



Biweekly Raltitrexed Combined With Irinotecan as Second-Line Therapy for Patients With Metastatic Colorectal Cancer: A Phase II Trial

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Abstract

Objective: Irinotecan-based doublet chemotherapy strategy was standard second-line backbone for patients with oxaliplatin-refractory metastatic colorectal cancer. The aim of this study was to evaluate tolerability and efficacy of raltitrexed combined with irinotecan biweekly administered as the second-line therapy for mCRC patients.

Methods: The study was a prospective, single-center, non-randomized, open-label phase II clinical trial. Patients with mCRC after failure with oxaliplatin and fluoropyrimidine or its derivatives were enrolled. Irinotecan (180 mg/m²) and raltitrexed (2.5 mg/m²) were given intravenously on day 1. Cycles were repeated every 2 weeks. The primary endpoint was progression-free survival (PFS), and the secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival (OS), and adverse events (AEs).

Results: Between December 2012 and October 2016, 33 and 35 patients enrolled were assessed for response and safety, respectively. The ORR was 8.6%, and the DCR was 71.4%. The median PFS was 4.5 months (95% CI 3.8–5.2). The median OS was 12.0 months (95% CI 8.5–15.5). Four patients received conversion therapy to no evidence of disease (NED), and 2 patients were still alive with beyond 24 months survival. The most common grade 3/4 AEs were anorexia (14.3%), vomiting (14.3%), nausea (11.4%), fatigue (8.6%), and leukopenia (8.6%). No one died from treatment-related events. The incidence and severity of toxicity were irrelevant to UGT1A1 status.

Conclusions: The combination of irinotecan with raltitrexed is an efficient, convenient, and acceptable toxic regimen for second-line treatment for mCRC patients.

Keywords

metastatic colorectal cancer, raltitrexed, irinotecan, second-line, chemotherapy

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide; over 1 million new cases diagnosed each year and also ranks the third in terms of mortality in 2018.¹ Only 4%–21% response rate (RR) is obtained in metastatic colorectal cancer (mCRC) patients who receive irinotecan-based second-line treatment.^{2,3} Although targeted therapies, such as inhibitor of the epidermal growth factor (EGFR) or vascular endothelial growth factor (VEGF), are valuable additions to first- or second-line

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options, chemotherapy remains the foundation of medical management of mCRC. Moreover, some of Chinese patients with mCRC could not be afford to targeted therapies due to their economic limitation. Therefore, irinotecan-based second-line chemotherapy also be a reasonable option for mCRC patients. Practically, FOLFIRI (leucovorin and fluorouracil plus irinotecan) is recommended as standard regimen in the second-line setting.² In addition, for Chinese mCRC patients, the second-line therapy of irinotecan-based chemotherapy, such as modified XELIRI (capecitabine plus irinotecan), is well tolerated and non-inferior to FOLFIRI with or without bevacizumab in terms of overall survival (OS).⁴ Irinotecan-based therapies were more effective than irinotecan alone⁵ and modified doses of irinotecan combined other therapies also exhibited a more feasible tolerability and favorable efficacy,^{4,6} suggesting irinotecan-based chemotherapy strategy was standard second-line backbone treatment for mCRC.

Raltitrexed, a direct thymidylate synthase (TS) inhibitor presenting different anticancer mechanism from that of 5-fluorouracil (5-FU), has been proved promising an efficacy, favorable toxicity profile, and convenient administration schedule in patients with 5-FU-refractory.^{7,8} What is more, administration of FOLFIRI requires a central venous catheter (CVC) and continuous infusion of 5-FU, which is inconvenient for patients and decreases their quality of life. Thus, regimen comprising raltitrexed via convenient and rapid venous injection was implemented to replace continuous infusion of 5-FU. Therefore, a single center, non-randomized, phase II trial was conducted to investigate the tolerability and efficacy of raltitrexed plus irinotecan (RIR) as a second-line therapy for mCRC patients.

Methods

Phase II Study Design

This study was a prospective, single-center, non-randomized, open-label phase II clinical trial registered in November 2012 (registration No. ChiCTR-ONC-12002767). This clinical study was approved by Committee of Clinical Trials and Biomedical Ethics, West China Hospital, Sichuan University (approval no. 2012 Clinical Trial (listed) Review (No. 19)) in 2012-10-29. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall response rate (ORR), disease control rate (DCR), overall survival (OS), and toxicity.

