

Efficacy and Tolerability of Irinotecan in Patients with Advanced Colorectal Cancer in Singapore

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Abstract

Introduction: Colorectal cancer is the commonest malignancy encountered in Singapore. The long-term outcome of patients with advanced diseases is poor. For many decades, 5-fluorouracil was the only effective cytotoxic drug against colorectal cancers. Randomised trials have documented the efficacy of irinotecan in patients with metastatic colorectal cancer. We investigated the efficacy and safety profile of irinotecan (CPT-11), as a second-line treatment for an Asian population who had failed 5-fluorouracil-based chemotherapy. **Materials and Methods:** A total of 33 patients were enrolled in the study between October 1996 and May 1999. This was an open label phase II study. All patients who had received at least one dose of CPT-11 were evaluated for toxicity. Thirty patients were evaluated for response. **Results:** Six patients (20%) had partial responses and 1 (3%) experienced minor response. Fourteen patients (47%) progressed. Nine patients (30%) had stable disease. The range of time to progression was 5.8 months to 21 months. The median survival was 9.5 months. There was no treatment-related death. Seven patients (23%) who received treatment had diarrhoea. Only 2 of the 7 patients had grade 3-4 diarrhoea. Eleven patients (37%) suffered from haematological toxicity, of whom 2 patients had grade 3-4 neutropenia. **Conclusion:** We demonstrated efficacy and tolerability of CPT-11 in Singaporean patients with advanced colorectal cancer.

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Key words: Chemotherapy, Diarrhoea, Irinotecan, Metastatic colorectal carcinoma

Introduction

Colorectal cancer is the second most commonly encountered malignancy in the developed countries; in Singapore, it is the commonest cancer.¹ With early detection, patients can be cured with surgery. However, long-term outcome of patients with disease relapsing after surgery, or patients presenting with metastatic diseases is poor. For the past 50 years, 5-fluorouracil was the only effective drug. However, monotherapy with 5-fluorouracil can only produce a modest 10% to 15% overall tumour response and 2-month improvement in survival. With the introduction of folinic acid biomodulation, the response approached 30%.² However, patients who failed 5-fluorouracil and folinic acid had little to look forward to. Best supportive care remained the treatment of choice for patients failing first-line chemotherapy as the toxicity of second-line chemotherapy could considerably impair the quality of life, without producing a significant advantage in terms of survival.

In 1995, a new agent was the focus at the 5th International Congress of Anticancer Therapy. This was irinotecan (CPT-11), a semisynthetic derivative of camptothecin. Its action is dependent on the inhibition of DNA eukaryotic enzyme, topoisomerase I.³ Since then, CPT-11 has been studied extensively.

The efficacy of CPT-11, first in second-line setting after 5-fluorouracil failure⁴ and, more recently, in the first-line setting,⁵ has been established through several large-scale phase III randomised trials. In the first-line setting, CPT-11 in combination with 5-fluorouracil and folinic acid has been shown to be significantly better than 5-fluorouracil and folinic acid in terms of both progression free and overall survival.⁶

The main toxicities are infusion-related symptoms, delayed onset diarrhoea, nausea and vomiting, neutropenia, fatigue and alopecia and acute cholinergic symptoms. Acute cholinergic syndrome is a syndrome where patients experience early diarrhoea, sweating, hypersalivation, visual

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disturbances and abdominal cramps. However, this can be entirely avoided with pre-medication, with subcutaneous atropine. This safety profile is acceptable and toxicities manageable.

It is well known that patients with different ethnic origin could have different responses to the same drug as a result of genetic or environmental factors. Glucuronidation of active metabolite SN-38 is determined by genetic factors. This may have significant impact on the outcome of patients treated with CPT-11.⁷ In order to assess the efficacy and tolerability of CPT-11 in our own population, we conducted a study to evaluate CPT-11 in an Asian population with advanced colorectal cancer as second-line chemotherapy after failure of 5-fluorouracil.

Materials and Methods

Study Design and Entry Criteria

We conducted a single institution open label phase II study of irinotecan (CPT-11) as second-line chemotherapy for advanced colorectal carcinoma. To be eligible, patients had to have histologically proven advanced colorectal cancer and measurable, progressive disease. They must have had prior chemotherapy by the following definition: one previous adjuvant chemotherapy without disease progression plus one palliative chemotherapy with disease progression, or one adjuvant chemotherapy with disease progression while on this regimen, or one palliative chemotherapy with disease progression while on this regimen.

In addition, all eligible patients must be between the ages of 18 to 70 years and have an Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2. Patients' life expectancy should be greater than 3 months, and there must be a washout period of at least 4 weeks since the last chemotherapy.

