Clinical Activity and Benefit of Irinotecan (CPT-11) in Patients with Metastatic Colorectal Carcinoma Pre-treated with Fluorouracil-Based Chemotherapy

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Abstract

The purpose of this prospective study was to assess the efficacy, clinical benefit and safety of irinotecan (CPT-11) in patients with 5-fluorouracil-resistant metastatic colorectal cancer (CRC). Sixteen patients with World Health Organization (WHO) performance status ≤ 2 were treated with CPT-11 350 mg/m^2 every 3 weeks. The observed partial response (PR) rate was 6.3 per cent with a high rate of stable disease (SD) (43.7%) which was of long duration (21.1 weeks for the best response ; 1PR, 7SD). The median survival time for the 16 patients entered into this study was 69.6 weeks. There was no toxic death. The most frequent adverse events were neutropenia (31% grade 3/4) and delayed diarrhea (9.7%). CPT-11 has definite activity in the treatment of progressive metastatic CRC truly resistant to 5-FU which translated into clinical survival benefit. Median survival from first administration of CPT-11 was 78.6 weeks for patients with best response (PR+SD) compared with 28.1 weeks for patients with progressive disease (PD) (P=0.01). With the appearance of new active drugs in this highly chemotherapy-resistant disease, the definition of response should be reassessed in CRC.

Key word : Advanced Colorectal Cancer (CRC), Irinotecan

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The primary management of localized colorectal cancer is surgical intervention, followed by adjuvant chemotherapy or radiotherapy for certain high-risk groups[1,2]. Although advanced disease can still be managed surgically in selected patients, Fluorouracil (5-FU) - based palliative chemotherapy has been the primary treatment for metastatic colorectal carcinoma (CRC) for nearly 40

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years[3,4]. Regimens based on 5-FU and leucovorin (LV) are considered to be the standard first-line chemotherapy[5]. The use of 5-FU based regimens in chemotherapy naive patients have been shown to prolong survival and even improve quality of life [6,7]. However, there has been no standard second-line therapy for individuals who develop progressive disease following initial 5-FU-based treatment until recently when two phase III studies reported the clinical benefit of irinotecan in patients with advanced colorectal cancer following 5-FU failure. Irinotecan was compared to the best infusional 5-FU regimens[8] and the best supportive care[9] and survival benefit was shown in both multicenter randomized clinical trials.

Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin, a plant alkaloid derived from the Chinese tree, Camptotheca acuminata[10]. After conversion to an active metabolite, SN-38, the antitumor activity of CPT-11 arises through a new and unique mechanism of action, inhibition of eukaryotic enzyme DNA topoisomerase I (topo-I)[11,12]. Topo-I is a nuclear enzyme that plays a key role in DNA replication and transcription. The enzyme binds to specific regions of supercoiled DNA and causes transient breaks in a single strand of DNA. The topo-I/DNA complex, also known as the cleavable complex, is the target for camptothecin and its derivatives. CPT-11 binds to the cleavable complex and inhibits resealing of parent DNA, thus halting nucleic acid synthesis and ultimately leading to cell death. The active metabolite, SN-38, is 250 to 1,000 times more potent inhibitor of topo-I than its parent compound and accounted for the major antitumor effect of CPT-11[13]. Topoisomerase I levels are reported to be substantially higher in colorectal cancer cells than in normal tissues[14,15]. Also, the topoisomerase I enzyme is expressed in both proliferating and quiescent cells. Therefore, it is likely to be active against slowly proliferating and actively dividing cancer cells.

In several phase II studies, CPT-11 has demonstrated activity both in chemotherapy-naive and previously treated patients with colorectal cancer, showing response rates of 15 per cent to 32 per cent[16-18]. In France, Abigerges et al established a recommended phase II dose of 350 mg/m^2 with a dose-limiting toxicity of diarrhea[19]. However, using an intensive regimen of loperamide in selected patients, they were able to escalate to CPT-11 MTD of 600 mg/m^2 before neutropenia became dose-limiting.

The present study was conducted to assess prospectively the efficacy, clinical benefit, and safety of CPT-11 in Thai patients with 5-FU-resistant advanced colorectal cancer.

