

RESEARCH COMMUNICATION

A Clinical Study on Safety and Efficacy of Aidi Injection® Combined with Chemotherapy

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Abstract

Objective: To observe the efficacy, side effects and impact on the quality of life of Aidi Injection® combined with leucovorin calcium/ 5-fluorouracil/ oxaliplatin (FOLFOX4 regimen) in the treatment of advanced colorectal cancer patients. **Methods:** A consecutive cohort of 100 patients were divided into two groups: the experimental group was treated with Aidi injection and FOLFOX4 while the control group was only administered FOLFOX4. After more than two courses of treatment, efficacy, quality of life and side effects were evaluated. **Results:** The response rate of experimental group was not significantly different with that of control group ($P>0.05$), but differences were significant in clinical benefit response and KPS score. In addition, gastrointestinal reaction and the incidence of leukopenia were lower than that of control group ($P<0.05$). **Conclusions:** Aidi injection combined with FOLFOX4 is associated with reduced toxicity of chemotherapy, enhanced clinical benefit response and improved quality of life of patients with advanced colorectal cancer. Aidi injection deserves to be further investigated by randomized control clinical trials.

Keywords: Aidi injection - chemotherapy - advanced colorectal cancer

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Introduction

Colorectal cancer is one of the main human malignant tumors (Parkin et al., 2005). In Western countries, the incidence of colorectal cancer ranks second behind that of lung cancer among malignant tumors and its mortality ranks third among the death rate of cancer (Ries et al., 2008). In China, the incidence of colorectal cancer has been increasing gradually with a speed of 4.2% along with changes of diet and lifestyle in recent years (Center for Statistic Information Ministry of Health, P.R. China, 2002). Therefore, now, colorectal cancer has become the common and frequently-occurring disease which seriously hazard to human health (Parkin et al., 2005; Zhou et al. 2011). Currently, the FOLFOX4 regimen is commonly administered for advanced colorectal cancer as an effective regimen (Masi et al., 2006; Souglakos et al., 2006). However, how to increase efficacy and decrease toxicity of FOLFOX4 remains a focus in this area.

Aidi Injection® has been developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acanthopanax Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng). Aidi Injection is one of Chinese herbal preparation with anti-cancer activity, which used for the treatment of gastrointestinal tumor. Our hypothesis of this study is that the combination

of Aidi Injection and FOLFOX4 could be superior to FOLFOX4 alone regarding treatment efficacy and toxicity.

Materials and Methods

Patients

Patients were required to be pathologically diagnosed as colorectal cancer, with Karnofsky performance status ≥ 70 . Other eligibility criteria were introduced elsewhere (Yao et al., 2010; Li et al., 2010; Xu et al., 2011) that included: adequate bone marrow (white blood cell count $>3.0 \times 10^9$ and platelet count $>150 \times 10^9$), liver function (bilirubin and transaminases <1.5 times the upper limit of normal and renal function (creatinine <1.5 upper limit of normal); and no evidence of metastatic disease; age between 18 and 75 years; signed an informed consent before chemotherapy.

Patients were excluded from the study if they had active cardiac disease (LVEF $<50\%$), significant arrhythmia, any serious medical or psychiatric condition, other malignancy, pregnant or lactating women were excluded from the study.

Treatment

The FOLFOX4 regimen were scheduled as follows: intravenous (iv) leucovorin calcium at a dose of 200 mg/m², iv bolus Fluorouracil (5-FU) at a dose of 400 mg/

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Table 1. Comparison of Treatment Efficacy in Two Groups Treated with FOLFOX4 Alone or Aidi Injection* combined with FOLFOX4

Treatment	N	CR	PR	SD	PD	CR+PR(%)	CR+PR+SD(%)
FFOLFOX4 and Aidi Injection*	50	0	24	16	10	48	80
FOLFOX4	50	0	22	10	18	44	64

N, number cases; CR, Complete Remission; PR, Partial response; SD, stable disease; PD, progressive disease; FOLFOX4, Leucovorin leucovorin /calcium Fluorouracil/ Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acanthopanax Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng)

Table 2. Karnofsky Performance Status Score in Two Groups Treated with FOLFOX4 and Aidi Injection* Combined with FOLFOX4

Treatment	Increased	Stable	Decreased
FOLFOX4 and Aidi Injection*	30	13	7
FOLFOX4	12	27	11

FOLFOX4, Leucovorin leucovorin /calcium Fluorouracil/ Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acanthopanax Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng); KPS, score; increased, ≥ 10 after treatment; stable, < 10 ; decreased, ≥ 10

m² and continuous iv 5-FU at a dose of 600 mg/m² on day 1, day2, Oxaliplatin 85 mg/m² repeated every 2 weeks. Treatment was biweekly administered until PD or unacceptable toxicity, withdrawal of consent, and physicians decision or treatment interruption for > 2 weeks. The control group received FOLFOX-4 regimen, the experimental group received Aidi Injection 60-80ml intravenous infusion on iv, once daily, for 7 days and FOLFOX4. Antiemetic treatment was granisetron 3mg by intravenous bolus infusion prior to chemotherapy. Routine blood test, blood biochemistry and tumor markers were reviewed during and after chemotherapy weekly.

Efficacy Observation

Treatment efficacy was evaluated after two months treatment. Complete Remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST criteria (Therasse et al., 2000). Quality of life was evaluated in accordance

with the Karnofsky Scale, designated increasing if the score increased by 10 after treatment, decreasing if the score decreased by 10 and otherwise stable.

Toxicity Assessment

Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1991).

Statistical analysis

The study data were analyzed by t and enumeration data by χ^2 test. Statistic significance was determined if $p < 0.05$.

