

Therapeutic effect of endostar combined with chemotherapy for colorectal cancer: An new evidence from meta-analysis.

Hui Zhao^{1*}, San Li Cai², Jing Feng Wang³

¹Department of Thoracic Surgery-1, Jilin Cancer Hospital, 1018 Huguang Road, Changchun, Jilin Province, PR China

²Department of Thoracic Oncosurgery-3, Jilin Cancer Hospital, 1018 Huguang Road, Changchun, Jilin Province, PR China

³Center of Intervention, Jilin Cancer Hospital, 1018 Huguang Road, Changchun, Jilin Province, PR China

Abstract

Objective: To compare the effect of Endostar in combination with chemotherapy for colorectal cancer with effect of chemotherapy alone.

Methodology: Take excluded criteria to select previous researches, evaluate the risk of bias and then propose the meta-analysis. The combined effect size is Odd Ratio (OR). If there is a negative result in the heterogeneity test, subjects can be combined by the fixed effects model, otherwise a sensitive test is proposed, negative sensitive researches cannot pass through into fixed effects model.

Results: Totally, there are 16 prospective cohort studies having a low risk of bias included in the meta-analysis. Compared with accepting chemotherapy alone, patients with Endostar therapy in combination with chemotherapy have significant improved outcomes, the probability of outcomes improvement increased 59 times (RR=1.59, 95% CI: 1.34,1.89). I² value is 0%, indicating a low heterogeneity.

Conclusion: In conclusion, compared with chemotherapy alone, Endostar treatment of colorectal cancer in combination with chemotherapy has a better effect rather than chemotherapy alone based on RR +CR.

Keywords: Archenteric cancer, Drug, Evidence based review.

Accepted on December 08, 2016

Introduction

Colorectal cancer is the most common cancer and is one of the most important causes of individual death around the world. The latest World Health Organization epidemiological data showed that in 2012, almost 8.2 million people worldwide died because of cancer, including 694,000 people died because of colorectal cancer. The detection rate was second high in both male and female patients [1]. In China, the colorectal cancer death ratio of male and female are 5.5% and 7.7% respectively among all cancer deaths [2]. Endostar (rh-endostatin, Shangdong Simcere-Medgenn Bio-Pharmaceutical Co., Ltd, China) is a recombinant of human endostatin. Plenty studies show that endostatin can be expressed through inducing endothelial cells apoptosis and inhibiting vascular endothelial growth factor (VEGF), and thus it plays an anti-angiogenesis role. VEGF is a pro-growth factor, with the promotion of the growth of blood vessels [3].

Endostar was used to aid the treatment of advanced non-small cell lung cancer at early stage. Short and long term observations showed it is an appropriate adjuvant therapy [4]. As one of anti-angiogenesis drugs, some small sample studies have reported the effect of endostatin in colorectal cancer. A

systematic review contains 5 studies analyzed endostatin treatment of colorectal cancer effects. However, 80% of the similar meta-analysis was published before 2009 years, and the total sample of only 220 [5]. Thus, the initial studies did not provide sufficient evidence to prove the effect of Endostar in the treatment of colorectal cancer, including effectiveness for both rectum cancer and colon cancer treatment. Therefore, in order to assess the outcomes of Endostar treatment for colorectal cancer, and its safety issues, we conducted a comparative meta-analysis among clinical trials with the Endostar consolidated chemotherapy to make a comparison with these who take chemotherapy alone or placebo treatment to assess the impact of endostatin treatment.

Material and Methods

Search strategy

We searched CNKI, WanFang, CQVIP, PubMed, The Cochrane library, Embase and Web of Science databases to retrieve clinical trials results. The searching key terms are: Endostar or recombinant human endostatin or YH-16 and colon cancer or colon carcinoma or rectal carcinoma or rectal cancer

or colorectal cancer or colorectal carcinoma. Publish date is restricted from July 2006 to August 2015.

