Preliminary Report

FOLFIRI Chemotherapy for Metastatic Colorectal Cancer Patients

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Objectives: *1) To confirm the efficacy of irinotecan plus folinic acid/continuous 5-fluorouracil as bimonthly FOLFIRI regimen in metastatic colorectal cancer patients. Efficacy evaluations will include response rate, duration of response, and survival. 2) To evaluate safety profiles on patients receiving this combination.*
Material and Method: *Nineteen patients with metastatic colorectal cancer received 180mg/m^2 intravenous (iv) day 1 of irinotecan, 200 mg/m^2 iv of folinic acid, 400 mg/m^2 iv bolus days 1 to 2, 5-fluorouracil (5-FU), and 600 mg/m^2 iv 5-FU infusion over 22 hours, days 1 to 2. Treatment was repeated every two weeks and one cycle contained three fortnightly administrations. Sites of disease were liver in nine patients, lungs in three patients, bowels in four patients, lymph nodes in three patients, and peritoneum in two patients. Two patients had >1 metastatic site. Previous treatments included adjuvant chemotherapy in seven cases and front-line chemotherapy for advanced disease in one case.*
Results: *A median of six treatment cycles was completed (range, 2-13 cycles). All patients were assessable for toxicity and 16 patients were evaluable for treatment response. The non-hematological toxicity was mild. Most had grade 1 or 2. Only one patient experienced grade 3 fatigue and anorexia, and discontinued chemotherapy after the second cycle. There were no cases with grade 4 toxicity. Fourteen patients had at least grade 2 alopecia. The most common hematological toxicity was neutropenia. Grade 3 and 4 neutropenia were observed in three and two patients, respectively. There was no case of febrile neutropenia. Based on intention to treat analysis, there were no complete responses (CR), five (26.3%) partial response (PR), and 11 (57.9%) stable disease. With the median follow-up of 6.6 months, the median time to disease progression was 4.7 months and the median survival time was 10.6 months.*
Conclusion: *Bimonthly irinotecan in combination with folinic acid and 5-fluorouracil was active with acceptable toxicities and a prolonged survival time in pretreated colorectal cancer. Additional trials to define the optimal dose and schedule of treatment are justified.*

Keywords: *Metastatic colorectal cancer, Irinotecan*

J Med Assoc Thai 2007; 90 (10): 2121-7
Full text. e-Journal: *http://www.medassocthai.org/journal*

Colorectal cancer is the second most common cause of cancer death in Western countries[1]. First-line systemic treatment of advanced colorectal cancer is currently based on irinotecan and oxaliplatin administered in combination with folinic acid and fluorouracil[2-6], by the side of the application of biologic therapies. The combination of irinotecan, folinic acid, and 5-fluorouracil has been proven effective for the treatment of metastatic colorectal cancer[2-4,16-18]. However, the most appropriate regimen as the first-line treatment for this group of patients still needs to be defined. The present study reports on the bimonthly FOLFIRI regimen consisting of irinotecan with continuous folinic acid/5-FU in the Division of Therapeutic Radiology and Oncology, Chiang Mai University, focusing on safety and efficacy.

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Material and Method

Patient selection

The eligibility criteria for inclusion in the

present study were pathological confirmed adenocarcinoma of colon or rectum; unresectable metastatic lesions; at least one measurable disease of > 1 cm; adequate bone marrow, renal (creatinine ≤ 2 x the upper limit of the normal [ULN]), and liver function (alkaline phosphatase < 5 x ULN), ECOG performance status (PS) not more than 2; age 18 to 75 years; life expectancy > 12 weeks; and no previous irinotecan chemotherapy administration. Patients with CNS metastases, second malignancies, bowel obstruction, symptomatic angina pectoris, or disease confined to prior radiation treatment fields were excluded. Written informed consent was needed.