Results

Efficacy

All 100 patients had completed at least 2 cycles of treatment. Total treatment cycle was 303 and average cycle was 3. No CR was observed in both two groups. The response rate of experimental group (CR+PR) was 48%, while that in control group was 44%. The differences were not statistically significant ($p > 0.05$). The disease control rates of two groups (CR+PR+SD) were 80% (experimental group), 64% (control group) respectively, with statistical significance ($p < 0.05$) (Table 1).

Quality of life before and after treatment

KPS score of experimental group increased in 30 cases (60%), 13 cases stable and 7 cases decreased. while that of control group increased in 12 cases (24%), 27 cases stable and 11 cases decreased. The difference between two groups was statistically significant ($p < 0.05$) (Table 2).

Table 3. Toxicity in Two Groups Treated with FOLFOX4 and Aidi Injection* Combined with FOLFOX4

Toxicity	FOLFOX4 and Aidi Injection* Number (%)				FOLFOX4 Number (%)			
	I	II	III	IV	I	II	III	IV
Leukopenia	10(20)	8(16)	5(10)	0(0)	9(18)	15(30)	10(20)	2(4)
Thrombocytopenia	5(10)	3(6)	1(2)	0(0)	8(16)	7(14)	4(8)	0(0)
Nausea, vomiting	15(30)	10(20)	0(0)	0(0)	20(40)	15(30)	3(6)	0(0)
Diarrhea	4(8)	2(4)	0(0)	0(0)	6(12)	4(8)	3(6)	0(0)
Constipation	10(20)	3(6)	0(0)	0(0)	12(24)	4(8)	0(0)	0(0)
Oral ulcer	3(6)	1(2)	0(0)	0(0)	7(14)	4(8)	0(0)	0(0)
Alopecia	4(8)	1(2)	0(0)	0(0)	5(10)	1(2)	0(0)	0(0)
Peripheral neuropathy	6(12)	3(6)	0(0)	0(0)	6(12)	5(10)	0(0)	0(0)
Hand-foot syndrome	2(4)	0(0)	0(0)	0(0)	3(6)	0(0)	0(0)	0(0)
Elevated ALT	8(16)	1(2)	0(0)	0(0)	9(18)	1(2)	0(0)	0(0)
Elevated Cr	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

FOLFOX4, Leucovorin leucovorin /calcium Fluorouracil/ Oxaliplatin; *Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Its main components include Ban Mao (Mylabri), Ci Wu Jia (Radix Acanthopanax Senticosi), Huang Qi (Radix Astragali) and Ren Shen (Radix Ginseng); ALT, alanine aminotransferase; Cr, creatinine

Toxicity

All patients underwent toxicity assessment. Treatment related side effects were reversible, and no termination of chemotherapy or death caused by adverse events occurred. In table 3, the main adverse effects were myelosuppression and gastrointestinal reactions. In experimental group, leukopenia rate was 46% , 10% of them with grade III-IV and none with infection; 16% patients showed grade I-II thrombocytopenia and 2% with grade III thrombocytopenia; grade I-II gastrointestinal toxicity rate was 50%, and grade III-IV 10%. In control group, leukopenia rate was 72%, 24% of them with grade III-IV; 30% patients with grade I-II thrombocytopenia and 8% with grade III thrombocytopenia; grade I-II nausea and vomiting was 70%, and 6% with grade III-IV. No statistically significant difference was detected in hand-foot syndrome or peripheral neuropathy. Both of two groups were tested mild liver damage, but recovered without dose modification on chemotherapy. Additionally, there was no apparent renal damage. In experimental group, 2 cases demonstrated allergic reaction. We considered it could be an allergic reaction to Chinese medical herbs, and could be prevented by slowing down the infusion speed and prescribing premedication containing dexamethasone.

Discussion

Recurrence and metastasis is the main cause of death in colorectal cancer (Le Voyer et al., 2003; Sobrero et al., 2007). Chemotherapy plays an important role in comprehensive treatment for colorectal cancer (Souglakos et al., 2006). Currently, FOLFOX4 regimen is one of the best treatments for advanced colorectal cancer patients (Haydon, 2003; Saltz et al., 2008). But, chemotherapy often brings about serious side effects. Therefore, how to reduce side effects of chemotherapy, in the meantime increase efficacy and improve quality of life have aroused more and more attention.

At present, objective of chemotherapy is not only to extend survival of patients, but also to improve quality of life. Thus, the Food and Drug Administration of the USA proposes that the evaluation of new drugs should involve survival time and quality of life. It is a distinguishing feature of traditional Chinese medicine to contribute in this area.

Aidi Injection is developed and manufactured by Guizhou Ebay Pharmaceutical Co., Ltd in China. Studies (Rong et al., 2000; Fang, 1993) have shown that the main active ingredient of Mylabri 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. Astragalus Polysaccharide is another important component which can improve the phagocytic function of reticuloendothelial system, and enhance anti-cancer activity of T cells, NK cells, LAK cells and IL-2 cells (Ma, 2007). Ginsenosides and Ginseng Polysaccharide can increase immunity and leukocyte. Acanthopanax Polysaccharide has the similar immunological enhancement as Ginseng and Astragalus

(Liu et al., 2001; Lu, 2009). Our study shows that the differences of short-term efficacy in two groups were not statistically significant, but the clinical benefit rate, and Karnofsky score improvement of experimental group were significantly higher than that of control group. Aidi Injection combined with FOLFOX4 regimen, which used for treatment of advanced colorectal cancer, can reduce side effects causing by chemotherapy, and improve quality of life. In summary, Aidi Injection deserves to be further investigated by randomized controlled clinical trails.

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