Criteria for inclusion and exclusion

The target trials should be double-blinded, randomized, controlled trails. Sample participants of these trails are proposed to be patients of colorectal cancer, including rectum cancer and colorectal cancer. These metastatic cancer, whose primary lesions were colorectal cancer and remains their primary lesions are also involved. Content of experimental evaluation is the comparison of Endostar or Endostar combined with chemotherapy and chemotherapy alone or placebo treatment. Outcomes of treatment are categorized as complete remission (CR), stable disease (SD), partial release (PR), disease development (PD), relative rate (RR: CR+PR) and clinical benefit rate (CBR: CR+PR+SD). The final document inclusion and exclusion is determined by two experts, which are oncology clinical experts and epidemiologists respectively. When they hold different opinions, the third person, who is the author, could ultimately determine inclusion or exclusion of the results.

Data extraction and assessment of risk of bias

From clinical researches, we extracted data including gender, age, colorectal cancer types, interventions and treatment outcome. Then we did risk assessment for all researches according to the evaluation of risk of bias tool provided by Cochran Collaboration Web. Each risk assessment is based on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting data with other topics. Each entry for every domain has three judgments result: yes, representing low risk; "unclear" representing not know or unclear risk of bias; no, representing a high risk. Results of the assessment would be expressed by the risk of bias bar chart, drawn by Revman software.

Heterogeneity test and combined effect size

We judge whether there is heterogeneity between studies according to the L'Abbe Figure and I² values. In L'Abbe figure, if each point represents the research is too far away from the OR straight, it suggests that the heterogeneity exists. I² value ≤ 25%, it suggests that there is a low heterogeneity between studies, I² value ≤ 50% and ≥ 25% suggests a moderate heterogeneity between studies, I² value >50% suggests a high heterogeneity. Based on L'Abbe and I² value, if there is heterogeneity between studies then we take meta regression analysis to identify sources of heterogeneity, and redefine the research literature, once meta regression analysis cannot identify the source of the heterogeneity, we choose random

Table 1. 16 clinic trails' participants baseline characteristics.

ID	Study	Year	Chemotherapy	Endostar Therapy1	Therapy	Follow(m) ²	Sex M/F	Age	Metastasis
1	Guozhong Li	2009	XELOX	-,1~14d,7d,repeat cycle	≥ 1 cycle	-		35~75	Liver, lung

effects model to combine effect size. If there is no heterogeneity, then we combine effect size through the fixed effects model. Relative Risk (RR) and 95% confidence intervals are used to assess the degree of Endostar or its combination with chemotherapy drugs effect in the treatment of colorectal cancer. Statistics related to the P values is estimated by bidirectional estimation, and 0.05 is the statistical cutoffs. The data was analyzed by the software of stata.

Result

Search results

According to the search strategy, inclusion and exclusion criteria, 16 randomized controlled trials were eligible for our analysis [6-21]. According to the search strategy, 301 studies were selected. By reading a summary, we excluded reports, reviews, and basic research papers. After screening, 16 studies were left, through a summary screening, to form systematic review (Figure 1).

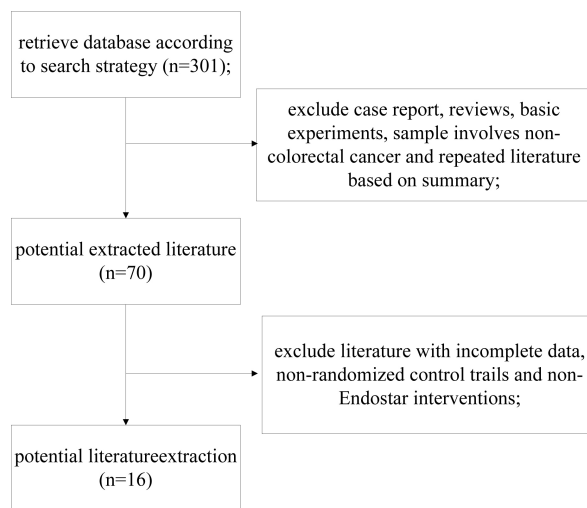


Figure 1: Literature extraction diagram

Figure 1. The boxes represent steps. The arrows represent the sequence of steps. Please insert into the section of "3.1 Search results".

Characteristics of the participants

From 16 clinical trials, we got 723 research participants' research data, including gender, age, colorectal cancer types, interventions and treatment outcome and so on. Among them, the chemotherapy regimen of XELOX, FOLFOX4, FOLFOX are 4, 4, and 2 respectively. Participants aged from 18 to 80 years old. The major metastasis is liver metastases. Baseline characteristics of participants are described in Table 1.