PATIENTS AND METHOD

Patient Characteristics

Sixteen eligible patients known to have advanced colorectal adenocarcinoma beyond surgical cure. All patients were required to have measurable disease that had progressed following treatment with 5-FU-based regimens. If the only site of disease was in a previously irradiated site, clear evidence of disease progression in that site was required. An interval of at least 4 weeks must have elapsed since one prior chemotherapy regimen (two if one was adjuvant); 6 weeks for mitomycin C, nitrosourea or extensive radiotherapy. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, pretreatment absolute granulocyte count (AGC) $\geq$ 1,500/μL, and platelet count $\geq$ 100,000 /μL. Adequate renal and hepatic function. The latter was defined as bilirubin level $\leq$ 1.25 x upper limit of normal (N), transaminases $\leq$ 2 x N, and alkaline phosphatase level $\leq$ 2 x N (unless liver metastases were present in which case transaminase level could be $\leq$ 4 x N, bilirubin $\leq$ 1.5 x N, and alkaline phosphatase without limit).

Exclusion criteria included the presence of CNS metastases or prior malignancies (with the exception of excised cervical or basal skin/squamous cell carcinoma) and those with uncontrolled concomitant nonmalignant disease (cardiac, pulmonary, renal, hepatic, and uncontrolled infection). Patients with complete or partial bowel obstruction were also excluded from this study.

Treatment Protocol

All patients were treated with CPT-11 350 mg/m^2 as a 30-minute intravenous infusion every 3 weeks, with provision for dose reduction (to 300 mg/m^2 and further to 250 mg/m^2) or delay if severe toxicity (diarrhea grade $\geq$ 3; neutropenia grade $\geq$ 3) occurred. Patients had to receive at least 2 consecutive cycles before the first assessment of tumor response, except in the case of progressive disease or severe toxicity. Patients who responded or who had stable disease after 2-3 treatment cycles could continue treatment for $\geq$ six cycles, except in the case of disease progression or excessive toxicity. Before

the next treatment cycle, all patients underwent a physical examination and assessment of clinical history.

Assessment of Response

The primary efficacy end point was response rate. Secondary efficacy end points included the duration of response (calculated from the start of treatment to the time of disease progression), time to disease progression, and survival (calculated from the start of treatment). Response to treatment was classified according to WHO criteria[20]. Safety was monitored at each cycle and graded according to WHO criteria where applicable.

Supportive Care and Antidiarrheal Therapy

Preventive anti-emetic treatment was given routinely. For patients who experienced an early cholinergic syndrome (lacrimation, diaphoresis, abdominal cramping, and/or diarrhea occuring during or shortly after CPT-11 administration), atropine 0.25 mg could be given intravenously or subcutaneously.

All patients were alerted to the importance of recognizing and reacting immediately to the onset of delayed diarrhea. If delayed diarrhea occurred, it was to be treated promtly with high-dose loperamide (2- to 4- mg loading dose of loperamide followed by 2 mg every 2 hours for 12 hours).

Table 1. Patient characteristics.

Characteristics		N	%
No. of patients	Male	11	68.8
	Female	5	31.2
Age, years			
Median (range)		56 (41-68)	
Performance status			
ECOG	0	14	87.5
	1	2	12.5
Histology			
Adenocarcinoma		16	100
Primary tumor site			
Colon		11	68.6
Rectum		5	31.4
Metastatic sites			
Liver		9	33.4
Lung		6	22.2
Lymph node		2	7.4
Adrenal gland		2	7.4
Bone		2	7.4
Other		6	22.2
No. of involved organ			
1 organ		9	56.3
2 organs		3	18.7
≥ 3 organs		4	25.0
Progression free survival with prior chemotherapy (months)			
Adjuvant, Median (range)		39.8 (11.9-55.7)	
Palliative, Median (range)		9.5 (1.5-22.8)	
Prior radiotherapy			
No		9	56.3
Yes, whole pelvis		7	43.7
Prior surgery			
Low anterior resection		10	62.5
Palliative surgery with colostomy		3	18.7
Rectosigmoidectomy		2	12.5
Rt. Hemicolectomy		1	6.3

If the diarrhea episode resolved, loperamide was stopped. If the diarrhea continued or recurred, loperamide was continued at 2 mg every 2 hours for a maximum of 2 days. If there was no control after 2 days, other supportive measures, including hospitalization, were to be considered for parenteral rehydration.

