotherapy with GP chemotherapy alone. Two studies compared the endostar combined DP chemotherapy with DP chemotherapy alone. And one studies compared the endostar combined the mixed chemotherapy with a mixed chemotherapy alone. The median sample size was 55 with the range of 32–486 cases for the 14 studies.

Tumor response

We calculate the heterogeneity for ORR before pooling the OR for ORR. The I^2 was 0.00% indicating no obviously statistical heterogeneity between the included 14 articles. The pooled OR for objective response was aggregated by fixed effect model. The pooled results showed adding endostar in the chemotherapy regimen can significant increase the ORR (OR = 2.42, 95% CI = 1.87–3.12, P = 0.00). For DCR (CR + PR), I^2 = 0.00% indicating no obviously statistical heterogeneity existence. The OR and its 95% CI were pooled by fixed effect model. The combined results showed the combined chemotherapy significant improve the DCR for advanced nonsmall cell lung cancer (OR = 2.22, 95% CI = 1.68–2.94, P = 0.00), [Figure 1].

Toxicity

We pooled the chemotherapy-related toxicities such as grade III-IV granulocytopenia, nausea and vomiting and alopecia. For granulocytopenia, nine studies reported the adverse event of granulocytopenia. The I^2 test showed no statistical heterogeneity, the combined OR for granulocytopenia was pooled by fixed effect mode. The pooled data indicated that there was no significant difference between the two groups for grade III-IV granulocytopenia risk (OR = 1.04, 95% CI = 0.74–1.44, P = 0.83). Nine studies reporting the side effects of nausea and vomiting, the pooled OR was 0.93 (95% CI: 0.51–1.52), P = 0.78. The endostar does not increase the incidence rate of grade III-IV nausea and vomiting. Two papers provided the incidence of alopecia, the pooled results showed there was not statistical difference grade III-IV alopecia risk between the combined treatment and chemotherapy along group (OR = 0.99, 95% CI: 0.76–1.29, P = 0.95), [Figure 2].

Publications bias

Funnel plot an Egger's test were employed to evaluate the publication bias, and it provided evidence that there was no publication bias among studies regarding response rate and toxicity. The shape of funnel plots was symmetrical [Figure 2].

Discussion

Lung cancer is the leading cause of cancer-associated death world-wide. It was reported that male lung cancer death rates are decreasing in most Western countries, including many European countries, North America, and Australia, where the tobacco epidemic peaked by the middle of the last century.[16,17] But in China, lung cancer rates are increasing for its smoking prevalence and increasingly serious environment pollution.[18,19]

And the lung cancer is general divided small cell lung cancer and nonsmall lung carcinoma (NSCLC). About 80% lung cancers are nonsmall lung cancer. And about 80% of nonsmall lung cancers are diagnosis with advanced stage that are not suitable for surgery treatment.[20] For these nonsmall cell lung cancer patients with advance stage, the systematic chemotherapy is the main treatment modality. But the response rate for the standard platinum-based chemotherapy regimen is <30% and reach its bottleneck. And clinical studies showed increased amount of chemotherapy drugs cannot significant improve the prognosis but increasing the risk of developing severe toxicity such and myelosuppression, nausea and vomiting and liver or renal function damage.

Recently, the clinical use of antiangiogenic therapy has brought the promise for the treatment of NSCLC and has become an important addition in the treatment of tumor invasion and metastasis. Recombinant human endostatin (Endostar) has been produced by the Entremed Company using a yeast expression system. In 2005, China State Food and Drug Administration licensed endostar plus