Therapeutic effect of endostar combined with chemotherapy for colorectal cancer: An new evidence from meta-analysis

2	Hong-Xia Xu	2011	FOLFOX4	15mg/d,1~14d,-, repeat cycle	≥ 2 cycle	-			
3	Shimin Ping	2013	Irinotecan/Oxaliplatin	15mg/d,1~14d,7d,repeat cycle	≥ 2 cycle	6~24m	1.765277778	18~75	Liver
4	Dong Yan	2011	XELOX	15mg/d,1~14d,7d,rpeat cycle	≥ 2 cycle	>1m	1.807638889	65~79	Liver, lung, bone
5	Li Ding	2009	FOLFOX4	-,1~14d,-,rpeat cycle	≥ 2 cycle	>1m	1.218055556	39~74	Liver
6	Rongrong Zhang	2009	FOLFOX4	-,1~14d,-,rpeat cycle	4~8cycle	>1m	-	38~70	-
7	Lin Lai	2014	New radiotherapy	-,1~14d,7d,rpeat cycle	2 cycle	-	0.756944444	31~69	None
8	Haipeng Wang	2012	FOLFOX	15mg/d,1~14d,-,repeat cycle	4 cycle	-	1.430555556	62~75	-
9	Zhuo Liu	2014	FOLFIRI	-,1~14d,-,repeat cycle	4 cycle	-	1.515277778	43~73	Liver
10	Zhongzhi Jia	2012	-	10~20mg/d,1~14d,7d,repeat cycle	-	5~12m	1.135416667	37~72	Liver
11	Biaosen Luo	2012	FOLFOX	15mg/d,1~14d,-,rpeat cycle	≥ 2 cycle	-	-	≥ 18	-
12	Lizhen Zhang	2013	Irinotecan/Oxaliplatin	-,1~14d,7d,repeat cycle	≥ 2 cycle	6~24m	1.765277778	18~75	-
13	Chuanqi He	2009	FOLFOX4	-,1~14d,7d,repeat cycle	3~6 cycle	>1m	1.345833333	18~70	-
14	Jing Liu	2009	IFL	15mg/d,1~14d,-,repeat cycle	2~4 cycle	>1m	2.008333333	36~62	Liver, lymph
15	Yan Lin	2012	XELOX	-,1~14d,-,repeat cycle	2~8 cycle	-	1.684027778	43~80	Liver, lung
16	Yitao Jia	2011	XELOX	15mg/d,1~14d,7d,rpeat cycle	≥ 2 cycle	-	1.1	39~65	-

1. Amount per day, sequential taking days, discontinued days, repeat. - represents no relative information.
 2. Follow-up time. "m" means month.

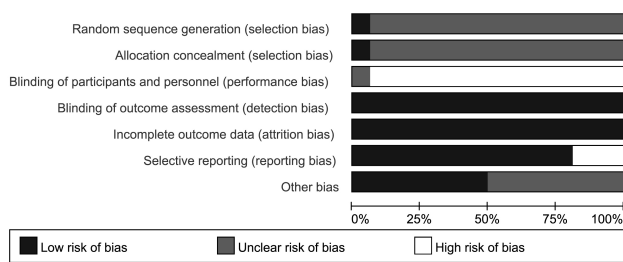


Figure 2 risk of bias ratio

Figure 2. The dark grey means low risk of bias. The grey means unclear risk of bias. The black means high risk of bias. Please insert into the section of "3.3 Bias risk assessment".

Bias risk assessment

Risk of bias assessment shows that, in terms of random sequence generation and allocation concealment, more than 90% of the study is not clear their risk of bias. In terms of binding of participants and personnel, the existence of high risk of bias appears in more than 90% of studies. Lower risk of bias appears in terms of income outcome data and blinding of outcome assessment. In terms of selective reporting bias, less than 25% of the study has a low risk. In addition, we believe that there is potential interest relationship between researchers and drug manufacturers, and hence whether manufactures were informed consent for other similar researches is another important source of bias. The evaluation results indicated that 50% of the studies fail to insure the risk of bias. However, because classification of the therapeutic effect is to be determined based on the results of imaging studies, subjects and investigators were blinded during trails or not has minimal

impact on determining the results. Therefore, we believed the involved 16 studies generally are not at a high risk of bias (Figure 2).