The following patients are excluded: patients who have had more than 2 lines of chemotherapy; who were previously treated with CPT-11; history of inflammatory bowel disease or extensive bowel resection; active bowel obstruction; severe uncontrolled infection, central nervous system metastases, bulky disease-lung metastases greater than 25%; liver metastases greater than 50% and abdominal mass greater than 10 cm. Patients with reproductive potential not using contraceptives, and who cannot be followed-up regularly because of social, psychological or family reasons were also excluded.

Laboratory data requirements for each patient before study were as follows: absolute white cell count $>2.0 \times 10^9/L$, platelet count $>100 \times 10^9/L$, serum creatinine $<135 \mu\text{mol/L}$, bilirubin level $<1.25 \times$ upper limit of normal ($1.5 \times$ upper normal with liver metastases) and serum liver

transaminases $<3 \times$ upper limit of normal ($5 \times$ upper normal with liver metastases).

Before study entry, all eligible patients were required to provide a complete medical history and to undergo a physical examination that included assessment of weight, height and ECOG performance status. Laboratory tests were performed within 7 days prior to treatment with study drug. Computed tomography (CT) scans were performed to assess measurable tumour.

This protocol was approved by an ethics committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent. Rhône-Poulenc Rorer sponsored the study by providing drugs and laboratory tests for patients.

Chemotherapy Regimen

All patients were treated with intravenous irinotecan (CPT-11) (Bellon-Rhône-Poulenc Rorer, Neuilly sur Seine, France) 350 mg/m^2 in 250 mL of physiological solution over at least 30 minutes, repeated every 3 weeks. Prophylactic subcutaneous atropine was used for acute cholinergic syndrome, and intravenous pre-medication with anti-emetics was given.

Evaluation of Toxicities

All patients who had received at least one dose of CPT-11 were evaluated for toxicity. During the administration of CPT-11 and the subsequent 24 hours, all signs of local or general intolerance that occurred (particularly cholinergic or related reactions), including early diarrhoea, were recorded. Haematological tests were performed weekly. Patients were reviewed before every cycle. At each follow-up visit, careful history taking and physical examination were performed. Laboratory tests were performed as that at baseline. Toxicities were evaluated with use of the NCI common toxicity criteria (Table I).

Subsequent doses of CPT-11 would not be initiated until a normal complete blood count could be verified (absolute neutrophil count $>1.5 \times 10^9/L$ and platelets $>100 \times 10^9/L$). If there was no recovery by day 21, the course would be delayed for 1 or 2 weeks. In the absence of recovery by day 35, the treatment would be terminated and the patient withdrawn from the study. In the event of grade 3-4 haematological toxicity, the dose will be reduced to 300 mg/m^2 . If grade 3-4 neutropenia recurred despite dose reduction, then the dose will be further reduced to 250 mg/m^2 . If in spite of such dose reduction the same complications persisted, the treatment was discontinued.

For patients with diarrhoea, loperamide was given at 2 mg every 2 hours at the sign of first liquid stool and continued for 12 hours until the last liquid stool. In case of

TABLE I: NCI (NATIONAL CANCER INSTITUTE) COMMON TOXICITY CRITERIA

Toxicity	0	1	2	3	4
WBC ($\times 10^6/L$)	≥ 4.0	3.0-3.9	2.0-2.9	1.0-1.9	≤ 1.0
Granulocytes ($\times 10^6/L$)	≥ 2.0	1.5-1.9	1.0-1.4	0.5-0.9	≤ 0.5
Nausea	None	Able to eat reasonable intake	Intake significantly reduced but can eat	No significant intake	—
Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	> 10 episodes in 24 hours
Diarrhoea	None	Increase of 2-4 stools/day over pre-treatment	Increase of 4-6 stools or nocturnal stools with moderate cramping	Increase of 7-9 stools or incontinence or severe cramping	Increase of >10 stools or grossly bloody diarrhoea or need parental support
Alopecia	None	Mild hair loss	Pronounced or total hair loss	—	—

WBC: white blood count

severe diarrhoea, the dose was reduced to 300 mg/m². If the same toxicity occurred at that dose, the dose was further reduced to 250 mg/m². If diarrhoea recurred, the patient would be withdrawn from the study.

Patients were hospitalised if they experienced concomitant vomiting or fever, grade 4 neutropenia or febrile neutropenia or if they had diarrhoea lasting more than 24 hours.

Assessment of Response

Patients had to receive 3 cycles of CPT-11 before evaluation of tumour response with CT scans (abdomen and pelvis) or chest X rays. Patients who were withdrawn from the study due to objective tumour progression were treated as treatment failures regardless of the number of courses received. Patients who were withdrawn from the study due to reasons other than progression of disease were not evaluable for response. Tumour response was evaluated according to WHO criteria. Secondary efficacy end points included the duration of response and the time to disease progression.

