Single-Agent Irinotecan for Recurrent/Metastatic Colorectal Cancer: A Retrospective Analysis

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Key Words

Irinotecan · Colorectal carcinoma, survival · Prognostic factors

Abstract

Objective: To evaluate the efficacy, toxicity and factors affecting the survival rate of patients treated with irinotecan. **Subjects and Methods:** Data from the medical records of 74 patients who had recurrent/metastatic colorectal cancer treated with single-agent irinotecan were analyzed. **Results:** The mean age for all the patients was 56 years (range 19–77). Forty-one (55%) and 33 (45%) patients had recurrent and/or metastatic colon cancer, respectively. All the patients were treated with irinotecan 350 mg/m² every 21 days. Grade 3–4 emesis, grade 3–4 diarrhea, grade 3–4 neutropenia and severe early cholinergic events developed in 7, 15, 7 and 1.3% of patients, respectively. One patient died due to acute renal failure. The overall response rate was 14% (complete response 5%, partial response 9%); 61% had stable response while another 25% had progressive disease. Patients with multiple metastatic foci, patients ≤50 years of age and patients with peritonitis carcinomatosa were shown to have worse outcomes than others. The median duration of response was 16.7 months. The median progression-

free survival and overall survival were 4 and 14 months, respectively. **Conclusion:** The data show that irinotecan was useful in the treatment of recurrent/metastatic colorectal cancer with acceptable toxicity.

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Introduction

Colorectal cancer is the second leading cause of death due to cancer; in the United States about 57,000 deaths were predicted in 2003 [1]. Early diagnosis of colorectal cancer and developments in therapy have led to a significant increase in the survival time. For the last 40 years, 5-fluorouracil (5-FU) has been the first-line treatment option for advanced colorectal cancer. The response rate to 5-FU treatment has been 11%, increasing up to 23% when folinic acid (FA) is added [2]. Continuous intravenous infusion has been shown to be superior to bolus treatment [3–5]. Until the 1990s, the 5-FU/FA combination was the standard treatment approach for advanced colorectal cancer; however, in the last decade, irinotecan, capecitabine, and oxaliplatin have become the major chemotherapeutic agents. Current studies are focused on targeted therapies.

Irinotecan acts by inhibiting topoisomerase I. Its efficacy in the treatment of colorectal cancer has been shown to improve survival in patients resistant to 5-FU therapy, receiving supportive treatment for advanced colorectal cancer or 5-FU infusion therapy [6–8]. Equally, a combination treatment of irinotecan/5-FU/FA has been shown to be more effective than 5-FU/FA [9, 10] with regard to progression-free survival (PFS) and overall survival (OS).

In patients with 5-FU-refractory colorectal cancer, phase II trials of irinotecan treatment demonstrated objective response rates of 12–15% and median survivals of 8–9 months [11, 12]. Diarrhea and neutropenia were the principal adverse events. Subsequently, two phase III trials demonstrated statistically significant survival advantages for patients randomly assigned to irinotecan, compared with patients given either best supportive care or second-line infusional 5-FU [7, 8]. In both trials, irinotecan was delivered on a 3-week schedule. Although phase II efficacy and safety results with the weekly and 3-week regimens seemed to be equivalent, no formal comparison of these regimens has been performed. Fuchs et al. [13] reported a randomized phase III study on two different irinotecan second-line dosing regimens in metastatic colorectal cancer. These authors concluded that irinotecan schedules of weekly and 3-week intervals demonstrated similar efficacy and quality of life in patients with FU-refractory metastatic colorectal cancer. The regimen of once every 3 weeks was associated with a significantly lower incidence of severe diarrhea.

In this study, we aimed to investigate the response rates, toxicity, PFS, OS and factors affecting PFS and OS in patients who have advanced stage colorectal cancer treated with irinotecan as a first- or second-line treatment.

Subjects and Methods

Patient Eligibility

Inclusion criteria for the analysis of patients with histologically proven adenocarcinoma of the colon or rectum were age 18–75 years, Eastern Cooperative Oncology Group performance status of 0–2, absolute neutrophil count $\geq 1,500$ cells/ μ l, hemoglobin ≥ 8 g/dl, platelets $\geq 100,000$ / μ l, bilirubin ≤ 1.5 mg/dl, creatinine ≤ 2.0 mg/dl and ALT, AST or alkaline phosphatase levels ≤ 1.5 times the upper limit of normal in the absence of bone or liver metastasis, or ≤ 2.5 times the upper limit of normal in the presence of liver or bone metastasis, respectively. The patients all had measurable disease, all had physical examination, chest X-ray, abdominal ultrasound or computerized tomographic scan of metastatic sites; bone scan was performed when symptoms were suggestive of skeletal involvement or prior metastatic bone disease.