Patient Eligibility

Inclusion criteria were as follows: (a) histopathologically proven colorectal adenocarcinoma; (b) non-resectable metastases; (c) aged 18 years or older; (d) life expectancy of ≥ 3 months at the time of enrollment; (e) ECOG performance status of 0 or 1; (f) no second-line treatment, and failure after prior fluorouracil or its derivatives-based (fluoropyrimidine or Capecitabine or S-1, plus oxaliplatin) chemotherapy as first-line therapy for metastatic disease or in the adjuvant setting (relapse within 6 months of adjuvant therapy); (g) at least 2 weeks since prior chemotherapy and 4 weeks since prior

radiotherapy, prior radiotherapy to non-target lesions allowed, and no prior radiotherapy to target lesions unless disease progression is documented within the radiation port; (h) at least one measurable lesion based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.0); (i) adequate hematologic, hepatic, and renal function; and (j) signed written informed consent. Exclusion criteria were as follows: (a) patients with diagnosed angina or myocardial infarction < 3 months prior to enrollment; (b) other prior malignancy; (c) with untreated or symptomatic central nervous system metastases; (d) severe and/or uncontrolled medical conditions or active infections; (e) active inflammatory bowel disease or other bowel disease causing long-term chronic diarrhea, or total or obvious bowel obstruction.

Treatment

All patients had previously failed oxaliplatin-based regimens in combination with fluoropyrimidines or its derivatives (FOLFOX/CapeOX). The patients had received intravenous infusion of irinotecan (180 mg/m^2) over 90 min, in combination with raltitrexed 2.5 mg/m^2 (max 6 mg) intravenous on day 1 every 2 weeks. Without a minimum or maximum number of treatment cycles, treatment would be discontinued in the event of progressive disease (PD), conversion surgery, unacceptable adverse events, patient's refusal to the treatment, withdrawal of consent, or by physician's decision. Patients were not forced to test for homozygosity or double heterozygosity for UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphisms (UGT1A1*6 and UGT1A1*28) at baseline or during the treatment.

Study Assessments

Efficacy and toxicity analyses were included patients who received at least one chemotherapy cycle. Laboratory tests and safety assessments were performed before the treatment and biweekly thereafter. Response evaluation was based on RECIST (version 1.0) criteria every 3-4 cycles of chemotherapy or every 2 months if treatment was delayed. PFS, defined as the time from enrollment until objective tumor progression or death. Conversion surgery was permitted after chemotherapy judged by MDT or surgeon, in the case of the patient underwent conversion surgery, the time from enrollment to the date of progression or death after operation was considered PFS. OS, defined as the time from enrollment until death from any cause. Toxicity was investigated according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0). Toxicities could be managed by dose reduction or discontinuation of chemotherapeutic drugs. The doses of irinotecan and raltitrexed were reduced by 25%, in case of grade 4 hematotoxicity and/or if any other grade 3/4 severe organ toxicity in the previous cycle was exhibited. Treatment would be delayed for up to 4 weeks until adverse effects resolved or at least recovered to grade 2 or judged by the investigator. The patients who required more than 4 weeks for recovery of adverse events were removed from the study.

Table 1. Baseline demographic and clinical characteristics of patients.

Variable	No. of Patients	%
Gender		
Male	18	51.4
Female	17	48.6
Age		
Median (Range)	54 (27-75)	
≥60	14	40
<60	21	60
Performance status (ECOG)		
0	8	22.9
1	23	65.7
2	4	11.4
Primary tumor site		
Rectum	19	54.3
Left-sided colon	6	17.1
Right-sided colon	10	28.6
Primary tumor resected		
Yes	25	71.4
No	10	28.6
Metastatic sites		
Liver	20	57.1
Lung	17	48.6
Lymph nodes	13	37.1
Peritoneal	4	11.4
Ovary	3	8.6
Bone	2	2.9
Adrenal gland	1	2.9
Others	4	11.4
No. of metastatic sites		
1	7	20.0
2	16	45.7
≥3	12	34.3
Previous chemotherapy failure		
First-line chemotherapy	24	68.6
Adjuvant chemotherapy	11	31.4
Previous adjuvant chemotherapy		
Yes	14	40
No	21	60
Adjuvant/first-line regimen		
FOLFOX	23	65.7
XELOX	10	28.6
SOX	2	5.7
UGT1A1		
Wild-type (6/6)	12	34.3
*6/28 heterozygous type (6/7)	3	8.6
*6/28 homozygous type (7/7)	1	2.8
Unknown	19	54.3
Previous radiation therapy		
Yes	8	22.9
No	27	77.1