Chemotherapy

The investigational treatment consisted of 180 mg/m^2 intravenous (iv) day 1of irinotecan, 200 mg/m^2 iv of folinic acid, 400 mg/m^2 iv bolus days 1 to 2, 5-fluorouracil (5-FU), and 600 mg/m^2 iv 5-FU infusion over 22 hours, days 1 to 2. Treatment was repeated every 2 weeks and one cycle contained three fortnightly administrations. Standard antiemetic therapy with ondansetron or granisetron and dexamethasone was administered to all patients. Treatment was delayed when granulocyte count was under 1500 /□l or the platelet count was less than 100,000/□l. In cases of febrile neutropenia, the dose of irinotecan was reduced by 15% in the next cycle. Treatment was continued until progression, unacceptable toxicity, or patient request. Tumors were assessed utilizing chest X-ray, CT, or magnetic resonance imaging before and after treatment. Chemotherapy-induced toxicity was graded according to the National Cancer Institute common toxicity criteria version 2[7]. The treatment could be postponed for up to 2 weeks until recovery from diarrhea, stomatitis, and other toxicities ≤ grade 2. The 5-FU dose was decreased to 300 mg/m^2 bolus and 500 mg/m^2 continuous infusion in cases of grade 3 or 4 stomatitis, diarrhea, neutropenia, thrombocytopenia, or other grade3 major organ drug-related toxicity. The irinotecan dose was decreased by 15% in cases of grade 3 or 4 neutropenia or thrombocytopenia, grade 3 diarrhea or stomatitis, or other grade 3 major organ drug-related toxicity. Irinotecan was stopped until symptom improvement in cases of severe diarrhea or persisting between cycles. Re-escalating doses that had been reduced due to toxicity were not allowed.

Evaluation criteria

Computed tomography scans of measurable lesions were assessed at baseline, and then repeated every 4 cycles. Complete response was defined as the absolute disappearance of all clinically assessable disease for at least 4 weeks. Partial response was defined as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% of measurable lesions, and progressive disease was defined as an increase of at least 25% of measurable lesions or the appearance of new malignant lesion(s). The present study endpoints were progression free survival (PFS), overall survival (OS), response rate, and tolerance. Surgery of residual disease was permitted in patients with tumor response and recommended right after achieving the maximal response.

Statistical consideration

Study assignment was performed utilizing the above inclusion criteria to recruit the patients. The Kaplan-Meier method for survival analysis was employed to demonstrate PFS and OS[8].

Table 1. Patient and disease characteristics at baseline

Characteristics	(Total n = 19)
Age, years	
Median	54
Range	27-73
Sex	
Male	11 (57.9%)
Female	8 (42.1%)
Median ECOG PS	
0	6 (31.5%)
1	12 (63.2%)
2	1 (5.3%)
Primary site	
Colon	10 (52.6%)
Rectum	9 (47.4%)
Metastases	
Metachronous	12 (63.2%)
Synchronous	7 (36.8%)
Metastatic site (s)	
Liver	9 (47.4%)
Lung	3 (15.8%)
Peritoneum/lymph nodes	7 (36.8%)
Previous treatments	
Surgery	6 (31.5%)
Chemotherapy	1 (5.3%)
Surgery + chemotherapy	6 (31.5%)
None	6 (31.5%)

Note: ECOG PS, Eastern Cooperative Oncology Group performance status

Patients with metastatic or recurrent colorectal cancer were enrolled in the present study. Inclusion criteria consisted of performance status 2 or less according to ECOG criteria, age between 18 and 75 years, interval from prior to treatment 4 weeks or more, adequate hematological, renal and hepatic functions, and patient informed consent. Patients and disease characteristics as well as responses to treatment were presented with number of patients and percents.

Results

Patient characteristic

Between April 2005 and July 2006, 20 consecutive patients were enrolled in the present study. One patient was not analyzed because the patient was not eligible and not treated. The characteristics of the 19 eligible patients are shown in Table 1. The median age was 54 years (range 27-73 years). More than one fourth of the patients had previously been treated with systemic chemotherapy as adjuvant treatment. Sites of disease were liver in nine patients, lungs in three patients, bowels in four patients, lymph nodes in three patients, and peritoneum in two patients. Two patients had more than one metastatic site. Previous treatments included adjuvant chemotherapy in 31.5%, and front-line chemotherapy for advanced disease in 5.3% of the cases. One hundred and thirty four cycles of chemotherapy were administered. The median follow-up time for surviving patients was 6.6 months (range 0.9-24.3).