Response Evaluation

Assessment of toxicity (including serum chemistries and blood counts) was done every 21 days. All toxicities were evaluated and scored according to the World Health Organization scale. Radiological assessment of the tumor was repeated every 3 cycles of therapy. Complete response was defined as disappearance of all clinical and radiological evidence; partial response as 50% or greater decrease in the sum of the products of diameters of all index lesions persisting for at least one cycle of therapy. Stable disease was defined as no change in tumor size or change that was too small to qualify as progressive disease and partial-response progressive disease as either an increase of $\geq 25\%$ in the sum of the products of diameters of any index lesions, 50% increase in the estimated size of nonmeasurable lesions, or appearance of any unequivocally new lesion. PFS was calculated from the date of the start of the first cycle to the date of the event occurrence.

Treatment Plan

Irinotecan 350 mg/m² was given every 3 weeks according to treatment protocol. Treatment was stopped if the disease progressed, the patient developed unacceptable toxic effects, or consent was withdrawn. Irinotecan was administered according to the guidelines used for irinotecan monotherapy, including recommendations for the use of concurrent antiemetics, atropine, and loperamide. Doses were lowered by 20% if severe toxic effects occurred and starting doses were reduced to 300 mg/m² in patients older than 70 years having had prior radiotherapy. At the end of the treatment period, patients were followed up for progression every 3 months. Further cancer treatment was also recorded.

Statistical Analysis

The PFS and OS curves were plotted according to Kaplan-Meier estimate. Statistical analyses were carried out with log-rank tests. Patients were subgrouped for further analyses into colon vs. rectal cancer, monofocal vs. multifocal metastasis, ≤ 50 vs. >50 years and with or without peritonitis carcinomatosa. SPSS (Statistical Package for Social Sciences) version 10.0 was used for the statistical analysis; p values are significant if less than 0.05.

Results

Of the 74 patients, 38 (52%) suffered from metastatic colon cancer, 29 (39%) metastatic rectum cancer, 3 (4%) recurrent local colon cancer and 4 (5%) recurrent local rectum cancer. Liver metastasis was present in 44 patients (59%), while 29 (39%) had lung metastasis, 13 (18%) peritonitis carcinomatosa, 1 (1.3%) lymph node metastasis and 1 (1.3%) bone metastasis. Single metastasis was present in 50 (68%) patients while 24 (32%) had multiple metastasis. General characteristics of the patient population are presented in table 1. Forty-six (62%) were male and 28 (38%) female with a mean age of 56 years (19–77); 53 (72%) patients received first-line treatment and 21 (28%) second-line treatment. The mean WHO performance status was 1 (0–2). A total of 501 cycles

Fig. 1. Progression-free survival.

Fig. 2. Overall survival.

Table 1. Patient characteristics

	Patients	%
Sex		
Male	46	62
Female	28	38
Age, years	56 (19–77)	
WHO Performance Status	1 (0–2)	
Primary disease		
Metastatic colon cancer	38	52
Metastatic rectum cancer	29	39
Recurrent colon cancer	3	4
Recurrent rectum cancer	4	5
Tumor involvement		
Liver metastasis	44	59
Pulmonary metastasis	29	39
Local recurrence	11	15
Peritonitis carcinomatosa	13	19
Lymph node metastasis	1	1.3
Bone metastasis	1	1.3
Metastatic focus		
Monofocal	50	68
Multiple foci	24	32
Chemotherapy		
First-line treatment	53	72
Second-line treatment	21	28

Number of patients is given unless otherwise indicated.

(mean 6.8 cycles with a range of 1–36 cycles) of irinotecan treatment was administered. In patients with grade 3–4 toxicity, emesis occurred in 5 (7%) patients, diarrhea in 11 (15%), neutropenia in 5 (7%) and severe early cholinergic symptoms in 1 (1.3%). One patient died due to acute renal failure.