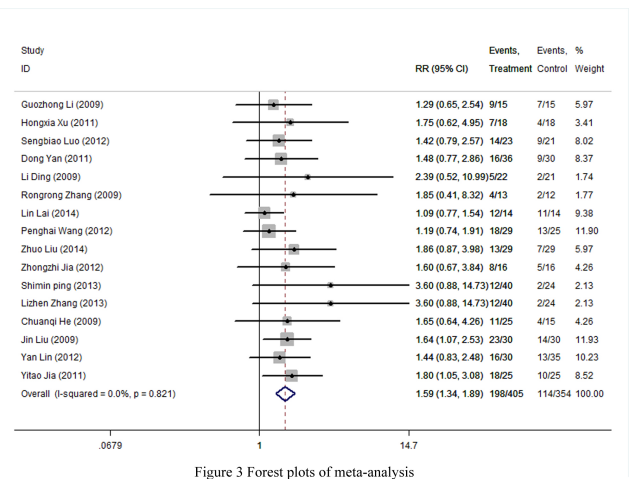


Figure 3 Forest plots of meta-analysis

Figure 3. Squares are study-specific relative risk. Diamonds are summary relative risks (SRRs). Horizontal lines represent 95% confidence intervals (CIs). Please insert into the end of the section of "3.4 Endostar for adjuvant therapy of colorectal cancer".

Endostar for adjuvant therapy of colorectal cancer

Forest plots of the fixed effects model shows that, compared with patients receiving chemotherapy alone, patients with Endostar therapy in combination with chemotherapy in patients have a significant improved outcomes (CR + PR), with 59% increased of improvement probability (RR=1.59, 95% CI: 1.34,1.89). I² is 0%, suggesting the presence of a low

heterogeneity in the studies extraction in the meta-analysis. It can be initially estimated that all participants come from the same population (Figure 3). Therefore, the fixed effects model effect size used above is appropriate.

Publication bias test

Harbord weighted linear regression (Table 2) reveals that there is a absence of publication bias among the 16 studies ($t=1.20$, $p=0.25$, 95% CI: -0.07, 0.24). Meanwhile, Harbord weighted linear regression (Figure 4) shows that almost regression line go through the 0 pot, suggesting that the meta-analysis of the literature in this analysis has a pretty low publication bias.

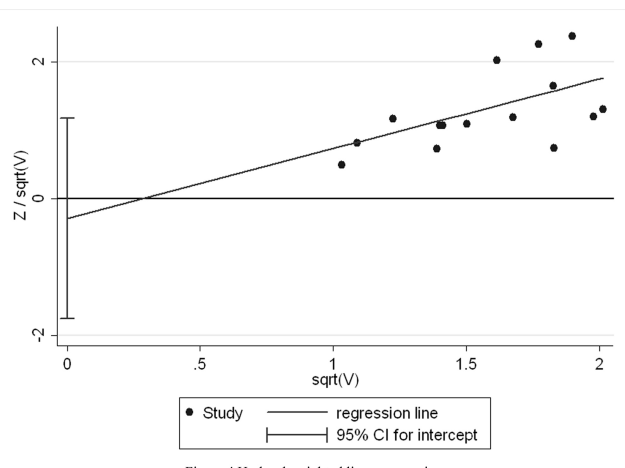


Figure 4 Harbord weighted linear regression

Figure 4. Circles are studies. Oblique line is the regression line. The 95% CI for intercept is presented as "I" form. Please insert into the end of the section of "3.5 publication bias test".

Table 2. Harbord weighted regression.