Table 2. Responses to treatment (Total n = 17)

Responses	N	%
OR: overall response	5	29.4
CR: complete response	0	
PR: partial response	5	29.4
SD: stable disease	10	58.8
PD: progressed disease	2	11.8
Not assessable (< 4 cycles)	2	
Response by intention to treat (n = 19)		
Responses	N	%
OR: overall response	5	26.3
CR :complete response	0	
PR : partial response	5	26.3
SD : stable disease	11	57.9
PD : progressed disease	3	15.8

Toxicity

According to this clinical study, patients received a median of seven cycles of chemotherapy (range, 2 to 13cycles). As shown in Table 3, non-hematological toxicity was mild and mainly of grade 1 or 2. Only one patient (5.3%) who experienced grade 3 anorexia and fatigue discontinued chemotherapy after the second cycle. One patient experienced grade 3 nausea and vomiting and recovered with 5-HT3 antagonist and dexamethasone. Almost 79% of the patients had grade 2 alopecia and two thirds of the patients experienced grade 1 mucositis. The most common hematological toxicity was neutropenia (Table 3). Grade 3 and 4 neutropenia were observed in 15.8% and 10.5% of the patients, respectively. There were no grade 3/4 anemia and there was no case of febrile neutropenia. Only one patient in the present study had grade 1 thrombocytopenia.

Table 3. Frequency of common toxicities (maximal toxicity-per patient)

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
1. Hematologic				
Anemia	7 (36.8)	4 (21.1)	0	0
Neutropenia	1 (5.3)	3 (15.8)	3 (15.8)	2 (10.5)
Thrombocytopenia	1 (5.3)	0	0	0
2. Non-hematologic				
N/V	10 (55.6)	3 (15.8)	1 (5.3)	
Acute diarrhea	6 (31.6)	1 (5.3)	0	0
Delayed diarrhea	2 (10.5)	4 (21.1)	1 (5.3)	0
Mucositis	12 (63.2)	1 (5.3)	0	0
Alopecia	1 (5.3)	15 (78.9)	0	0
Fatigue	12 (63.2)	0	1 (5.3)	0

Overall survival (OS) and progression free survival (PFS)

At the median follow up of 6.6 months (0.9-24.3), the median survival time was 10.6 months (6.4-14.0) (Fig. 1) in patients treated with the present study. The median PFS was 4.7 months (range 3.28-6.01) (Fig. 2).

Objective tumor response

Based on intention to treat analysis, sixteen patients (84.2%) achieved clinical benefit with 26.3% clinical response (Table 2). None achieved complete responses (CR) and two patients had progression of disease (PD). Five patients (26.3%) had partial response (PR) and 11 patients (57.9%) had stable disease (SD).