Statistical Considerations

Based upon the data from the previous study about 6-month PFS rate and ORR, the Simon two-stage optimal design was applied to calculate the number of patients in this study. With a 5% alpha risk and a 15% beta risk, the first-stage 6-month PFS probability of 10% (which if true, meant to discontinue this trial) and a minimal rate of 6-month PFS of 30% (which if true, meant to continue the second stage of this trial) were determined. The number of cases was calculated to be 12 in the first stage, 23 in the second stage, and 35 in total. SPSS 25.0 software was used to analyze all data in this study. Categorical variables were calculated as percentage. PFS and OS were calculated by the Kaplan–Meier method. For significance of area under the curves, the log-rank test was used. To determine the relationship between variables, Pearson correlation coefficients were calculated. $P < .05$ was considered as statistically significant for all tests.

Ethical Statement

This study was conducted according to the World Medical Association Declaration of Helsinki and the principles of good clinical practice. All written informed consents were provided by enrolled patients, and the written consents were for the participation in this trial. This study was approved by the institutional review board (IRB) of the participating institutions (IRB No. 2012-019) and registered in November 2012 (registration No. ChiCTR-ONC-12002767).

Results

Patients' Characteristics and Treatment

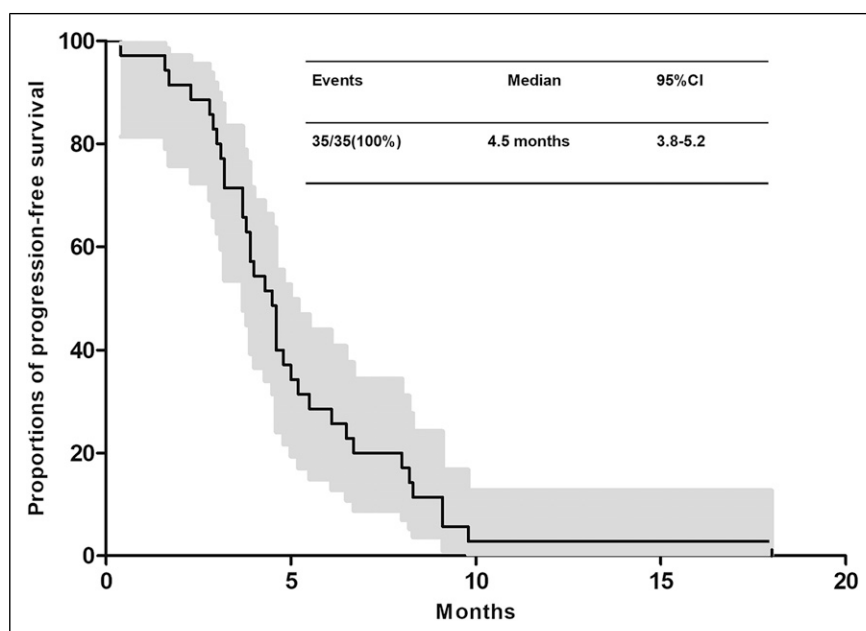
Between December 2012 and October 2016, a total of 35 patients were enrolled in this trial, 33 of whom were considered evaluable for response and 35 patients for toxicity assessment. All patients received at least one planned treatment with RIR; 2 patients were not evaluated for efficacy after completing only 1 cycle of chemotherapy due to refusal to the further treatment and lack of immediate radiological assessment. Their demographic and clinical data are summarized in Table 1. 18 men and 17 women were comprised with a median age of 54 years (range 27-75 years). ECOG PS was 0 in 8 patients, 1 in 23 patients, and 2 in 4 patients. Sixteen patients were tested for analysis for UGT1A1 status, 12 patients were Wild-type (6/6) for UGT1A1*6 and UGT1A1*28, 3 patients were heterozygous type (6/7) for UGT1A1*6 and/or UGT1A1*28, and one patient present homozygous type (7/7) for UGT1A1*28.