	Coef.	Std. Err.	t	P value	95% CI	
Slope	2.77	0.03	80.64	0	2.69	2.84
Bias	0.09	0.07	1.2	0.25	-0.07	0.24

Discussion

Our research found, compared with chemotherapy alone in the treatment of colorectal cancer, endostar combined with chemotherapy has a significant improved effect (based on CR+RR). Moreover, there is no significant heterogeneity as well as publication bias among those 16 prospective cohort studies included in this research. The metastasis and growth of solid tumor depend on its induced ability of new blood vessels in the tumor. Endostar, as a recombinant human endostatin, and also due to that endostatin presents targeting effect for vascular endothelial cells and vascular endothelial growth, is now known as one of the most effective anti-angiogenic agents. Findings from Phase III clinical reports indicates that after at least six weeks of Endostar combined with vinorelbine, cisplatin treatment, the efficient treatment of advanced non-small cell lung cancer have significantly improved, while within 6 months, the median tumor progression time is

significantly suspended [22]. A three-year follow-up visit of these patients reveals that the average median survival time of combined treatment is 6.3 months while control group received chemotherapy alone is only 3.6 months [4].

Endostar not only could control advanced non-small cell lung cancer, animal experiments and clinical trials show that it also works for colorectal cancer. Zhang [23] reported the Endostar by loaded ultrasonic micro-bubble could effectively reduce the expression of vascular endothelial growth factor of colorectal cancer in mouse experiments, meanwhile, it can also increase tumor cells' apoptosis and tumor ultra structure's degradation. Jia found that in a mouse xenograft model, Endostar can inhibit tumor growth and the rate of lymph node metastasis by suppressing angiogenesis and lymph angiogenesis. The expression of VEGF-A, -C and -D in cells of Endostar treatment was substantially lower than that of controls [24]. Amounts of studies have reported the same results, Endostar loaded nanoparticle carriers or anti-B powder jointed with Endostar also showed the inhibitory effect on the growth of colorectal cancer cells [25].

However, there are still some limitations in this research. First, in term of the sample source, the participants were Asian populations, the difference of Endostar and chemotherapy joint treatment and chemotherapy treatment alone for colorectal cancer is not clear if it applies to Europe, America, Africa, Australia and other people. Second, in terms of confounding factors, the study collected 16 studies which do not contain accurate information about the age and gender mostly, we are unable to estimate the difference between chemotherapy combined Endostar treatment and chemotherapy treatment among colorectal cancer patients with different demographic characteristics. Third, when talking about the treatment effect, the outcome is based on CR+RR, we did not collect enough other data such as survival time, symptoms, imaging results and the variety of the laboratory indexing. To an extent, whether CR+RR is enough for judging the outcome is not clear. Therefore, when we draw the conclusion that endostar combined with chemotherapy has a significant improved effect on colorectal cancer, we should be more careful. In order to improve the study, comprehensive, quality systematic reviews and meta-analysis are needed worldwide with multi-centers cooperation to study multi-human races.

References

1. Li X. Tes, a potential Mena-related cancer therapy target. *Drug Discov Ther* 2008; 2: 1.
2. http://www.who.int/cancer/country-profiles/chn_en.pdf?ua=1
3. Poon RT, Fan ST, Wong J. Clinical implications of circulating angiogenic factors in cancer patients. *J Clin Oncol* 2001; 19: 1207-1225.
4. Sun Y, Wang JW, Liu YY, Yu QT, Zhang YP, Li K. Long-term results of a randomized, double-blind, and placebo-controlled phase III trial: Endostar (rh-endostatin) versus placebo in combination with vinorelbine and cisplatin in

Therapeutic effect of endostar combined with chemotherapy for colorectal cancer: An new evidence from meta-analysis