Results

Patient Characteristics

A total of 33 patients were enrolled to the study between March 1997 and May 1999. Table II shows the baseline characteristics of the patients.

All patients received 5-fluorouracil with levamisole or folinic acid as their first-line chemotherapy. Twenty-two patients had prior palliative chemotherapy, 7 had adjuvant 5-fluorouracil and 4 patients had both adjuvant and palliative chemotherapy with 5-fluorouracil and folinic acid.

Treatment

A total of 167 cycles of CPT-11 were given. The median

TABLE II: PATIENT CHARACTERISTICS

Age (y)	
Median	58
Range	39-70
Ethnicity	
Chinese	31
Malay	2
Sex	
Male	24
Female	9
Prior chemotherapy	
Adjuvant	7
Palliative	22
Both adjuvant and palliative	4
Site of primary tumour	
Colon	18
Rectum	15
Prior radiotherapy (RT)	
Adjuvant RT to pelvis	6
Adjuvant RT to caecum	1
RT to spine	1

number of cycles was 4 (range, 1 to 12) and the mean number of cycles was 3.

Safety

Thirty patients were evaluated for toxicity after receiving a total of 164 cycles. Three patients were excluded because of protocol violation. All 3 patients had high creatinine level. These patients subsequently passed away. Two patients had fever and 1 patient suffered from intestinal obstruction. Table III lists the overall incidence of all frequent adverse events.

Seven patients (23%) who received treatment had diarrhoea. Only 2 of the patients had grade 3-4 diarrhoea. Two patients had prior radiotherapy to the pelvis. Neither

TABLE III: ADVERSE EVENTS AMONG PATIENTS WHO RECEIVED TREATMENT WITH CPT-11 (n = 30)

Adverse events	No. of patients (%) (n = 30)	No. of cycles (%) (n = 164)
Neutropenia		
Grade 1-2	9 (30)	11 (7)
Grade 3-4	2 (7)	7 (4)
Overall	11 (37)	18 (11)
Diarrhoea		
Grade 1-2	5 (16)	8 (5)
Grade 3-4	2 (7)	3 (2)
Overall	7 (23)	11 (7)
Vomiting		
Grade 1-2	13 (43)	49 (30)
Grade 3-4	5 (17)	15 (9)
Overall	18 (60)	64 (39)
Alopecia		
Overall	30(100)	

patient who suffered grade 3-4 diarrhoea received radiotherapy to the pelvis. Two had anterior resection and one had abdominoperineal resection. The last 2 had metastatic disease at diagnosis and had not undergone surgery or radiotherapy. One patient (3%) had fever. The most common side effect was alopecia (100%). Eleven patients (37%) suffered from haematological toxicity: 9 had grade 1-2 neutropenia and 2 patients had grade 3-4 neutropenia. Of the patients who had grade 1-2 neutropenia, only 1 patient had had prior radiation. Both patients who had grade 3-4 neutropenia have had prior pelvic irradiation.

Efficacy

The overall response was 23% (6 partial responses and 1 minor response). Nine (30%) had stable disease. Disease progressed in 14 patients (47%). The range of time to progression was 5.8 months to 21 months. The number of responders is too small to make further conclusion.

Survival

The median survival of all patients from the start of CPT-11 treatment was 9.5 months (Fig. 1). The median survival from the time of diagnosis of metastases to the time of death was 20.9 months (Fig. 2). The median survival of the responders was 31.8 months from diagnosis.

Discussion

Colorectal carcinoma is the commonest cancer in Singapore. The rate of colon cancer has increased 2-fold between 1993 and 1997. Studies on the natural history of the cancer have shown that it generally progresses slowly compared with most other cancers. Even then,

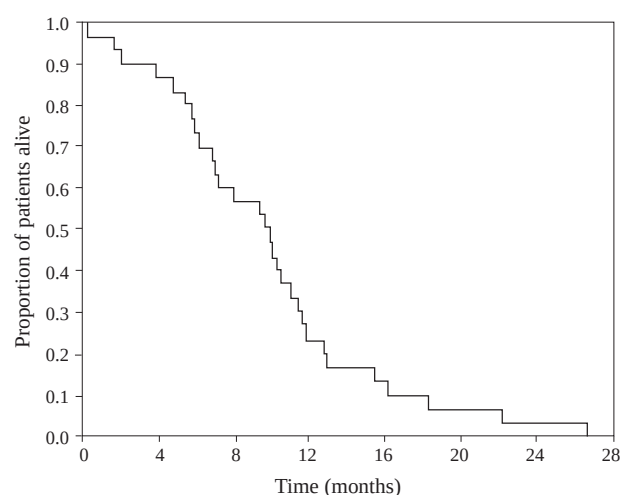


Fig. 1. Survival of patients (n = 30) from first cycle.