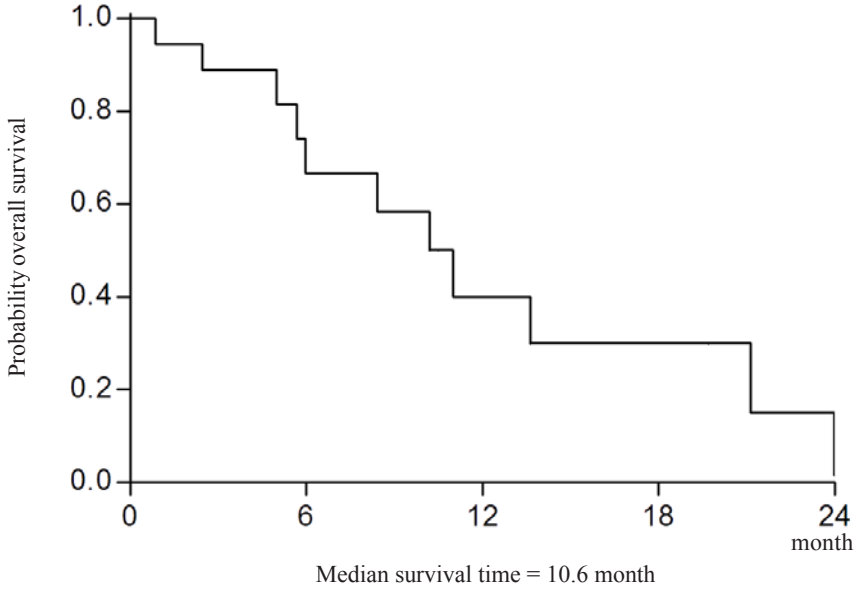


Fig. 1 Overall survival

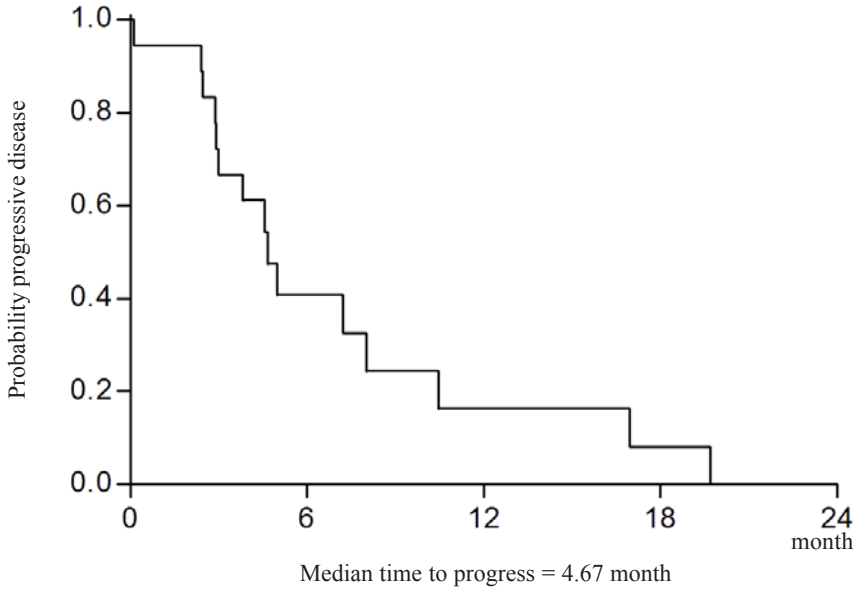
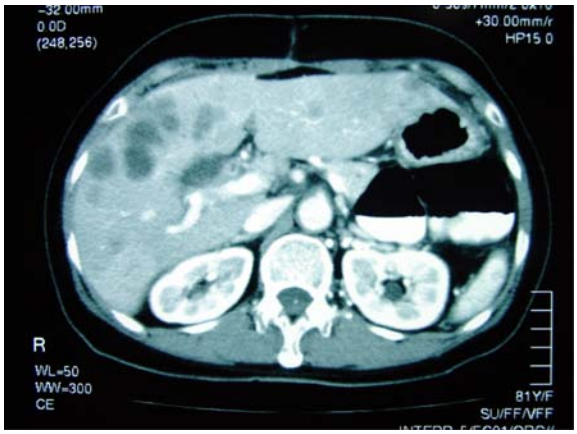
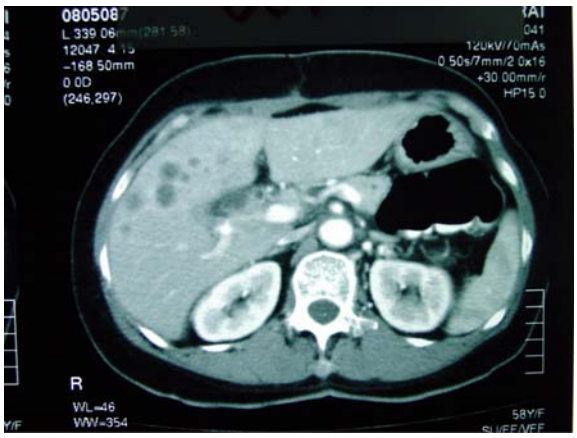


Fig. 2 Progression free survival



A: previous treatment of liver lesions



B: partial response of liver metastases

Fig. 3 Photographs

Table 2 shows the results based on the protocol study, which defined that the assessable cases had to receive at least 4 cycles of the chemotherapy.

Weight and performance status (PS)

A weight increase of at least 5% was noted for six patients (31.5%). The PS improved in nine (47.4%) of assessable patients with a PS more than 0.