- advanced non-small cell lung cancer. *Thoracic Cancer* 2013; 4: 440-448.
5. Pan Y, Jiao G. Short-term therapeutic effect of Endostar combined with chemotherapy for advanced colorectal cancer: a meta-analysis. *Nan Fang Yi Ke Da Xue Xue Bao* 2014; 34: 270-274.
 6. Xu HX, Huang XE, Qian ZY, Xu X, Li Y. Clinical observation of Endostar® combined with chemotherapy in advanced colorectal cancer patients. *Asian Pac J Cancer Prev* 2011; 12: 3087-3090.
 7. Chuanqi H, Zheng W, Jinxian C. Controlled clinical studies of recombinant human endostatin combined with FOLFOX4 treatment of advanced colorectal cancer. *Gastroenteropathy* 2009; 08: 453-457.
 8. Tao JY, Yin RC, Lu YX, Fang LC, Hui zX, Xin LZ. Clinical observation of treatment of advanced colorectal cancer by recombinant human endostatin combined with chemotherapeutics. *Clinical Meta Anal* 2011; 4: 332-334.
 9. Zhi JZ, Qin LS, Feng T, Wei ZJ, Kai W, Yun W. Recombinant human endostatin inhibition in combination with hepatic artery embolism chemotherapy treatment of clinical application of postoperative colorectal cancer liver metastases. *J Practical Oncol* 2012; 2: 148-151.
 10. Lin L, Quan CJ, Dian C. Endostar combined with radiotherapy in new low T_1 stage colorectal cancer. *Modern Oncol* 2014; 1: 115-117.
 11. Zhong LG, Qun LH, Qi ZL, Yin X, Bo WH, Guang SW. Clinical investigation of recombinant human endostatin combined with XELOX treatment of advanced colorectal cancer. *Chinese J Clin Oncol* 2009; 12: 688-689.
 12. Yan L, Hua YS, Min L. Clinical observation of recombinant human endostatin combined with chemotherapy in treatment of advanced colorectal. *Practical Clin Med* 2012; 11: 114-116.
 13. Jin L. Clinical analysis of 30 cases with advanced colon cancer treated by IFL combined with recombinant human endostatin. *Chinese J Coal Industry Med* 2009; 12: 8.
 14. Zhuo L, Shan Z, Pin LY, Jia AX, Pin X, Gang WH. Clinical observation of patients with colon cancer treated by FOLFIRI combined with recombinant human endostatin. *Progress Modern Biomed* 2014; 22: 4265-4268.
 15. Biao LS. Clinical observation of 25 patients with colon cancer treated by Endostar. *China Pharmaceuticals* 2012; 23: 71-73.
 16. Min PS, Xia GL, Li W. The efficacy of recombinant human endostatin combined with chemotherapy in the treatment of colorectal cancer liver metastases. *Basic Med Forum* 2013; 1: 21-22.
 17. Pen WH, Jia ZX, Lin TX. Capecitabine, oxaliplatin combined with recombinant human endostatin therapy for elderly patients with advanced colorectal cancer. *Chinese J Gerontol* 2012; 16: 3542-3543.
 18. Dong Y, Hong D. Clinical observation of endostar joint first-line XELOX treatment of advanced colorectal cancer. *Chinese J Cancer Prevention Treatment* 2011; 12: 961-964.
 19. Zhen ZL, Hong L. Clinical observation of treatment of patients with advanced colorectal cancer by recombinant human endostatin combined with chemotherapy. *Strait Pharmaceutical J* 2013; 1: 222-223.
 20. Rong ZR, Shu LM, Yu TS, Li Z, Yi K, Kai Z. Study of treatment of endostatin combined with chemotherapy for advanced colorectal cancer clinical Shenzhen. *J Integrated Traditional Chinese Western Med* 2009; 6: 339-341.
 21. Li D. clinical studies of treatment of endostar combined with chemotherapy for advanced colorectal cancer. *Sino-foreign health abstract* 2009; 20: 6-7.
 22. Wang J, Sun Y, Liu Y, Yu Q, Zhang Y. [Results of randomized, multicenter, double-blind phase III trial of rh-endostatin (YH-16) in treatment of advanced non-small cell lung cancer patients]. *Zhongguo Fei Ai Za Zhi* 2005; 8: 283-290.
 23. Zhang C, Huang P, Zhang Y, Chen J, Shentu W. Anti-tumor efficacy of ultrasonic cavitation is potentiated by concurrent delivery of anti-angiogenic drug in colon cancer. *Cancer Lett* 2014; 347: 105-113.
 24. Jia Y, Liu M, Huang W, Wang Z, He Y, Wu J. Recombinant human endostatin endostar inhibits tumor growth and metastasis in a mouse xenograft model of colon cancer. *Pathol Oncol Res* 2012; 18: 315-323.
 25. Qian X, Yan B, Zhou X, Xie L, Wei J, Li R. Synergistic antiangiogenic activity of tetrandrine combined with Endostar on the human umbilical vein endothelial cell model. *Cancer Biother Radiopharm* 2013; 28: 385-390.

***Correspondence to**

Hui Zhao
Department of Thoracic Surgery
Jilin Cancer Hospital
PR China