Number of treatment cycles: the median number was 4 (from 1 to 9 cycles). Dose reduction and administration delay caused by treatment-related adverse events (TAEs) occurred in

Table 2. Tumor responses.

	Number of Patients	Proportion (%)
Eligible patients	35	100
CR	0	0
PR	3	8.6
SD	22	62.9
PD	8	22.9
NE	2	5.7
Response rate (CR+PR)	3	8.6
Disease control rate (CR+PR+SD)	25	71.4

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

**Figure 1.** Kaplan–Meier analysis of progression-free survival.

15(42.8%) and 4(11.4%) patients, respectively. Treatment discontinuation because of PD was observed in 17 patients (48.6%), conversion to surgery/radiotherapy to no evidence of disease (NED) in 4 (3 in surgery and 1 in radiotherapy, 11.4%), TAEs in 2 (5.7%), non-TAEs (ileus) in 1 (2.9%), patient refusal to continuous chemotherapy or other reasons in 10 patients (28.6%), and 1 patient (2.9%) discontinued due to sudden death after 1 cycle chemotherapy (regard associated with disease). Adverse events (AEs) caused to withdrawal in 2 patients were gastrointestinal toxicities (Anorexia/Nausea/Vomiting).

Efficacy

The percentages of the relative dose intensities (RDI) of the planned dose were 100% (median) and 97.9% (mean) for raltitrexed and irinotecan. Tumor responses are listed in [Table 2](#). Response rate and the disease control rate (DCR) were 8.6%

and 71.4%, respectively. The median PFS was 4.5 months (95% CI 3.8-5.2) ([Figure 1](#)), ranged from .5 to 18 months, and 1 patient was progressive after conversion surgery receiving re-surgery presenting 18 months in PFS. The median OS was 12.0 months (95% CI 8.5-15.5), ranged from .5 month to not reached ([Figure 2](#)). The median follow-up period was 12 months (ranged .5-52). 2 patients were still alive with beyond 24 months survival up date to the last following-up in June-2020.

Toxicity

The TAEs are summarized in [Table 3](#). The most common AEs were nausea (80.0%), increased AST (71.4%), fatigue (71.4%), alopecia (65.7%), and increased ALT (62.9%). Hematological AEs \geq grade 3 were as follows: 8.6% decrease in white blood cell count, 5.7% decrease in neutrophil count, 2.9% febrile neutropenia, and 2.9% decrease in platelet count,

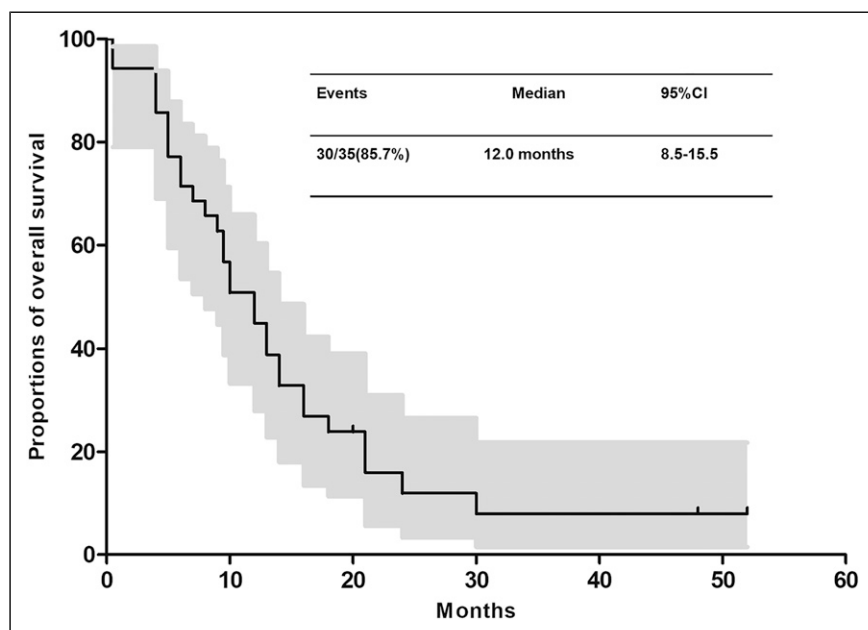


Figure 2. Kaplan–Meier analysis of overall survival.

Table 3. Treatment-related adverse events.