Discussion

The clinical studies achieved a median survival time beyond 20 months in advanced colorectal cancer treatment are still not common[9-13]. Without any treatment after the documentation of metastases, the median survival is approximately 9 months, relating to the extent of the disease at the time of diagnosis[14]. First-line treatment of metastatic disease with FOLFIRI regimens yielded the median time to progression 7-8.5 months and overall survival 14-17 months[9,15-17]. The survival increased to 21.5 months when irinotecan was replaced by oxaliplatin at progression[9]. In pretreated metastatic colorectal cancer patients, the median progression-free survival and median survival decreased to 4.1 months and 9.7 months, respectively[18]. The present study demonstrates the comparable results to the prior study. The authors demonstrate the median survival time of 10.6 months and the median time to progression of 4.7 months. Although one third of the patients in the present study received chemotherapy as the adjuvant treatment, combination chemotherapy with irinotecan, folinic acid, and 5-fluorouracil produced excellent disease-controlled rate of 88.2% (29.4% PR and 58.8% SD). At present, several effective chemotherapeutic agents and regimens are available, and multiple lines of treatment typically are planned for patients with metastatic colorectal cancer. FOLFIRI chemotherapy is one of the common regimens[9,14-19]. However, these new agents have the potential for cumulative toxicities; additionally, the financial strains on patients treated with extended chemotherapy are considerable. Stop-and-go rationale for irinotecan-based regimen, the new common approach in first-line therapy for advanced colorectal cancer, would potentially yield benefits to the patients and reduce costs of the treatment. A recent report suggests that a stop-and-go strategy is feasible for FOLFIRI chemotherapy[19]. Longer follow-up time and randomized control trials are needed for further study including potential advantages in cost saving and drugs for future use, which do not compromise treatment efficacy.

Conclusion

The bimonthly irinotecan in combination with folinic acid and 5-fluorouracil was active with acceptable toxicities and produced a prolonged survival time. Additional trials to define the optimal dose and schedule of treatment are justified.

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การศึกษาเคมีบำบัด ฟอลฟิริ (FOLFIRI) ในผู้ป่วยมะเร็งลำไส้ใหญ่ชนิดแพร่กระจาย

พิมพ์ขวัญ กำเนิดศุภผล, วิชาญ หล่อวิทยา, อิ่มใจ ชิตาพนารักษ์, อนันต์ โทนุสิน, วิมล สุขถมยา

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาเคมีบำบัดอิริโนทีแคน ร่วมกับ ฟอลินิกแอซิค และฟลูออโรยูราซิล ซึ่งมีชื่อเรียกว่าสูตร ฟอลฟิริ เมื่อให้แก่ผู้ป่วยมะเร็งลำไส้ใหญ่ชนิดแพร่กระจาย โดยการประเมินจะใช้อัตราการสนองต่อการรักษา, ระยะเวลาการควบคุมโรคและอัตราการรอดชีวิต และเพื่อประเมินถึงความปลอดภัยของยาชนิดดังกล่าวในผู้ป่วยที่ได้รับการรักษานี้*

วัสดุและวิธีการ: *ผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคมะเร็งลำไส้ใหญ่ระยะแพร่กระจาย จะได้รับการรักษาวันที่ 1 โดยใช้ยาอิริโนทีแคน 180 mg/m^2, ยาฟอลินิคแอซิค 200 mg/m^2, และยาฟลูออโรยูราซิล 400 mg/m^2 ฉีดเข้าทางหลอดเลือดดำตามด้วยฟลูออโรยูราซิล 600 mg/m^2 โดยให้ช้าๆ เข้าทางหลอดเลือดดำเป็นเวลานาน 22 ชั่วโมง ในวันที่ 2 ผู้ป่วยจะได้รับยาเช่นเดียวกันกับวันที่ 1 ทุกอย่าง ยกเว้นยาอิริโนทีแคน ในการให้แต่ละครั้งผู้ป่วยจะใช้เวลาในการรักษาในโรงพยาบาลนานประมาณ 3 วัน และการให้ยาในครั้งถัดไปจะมีระยะเวลาห่าง 2 สัปดาห์จากยาชุดก่อนหน้า บริเวณที่พบโรคแพร่กระจายได้แก่ ตับ ในผู้ป่วย 9 ราย, ปอดในผู้ป่วย 3 ราย, ลำไส้ในผู้ป่วย 4 ราย, ต่อมน้ำเหลืองในผู้ป่วย 3 ราย และ เยื่อบุผนังช่องท้องในผู้ป่วย 2 ราย พบว่าร้อยละ 16 ของผู้ป่วย มีโรคแพร่กระจายมากกว่า 1 ตำแหน่ง การรักษาเชิงระบบที่ได้รับมาก่อนหน้าประกอบไปด้วย เคมีบำบัดเสริมร้อยละ 31.5% และเคมีบำบัดแรกเริ่มในผู้ป่วย 1 ราย ซึ่งมีโรคลุกลาม*