Statistical Methods

All statistical analyses were performed using SPSS software. Progression free survival and overall survival were estimated by the method of Kaplan and Meier[21].

RESULTS

Patient Characteristics

Sixteen patients received treatment in this study. A summary of baseline patient characteristics is listed in Table 1.

Most patients (81.2%) were originally diagnosed and treated for metastatic (Dukes' stage D) colorectal cancer before study entry. The remainder of the patients had localized (Dukes' stage B_2) or locally advanced disease (Dukes' stage C) that had progressed and metastasized despite prior adjuvant treatment with a 5-FU-based regimen, the median disease-free-survival for this group of patients was 39.8 months (range, 11.9-55.7).

Response and Survival

A total of 82 cycles of CPT-11 were administered to this group of 16 patients with disease progression while receiving 5-FU-based chemotherapy. The median number of cycles given was 4 (range , 2-9). Five patients (31.2%) received more than 6 cycles. Infusions were delayed by 7 days or more in 20 cycles (24.4%).

The overall objective response rate in the 16 eligible patients was 6.3 per cent (1 patient) (Table 2).

Of the remaining 15, 7 (43.7%) had stabilization of their diseases, which had been progressive at baseline. Included in the stable disease category are 2 patients with minor responses, defined as a regression of between 25 and 49 per cent of the overall tumor mass. Median duration of stable disease as best response was 21.1 weeks (range, 12.4-44.1). The progression-free survival was 11.6 weeks (95% CI, 7.4 -15.8). Median survival from the administration of CPT-11 was 69.6 weeks (95% CI, 39.6 - 99.5) (Fig. 1).

Clinical benefits were also analyzed between patients who achieved best clinical response (partial response, minor response, and stable disease) *versus* patients who had disease progression[22]. The median survival time was 78.6 weeks and 28.1 weeks, respectively (p =0.01). (Fig. 2)

Table 2. Summary of response and survival.

Response	N	%
No. of patients	16	100
Partial response	1	6.3
Minor response	2	12.5
Stable disease	5	31.2
Progressive disease	8	50.0
Death status		
Alive	6	37.5
Dead	10	62.5
Survival time		
Median (weeks)	69.6	(95% CI, 39.6-99.5)
Time to progression		
Median (weeks)	11.6	(95% CI, 7.4-15.8)
Response duration		
Median (weeks)	21.1	
Range	12.4-44.1	
Follow-up time		
Median (weeks)	60.9	
Range	14.7-96.1	

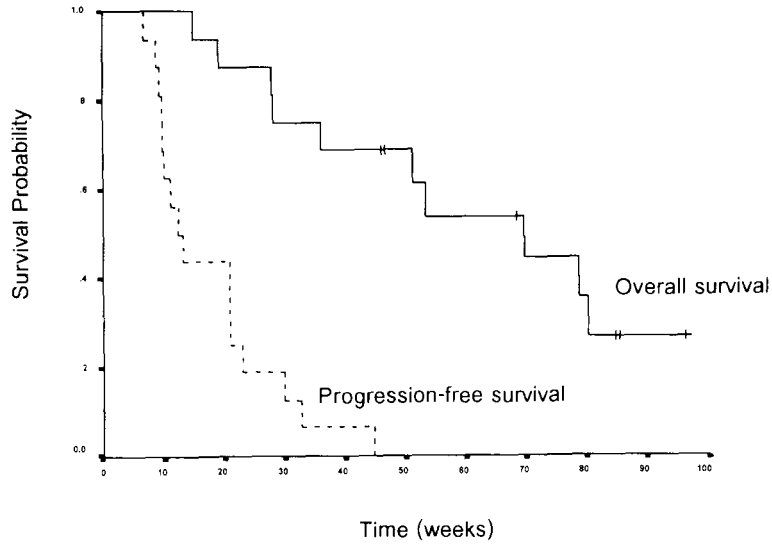

Fig. 1. Survival and progression-free survival.