The overall response rate was 14% (complete response 5% and partial response 9%). Sixty-two percent (62%) had a stable disease, whereas progressive disease was seen in 24% of patients (table 2). The median duration of response was 16.7 months; median PFS was 4 months (fig. 1) and median OS 14 months (fig. 2). Patients with multifocal metastasis, peritonitis carcinomatosa or age ≤ 50 years did not respond as well as others, but this was not statistically significant. Liver metastasis had no adverse effects on results. Median PFS and OS time for patient subgroups are presented in table 3.

Discussion

Irinotecan has an important role in the treatment of colorectal cancer and has been proven to be effective in the treatment of metastatic colorectal cancer [6–10]. Irinotecan acts by inhibiting topoisomerase I through in vivo conversion to SN-38 [14–16]. In this study, the overall response rate (14%) and stabilization rate (61%) in

Table 2. Response rates according to subgroups

	Complete	Partial	Stable	Progression
First-line (n = 53)	3 (6)	4 (8)	33 (62)	13 (24)
Second-line (n = 21)	1 (5)	2 (10)	12 (57)	6 (28)
Monofocal metastasis (n = 50)	4 (8)	5 (10)	26 (52)	15 (30)
Multiple metastasis (n = 24)	0 (0)	1 (4)	19 (79)	4 (17)
Monofocus (n = 24) (excluding liver or peritoneum)	1 (4)	1 (4)	15 (63)	7 (29)
Liver metastasis (n = 44)	2 (5)	5 (11)	28 (64)	9 (20)
Peritonitis carcinomatosa (n = 13)	1 (8)	1 (8)	7 (54)	4 (30)
Rectum (n = 33)	1 (3)	3 (9)	21 (64)	8 (24)
Colon (n = 41)	3 (7)	3 (7)	24 (59)	11 (27)

Figures in parentheses are percentages.

Table 3. Median PFS and OS for patient subgroups

	PFS months	p	OS months	p
First-line	4	0.99	13	0.52
Second-line	4		15	
Monofocal metastasis	4	0.6	15	0.29
Multifocal metastasis	4		13	
Focus excluding peritoneum	5	0.2	15	0.2
Peritonitis carcinomatosa	4		12	
Rectal cancer	4	0.82	12	0.4
Colon cancer	5		17	
≤ 50 years	4	0.24	14	0.05
> 50 years	5		16	

patients receiving irinotecan as first-line treatment and overall response rate (15%) and stable disease rate (57%) in patients receiving irinotecan as second-line treatment are similar to reported values (18–39%) for first-line [9, 10] and second-line treatment (10.4–22.0%) [17–21]. Clinical studies have shown that diarrhea and myelosuppression are the most important toxicities of irinotecan. Uridine diphosphate glucuronyl transferase 1A1 (UGT1A1), an enzyme in hepatic glucuronidation of SN-38, is the most important factor determining toxicity and it shows genetic polymorphism [22, 23]. Prevalence of diarrhea has decreased with concomitant use of high-dose loperamide leading to increased safety of the drug.

In our study, grade 3–4 toxicity was seen in about 30% of patients. Therefore, close follow-up of patients for toxicities and dose adjustments is necessary. Due to the high

rates of early mortality related to weekly IFL treatment, oncologists decreased starting doses by 20% [24].

Analysis of previous studies revealed that parameters such as performance status, weight loss, alkaline phosphatase level, bilirubin level, leukocyte count, hemoglobin level, number of organs with metastatic involvement and liver involvement affected response rates in irinotecan therapy [25, 26]. Negative prognostic factors were investigated in this patient group. As a result, patients with multiple metastasis, patients ≤ 50 years of age and patients with peritonitis carcinomatosa had worse outcomes. In a meta-analysis of patients with metastatic colorectal cancer treated with 5-FU, an increase in the number of metastatic foci and presence of peritonitis carcinomatosa are shown to worsen the prognosis [27]. Liver metastasis did not adversely affect the results. Metastectomy after irinotecan treatment and longer PFS in some patients with liver metastasis (3 patients) are thought to improve results.

In recent years, significant improvements in the treatment of colorectal cancer occurred with the use of chemotherapeutic agents such as irinotecan, oxaliplatin and capecitabine. In recent studies, irinotecan has been used in combination with oxaliplatin [28], cetuximab [29] and COX-2 inhibitors [30] to increase its efficacy. Results of these studies will improve the response rates and quality of life scores of patients with metastatic colorectal cancer.

Conclusion

In this study, the data showed that irinotecan, as a single agent, is effective in metastatic colorectal cancer treatment with manageable toxicities.

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