TAEs	G1 (n)	G2(n)	G3(n)	G4(n)	All(n/%)	G3/4(n/%)
Hematological toxicity						
Anemia	9	7	0	0	16(45.7%)	0
Leukemia	10	2	3	0	15(42.9%)	3(8.6%)
Neutropenia	9	2	2	0	13(37.1%)	2(5.7%)
Thrombocytopenia	6	1	1	0	8(22.9%)	1(2.9%)
Non-hematological toxicity						
Febrile neutropenia	-	-	1	0	1(2.9%)	1(2.9%)
Hypokalemia	1	0	2	0	3(8.6%)	2(5.7%)
Fatigue/malaise	11	11	3	-	25(71.4%)	3(8.6%)
Anorexia	2	6	5	0	13(37.1%)	5(14.3%)
Alopecia	12	11	-	-	23(65.7%)	-
Nausea	15	9	4	0	28(80.0%)	4(11.4%)
Vomiting	8	7	5	0	20(57.1%)	5(14.3%)
Mucositis/stomatitis	2	3	1	0	6(17.1%)	1(2.9%)
Diarrhea	7	3	0	0	10(28.6%)	0
Bloating	1	4	1	0	6(17.1%)	1(2.9%)
Constipation	3	4	0	0	7(20.0%)	0
Bilirubin increased	5	1	0	0	6(17.1%)	0
ALT increased	18	3	1	0	22(62.9%)	1(2.9%)
AST increased	20	4	1	0	25(71.4%)	1(2.9%)
Creatinine increased	1	0	0	0	1(2.9%)	0
Hypoalbuminemia	8	1	0	0	9(25.7%)	0

ALT, Aspartate aminotransferase; AST, Aspartate aminotransferase.

without severe anemia, and 2.9% increase in AST and ALT in one patient. Grade 3/4 anorexia (14.3%), vomiting (14.3%), nausea (11.4%), and fatigue (8.6%) were the common severe treatment-related non-hematological AEs. No patient died because of treatment. 2 patients discontinued the protocol

treatment because of treatment-related gastrointestinal AEs (1 presenting Grade 3 anorexia and vomiting and 1 presenting Grade 3 anorexia, vomiting, and fatigue). Of 15 patients tested for UGT1A1 status, 1 patient was *6/28 homozygous type (7/7), 3 patients were *6/28 heterozygous type (6/7), and all 4

patients accepted 14 cycles chemotherapy in total suffered grade 1/2 TAEs, suggesting no correlation between UGT1A1 status and severe treatment-related toxicity in this study.

Discussion

In this study, irinotecan combined with raltitrexed might be an efficient and tolerable second-line regimen for patients with oxaliplatin-refractory mCRC, achieving a median PFS with 4.5 months, a median OS with 12.0 months, and ORR with 8.6%, respectively. RIR as an active regimen in gastrointestinal malignancies has been demonstrated in a phase I clinical and pharmacogenetic trial.⁹ Other published single-arm studies also considered RIR as a suboptimal efficient schedule at the expense of moderate toxicity for patients with mCRC in first- or second-line treatment.¹⁰⁻¹² Moreover, a randomized phase II study also indicated that RIR with superior survival compared with raltitrexed alone in patients with gemcitabine pretreated pancreatic cancer.¹³ However, no available randomized data evaluating the effects of RIR vs FOLFIRI in the second-line setting was reported previously in mCRC. The median PFS and ORR in this study (4.5 months and 8.6%) were comparable or relatively better in comparison to those observed in the randomized GERCOR study (second-line FOLFIRI achieved 4% for ORR and 2.5 months for median PFS),² whereas, was inferior to the results in the FIRIS study (median PFS and ORR were 5.1 months and 16.7% in the FOLFIRI group, 5.8 months and 18.8% in the irinotecan plus S-1 group).¹⁴ Four patients (11.4%) experienced tumor regression during treatment and their lesions were converted to be resectable lesions that could obtain NED, which enable them to achieve a better survival. Notably, most patients enrolled in the study with heavy metastatic tumor burden: only 7(20%) patients presented single metastatic site, while 12 (34.3%) patients presented multiple metastatic sites (≥ 3). The prognosis of the enrolled patients in our study might be worse than the similar studies of irinotecan-based regimen as second-line therapy, such as beyond 40% patients with one metastatic site enrolled in the FIRIS study,¹⁴ indicating that the efficacy of RIR was warranted.