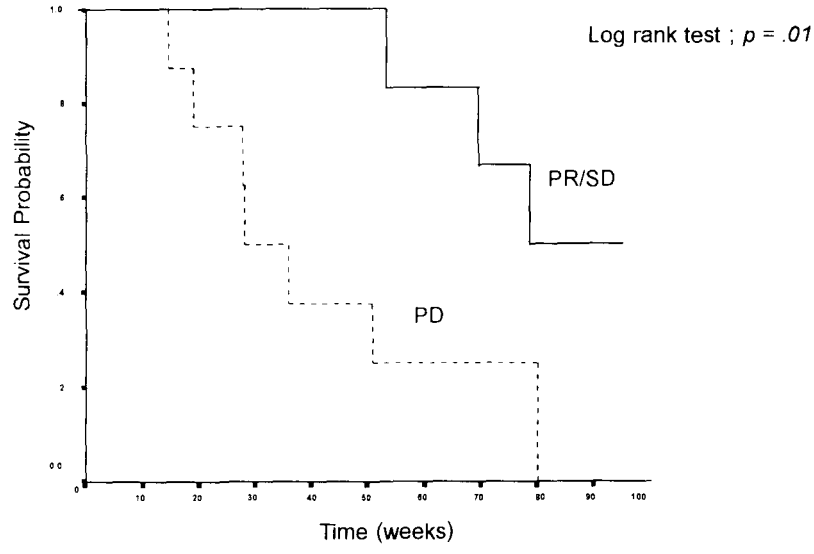

Fig. 2. Probability of survival according to response (PR/SD *versus* PD).

Toxicity

All patients were assessed for tolerability (Table 3).

The principal hematological toxicity was neutropenia (30.4% grade 3/4) with 7 episodes of febrile neutropenia. However, there were no deaths attributed to CPT-11 in the present study. The most frequent grade 3 or 4 nonhematologic toxicities were acute cholinergic-like syndrome (15.9%) and delayed diarrhea (9.7%).

DISCUSSION

Chemotherapy management of advanced colorectal cancer has been a challenge to medical oncologists for the past four decades. Until recently, 5-FU has been the only available drug with consis-

Table 3. Toxicity (N = 82 Cycles).

Toxicity	WHO Toxicity Grade (no. of patients)				Over all		% grade 3 or 4
	1	2	3	4	N	%	
Neutropenia	8	15	9	16	48	58.5	30.4
Anemia	68	14	0	0	82	100	0
Thrombocytopenia	13	1	0	0	14	17.1	0
Fever	4	7	0	0	11	13.4	0
Acute cholinergic-like syndrome	19	33	13	0	65	79.2	15.9
Abdominal pain	5	1	0	0	6	7.3	0
Delayed Diarrhea	16	20	2	6	44	53.6	9.7
Nausea	27	33	4	0	64	78	4.9
Vomiting	12	20	7	1	40	48.7	9.7
Alopecia	12	66	-	-	78	95.1	-
Anorexia	18	20	1	0	39	47.5	1.2
Fatigue	16	7	2	0	25	30.4	2.4
Mucositis	1	1	1	0	3	3.6	1.2
Hiccough	9	4	0	0	13	15.9	0
Skin rash	0	1	0	0	1	1.2	0

tent activity, albeit moderate, against CRC. Hence, clinical research focused mainly on biochemical modulation and new administration schedules of 5-FU. Although these developments occasionally have led to improved response rates or a more favorable toxicity pattern, to date they have not resulted in a meaningful increase in survival. Randomized comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer showed a significantly longer overall survival in the former group of patients (11.0 months *versus* 5.0 months ; p = 0.006)[23]. However, this study consisted of a small number of patients.

In this small trial, we observed a 6.3 per cent partial response rate with a significant percentage of the patients with minor response or stable disease (43.7%). The median survival from the start of second-line treatment was 69.6 weeks, which is of clinical importance especially as they had poor prognostic factors : strictly defined as progression on 5-FU therapy. The response rate of 6.3 per cent in the present study is quite low compared with the earlier French multicenter study and American study[18-24]. There was a high rate of disease stabilization (43.7%) which was of long duration (median 78.6 weeks). Other studies have shown that stabilization of progressive CRC is associated with both prolonged survival and subjective improvement[25]. The survival advantage conferred by stable disease (SD) was almost as great as that associated with partial response (PR)[22]. Van Cutsem reported a median survival time of 12.5 months for patients with stable disease after treatment with CPT-11 administered at a dosage of 350 mg/m^2 every 3 weeks, they were all documented truly 5-FU-resistant CRC[26]. This clinical benefit is not unique to patients with advanced CRC. There is randomized evidence that NSCLC patients with stable disease on chemotherapy have similar survival to those with objective response[27]. Furthermore, Finkelstein et al found that patients who responded very slowly fared as well or better than those who responded quickly[28]. Similar phenomena have been observed in multiple myeloma[29] and lymphoma[30]. The taxanes in particular have been noted to cause late responses in patients with lung cancer or breast cancer[31].