ผลการศึกษา: *มีผู้ป่วยทั้งสิ้น 19 ราย ที่เข้าร่วมในการศึกษาครั้งนี้ โดยมีจำนวนครั้งของการให้ยาเคมีบำบัดเฉลี่ยคิดเป็น 7 ชุด ของการรักษา (โดยมีพิสัยตั้งแต่ 2-13 ชุด) ผู้ป่วยทุกรายสามารถประเมินผลข้างเคียงได้ และมีผู้ป่วยจำนวน 17 รายที่สามารถประเมินผลการตอบสนองต่อการรักษาได้ ผลข้างเคียงที่ไม่ใช่ระบบโลหิต ส่วนใหญ่จะไม่รุนแรง โดยพบอยู่ในระดับความรุนแรง 1 หรือ 2 ไม่พบมีผู้ป่วยที่มีระดับความรุนแรง 4 ในผู้ป่วย 1 ราย ที่พบมีผลข้างเคียงชนิดเบื่ออาหารและอ่อนเพลียในระดับความรุนแรง 3 ได้ขอหยุดยาหลังจากได้รับยาชุดที่ 2 ประมาณร้อยละ 79 ของผู้ป่วยพบมีอาการผมร่วงในระดับความรุนแรง 2 ผลข้างเคียงทางระบบโลหิต ที่พบได้บ่อยที่สุดคือ ภาวะเม็ดเลือดขาวต่ำ โดยภาวะเม็ดเลือดขาวต่ำที่มีความรุนแรงระดับ 3 และ 4 พบได้ร้อยละ 15.8 แล้ร้อยละ 10.5 ตามลำดับ และไม่พบว่ามีผู้ป่วยประสบภาวะที่เรียกว่า febrile neutropenia ในการศึกษาครั้งนี้ จากการวิเคราะห์ข้อมูลไม่พบว่าผู้ป่วยรายใดตอบสนองต่อการรักษาแบบครบสมบูรณ์ มีผู้ป่วย 5 รายที่ตอบสนองบางส่วน ซึ่งคิดเป็นร้อยละ 26.3 และมีผู้ป่วย 11 รายที่โรคไม่ดำเนินต่อไป คิดเป็นร้อยละ 57.9 ที่ระยะเวลาเฉลี่ยในการติดตามผู้ป่วย 6.6 เดือน ได้พบว่ามีระยะเวลาเฉลี่ยในการควบคุมโรค 4.7 เดือน และมีระยะเวลาการรอดชีวิตเฉลี่ย 10.6 เดือน*

สรุป: *การใช้ยาอิริโนทีแคน ร่วมกับ โฟลินิกแอซิค และ ฟลูออโรยูราซิล พบว่ามีประสิทธิภาพ, เกิดผลข้างเคียงในปริมาณและความรุนแรงที่ยอมรับได้, และช่วยเพิ่มการรอดชีวิตในผู้ป่วยโรคมะเร็งลำไส้ใหญ่ที่เคยได้รับการรักษาชนิดอื่นมาก่อนแล้วมีโรคแพร่กระจายหรือกลับเป็นซ้ำในการระบุถึงขนาดของยาที่เหมาะสมและตารางการให้ยาที่เหมาะสมต้องอาศัยการศึกษาเพิ่มเติมต่อไป*