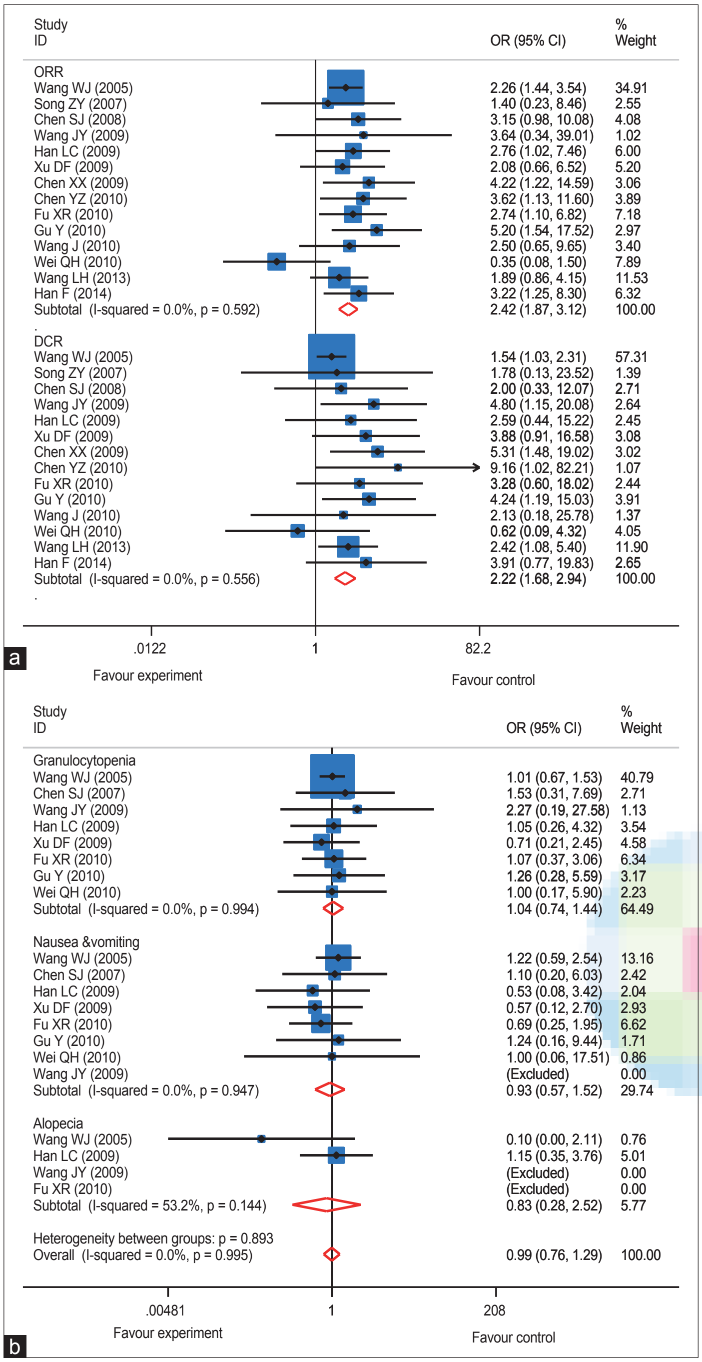

Figure 1: (a) Forest plot of odds ratio (ORs) for response of endostar combine chemotherapy versus chemotherapy alone in the treatment of NSCLC (the squares and horizontal lines correspond to the study-specific OR and 95% confidence interval [CI]. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI), (b) forest plot of odds ratio (ORs) for related adverse events of endostar combine chemotherapy versus chemotherapy alone in the treatment of NSLC (the squares and horizontal lines correspond to the study-specific OR and 95% confidence interval [CI]. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI)

vinorelbine-cisplatin (NP) to treat advanced NSCLC as a first-line therapy. And the Endostar has been broadly used in Chinese advanced nonsmall lung cancer patients with promising prognosis.[8,15]

In the present meta-analysis, we brought in 14 published articles comparing the endostar combined chemotherapy versus chemotherapy alone in the treatment of NSCLC. The pooled results showed combined treatment with endostar can improve the response rate for NSCLC patients without

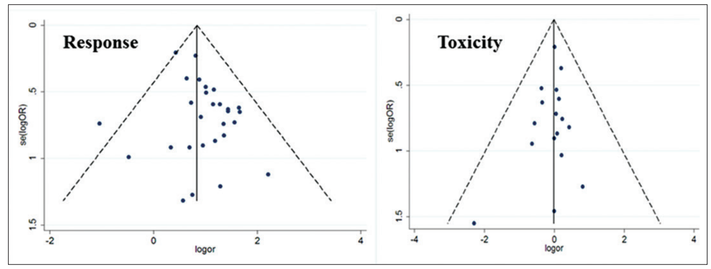

Figure 2: Publication bias on response and toxicity (the dots represent each included studies)

increasing the risk of developing severe adverse event. Several limitations were existed in this meta-analysis: Firstly, the patients number in each of the included study was small except for Wang.[6] Secondly, the general quality of the included study was relatively poor. Thirdly, no overall and progression-free survival was provided in this meta-analysis that was more important than response rate.

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