The median survival time for the 16 patients entered into this study was 69.6 weeks. Given that the median survival time for patients with newly diagnosed metastatic colorectal cancer is only 11 months,[23] the results of this trial appeared encouraging considering they were all 5-FU-resistant disease. However, we recognize that patient selection could have also contributed substantially to these results.

Neutropenia, and diarrhea were the main toxicities observed during this study with no treatment related death. Simultaneous development of

febrile neutropenia and delayed diarrhea, although rare (8.5% of cycles), could potentially result in adverse events from severe damage of the intestinal mucosa, posibly caused by CPT-11, which enhances microbial translocation from the gastrointestinal tract to the bloodstream[32,33].

Our data also confirmed the lack of clinical cross-resistance between 5-FU and CPT-11. This is consistent with previous phase II results[18,24]. The strategy of combining 5-FU and irinotecan is a very attractive one and has already been evaluated in some phase I/II studies. However, schedule and sequence dependent interactions probably play a significant role in contributing to the cytotoxicity of these two drugs when used in combination[34]. Future studies using this combination should take into account the molecular and cell cycle interactions between the two drugs.

In conclusion, approximately 50 per cent (PR+SD) of patients with metastatic CRC that has progressed on 5-FU-based palliative chemotherapy are likely to benefit in terms of tumor growth control from CPT-11. The value of irinotecan was confirmed in terms of survival and should be considered as a standard second-line therapy in colorectal cancer.

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การประเมินผลการใช้ยาอิริโนทีแคนในผู้ป่วยมะเร็งลำไส้ใหญ่ระยะแพร่กระจายที่ดื้อต่อยาฟลูโอโรยูเรซิล

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รายงานการศึกษาประสิทธิภาพ และความปลอดภัยของการใช้ยา Irinotecan ในผู้ป่วยมะเร็งลำไส้ใหญ่ระยะแพร่กระจายที่ดื้อต่อสูตรยาซึ่งมี Fluorouracil (5-FU) เป็นยาประกอบหลัก และมี performance status ประเมินด้วยเกณฑ์ขององค์การอนามัยโลก (WHO) น้อยกว่าหรือเท่ากับ 2 ขนาดยา Irinotecan ที่ให้ 350 มิลลิกรัมต่อพื้นที่ผิวหนึ่งตารางเมตร ทุก 3 สัปดาห์ ผลการรักษาพบว่า ผู้ป่วยทั้งหมด 16 ราย มีการตอบสนองบางส่วน (partial response หรือ PR) 6.3%, อาการคงที่ (stable disease หรือ SD) 43.7% โดยมีระยะเวลาที่ตอบสนองต่อการรักษาเท่ากับ 21.1 สัปดาห์ อัตราการอยู่รอดของผู้ป่วยทั้งหมด 16 ราย เท่ากับ 69.6 สัปดาห์ ผลข้างเคียงจากการรักษาที่พบบ่อย ได้แก่ ภาวะเม็ดเลือดขาวต่ำในระดับเกรด 3 และ 4 เท่ากับ 31% อาการท้องเสีย 9.7% ไม่มีผู้เสียชีวิตจากผลข้างเคียงดังกล่าว สรุปได้ว่า การใช้ยา Irinotecan ในผู้ป่วยมะเร็งลำไส้ใหญ่ระยะแพร่กระจายที่ดื้อต่อยา 5-FU ช่วยให้อัตราการอยู่รอดดีขึ้นอย่างมีนัยสำคัญทางสถิติเมื่อเปรียบเทียบระหว่างผู้ป่วยกลุ่มที่ตอบสนอง (PR+SD) กับกลุ่มผู้ป่วยที่ไม่ตอบสนองต่อการรักษา (progressive disease หรือ PD) p = 0.01

คำสำคัญ : มะเร็งลำไส้ใหญ่ระยะแพร่กระจาย, ยาอิริโนทีแคน

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