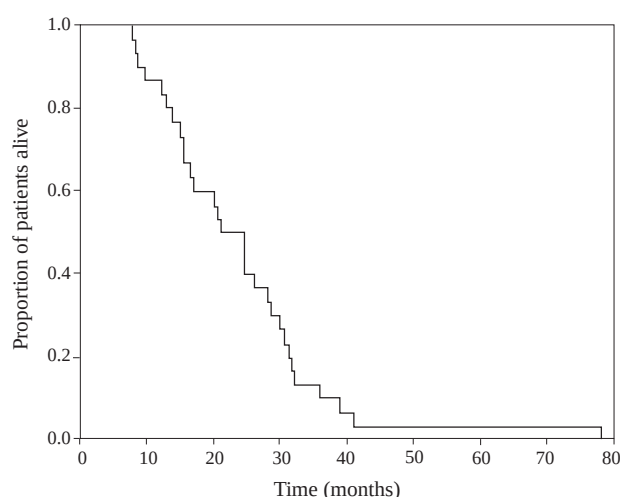


Fig. 2. Survival of patients (n = 30) from first diagnosis.

for patients with advanced disease, systemic chemotherapy was ineffective until the combination of 5-fluorouracil with folinic acid was developed. This combination achieves a higher tumour regression rate than with 5-fluorouracil alone.^{2,8}

For many decades, there had been no effective second-line chemotherapy for patients whose tumour demonstrated refractoriness to 5-fluorouracil and folinic acid. The development of alternative agents was therefore of great interest. Camptothecin is a natural alkaloid product first extracted from a Chinese tree, *Camptotheca acuminata*. The original preparation, camptothecin sodium, was evaluated in clinical trials in the late 1960s and early 1970s. Its significant toxicities in early phase II studies led to the development of a water-soluble derivative, irinotecan (CPT-11).⁹

CPT-11 is characterised by its unique mechanism of

action, the inhibition of DNA topoisomerase-I.³ Topoisomerase-I is a nuclear enzyme that plays a key role in DNA replication and transcription. The enzyme binds to specific regions of super coiled DNA and causes transient breaks in a single strand of DNA. This topoisomerase-I/DNA complex is the target of CPT-11. It impairs the resealing of the parent DNA, thus halting nucleic acid synthesis and therefore causing cell death. CPT-11 is converted by cellular carboxylesterases to SN-38, an active metabolite that is 250-1000 times more potent than its parent compound. This constitutes the major anti-tumour effect of CPT-11.¹⁰

The clinical efficacy and the utility of CPT-11 have been documented in numerous clinical trials conducted in Europe and North America. The dose-limiting toxicities were neutropenia and gastrointestinal disturbances (diarrhoea, abdominal cramps, nausea, vomiting and anorexia). In France, Adigerges et al¹¹ recommended a dose of 350 mg/m² with diarrhoea being the dose-limiting toxicity. However, with an intensive regimen of loperamide, they were able to escalate the dose until neutropenia became the limiting factor.¹² This regimen provided the best compliance and tolerability with the greatest dose intensity.

Rougier et al¹³ reported a response of 18% using the same schedule with stable disease in 37%. In our current study, we reported a 23% response rate with 30% stable disease. The French study reported 47% neutropenia, 39% diarrhoea and 20% vomiting. In our current study, 37% overall neutropenia, 23% overall diarrhoea and 17% grade 3-4 vomiting were noted. Pitot et al,¹⁴ in a phase II study in 1997, cautioned the use of CPT-11 for patients who had prior pelvic irradiation as they demonstrated a statistically significant correlation with prior irradiation and grade 4 neutropenia. Although both of our patients who suffered grade 4 neutropenia had previous pelvic irradiation, our number was too small to make any statistical conclusion. In the same study, the authors did not see an association with grade 3-4 diarrhoea with previous exposure to pelvic irradiation. In our centre, only 2 patients of the 7 who suffered diarrhoea had undergone pelvic irradiation. The other 4 patients who had radiotherapy did not suffer from diarrhoea.

The role of CPT-11 as second-line chemotherapy has been confirmed. The efficacy and tolerability of CPT-11 in Singaporean patients is comparable to the results in the West. Most recently, studies have shown that combination of CPT-11 plus 5-fluorouracil and leucovorin (folinic acid) for metastatic colorectal cancer is significantly better than

regimen of 5-fluorouracil alone in terms of progression free survival and overall survival.³ If that is to become the standard chemotherapy for advanced colorectal cancer, it is reassuring to know that our study confirmed the safety and tolerability in our patients.

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