Previously, major concerns regarding the safety of irinotecan plus raltitrexed were observed in several phase II studies, high incidence of grade 3/4 diarrhea and/or neutropenia even regarded this combination as a suboptimal regimen for mCRC.^{10,12,15} To avoid the onset of TAEs caused by RIR, dose-reduced combination administrated biweekly was adopted in our study. The incidence of nausea (80.0%), fatigue (71.4%), and alopecia (65.7%) were shown; the grade 3 treatment-related hematological and nonhematological AEs were under 15%, with 28.6% diarrhea and no grade 3/4 diarrhea. However, the gastrointestinal toxicities seemed to be manageable and no grade 4 TAEs were observed. Likewise, in BICC-C trial¹⁶ and EORTC 40015 study,¹⁷ grade 3-4 AEs, consisting mainly of gastrointestinal toxicities and even treatment-related deaths, occurred more frequently in patients

treated with XELIRI than in those treated with FOLFIRI. Therefore, XELIRI regimen has not yet been accepted as a standard therapy in authoritative guidelines.^{18,19} Whereas, modified XELIRI (relatively dose-reduction) as a well-tolerated and effective treatment for mCRC has been proved in several studies.^{4,6} The lower dose intensity of irinotecan plus raltitrexed in patients with advanced pancreatic adenocarcinoma who pretreated by gemcitabine also exhibited a better tolerability and ease of administration.¹³

In accord with previous reports,²⁰ expected hepatic toxicity mainly included the increases in transaminases was observed, although grade 3 or 4 hepatotoxicity was infrequent. Moreover, in view of fluoropyrimidines-induced cardiotoxicity^{21,22} and hand-foot syndrome (HFS),^{23,24} the cardiotoxic safety profile of raltitrexed in patients with CRC was fully confirmed in a series of studies,²⁵⁻²⁷ since neither cardiotoxic AEs nor HFS were observed in our study, suggesting raltitrexed seemed to have a better toxicity profile compared to capecitabine or 5-FU. Moreover, the replacement of continuous intravenous 5-FU with raltitrexed could be more convenient, which is a promising method for reducing side effects and supposed to be a feasible schedule administration on an out-patient basis.

The addition of targeted agents (such as bevacizumab, cetuximab for patients whose tumors harbor wild-type RAS) to the second-line chemotherapy has improved efficacy in patients with mCRC.²⁸⁻³¹ However, chemotherapy alone remains major mainstream treatment, especially for patients in developing countries, where targeted agents are not covered by health insurance. RIR was seldom reported in previous studies; thus, this study was to evaluate efficacy and safety of RIR, and it was meaningful to accept RIR as a new treatment for mCRC patients before the combination bevacizumab or cetuximab with RIR in current study. Meanwhile, ulterior exploring the efficacy and toxicity of RIR plus targeted agents is necessary in further investigations. Nevertheless, the limitation of this study was the difficulty in comparing efficacy and toxicities with the standard second-line regimen such as FOLFIRI, because the present study was a single-arm phase II study, and without addition standard targeted agents to this combination.

Conclusion

This study suggests that irinotecan combined with raltitrexed is an efficient and acceptable toxic regimen for second-line treatment of the mCRC. Thus, this combination represents a viable and convenient alternative regimen in the treatment for patients with mCRC. A randomized trial with large sample is needed to compare the efficacy and toxicity of this combination with the standard regimen (FOLFIRI) with or without targeted agents in mCRC in the future.

Acknowledgments

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Authors Contributions

KC designed the investigation and contributed to writing the paper and manuscript preparation. YWZ and YC participated in the administration of this study and literature search, data acquisition, and data analysis. ZPL participated in the data analysis and statistical analysis. MQ and JYL participated in the manuscript editing and manuscript review.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author's Note

This study was registered in November 2012 (registration No. ChiCTR-ONC-12002767). The trial registry name: A Study of the Combination of Raltitrexed and Irinotecan Every Two Weeks as second Line Treatment of Metastatic Colorectal Cancer. And the trial registry URL: <http://www.chictr.org.cn/showprojen.aspx?proj=6787>.

Ethical approval

This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was registered in November 2012 (registration No. ChiCTR-ONC-12002767).

Informed consent

Informed consent was obtained from all participants enrolled in the study.

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