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Original Article

Fluorouracil and folinic acid bolus schedule (nordic regimen) combined with irinotecan as a first-line chemotherapy in metastatic colorectal cancer

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Abstract. The recent incorporation of irinotecan (CPT-11) for the management of advanced colorectal cancer has generated further improvement in survival. The goal of this retrospective analysis was to evaluate the efficacy and toxicity of irinotecan plus bolus FU/FA (Nordic regimen) as first-line therapy in patients with advanced colorectal cancer. A total of 43 patients with metastatic colorectal cancer treated with irinotecan plus bolus FU/FA (Nordic regimen) as first-line chemotherapy were reviewed. Patients with metastatic adenocarcinoma of the colon or rectum and who had measurable disease and WHO performance status of 2 or less were treated with irinotecan 210 mg/m^2 as a 30-90 min intravenous infusion on day 1, followed by 5-FU 500 mg/m^2 and FA 60 mg/m^2 bolus on days 1 and 2, every 2 weeks, until disease progression or unacceptable toxicity. Patients were evaluated for response rates, survival and toxicity. Median patient age was 56 (29-76) years. Response rates were 72% as a carcino embryogenic antigen (CEA) level and 45% as a clinic evaluation. Disease control rates were 76% as a CEA level and 80% as a clinic evaluation. Median duration of response was 5,8 (2-9) months as a clinic evaluation and median duration of response was 6,6 (2-11) months as a CEA level. Median progression free interval was 9 (2-13) months and median overall survival was 16 (3-18) months. Grade 3-4 neutropenia occurred in 30% of the patients. Non-haematological toxicities were mild. There was no treatment-related death. Irinotecan - Nordic regimen is considered as a reasonable option for first-line treatment of patients with metastatic colorectal cancer

Key words: First-line chemotherapy,metastatic colorectal cancer, nordic regimen, irinotecan

1.Introduction

Colorectal cancer is the third most common cancer after the lung cancer and breast cancer and has a significant role in morbidity and mortality (1-3). Colorectal cancer mortality rates have been reported to decline over the years, reflecting strides made in earlier diagnosis and advances in therapeutic strategies with the identification of new agents that have been demonstrated to extend patients survival.

The primary therapy for colorectal cancer remains surgical (4,5). Although 50-60% patients may be cured with surgery, many of patients will go on develop metastatic disease after surgery (6). Furthermore it is estimated that 10-15% of patients will have detectable metastatic disease upon initial diagnosis of their tumours. Patients diagnosed with synchronous metastases that may be considered resectable may be eligible for definitive resection of the primary tumour (7). However, the main treatment in the patients with metastatic disease is chemotherapy because of the extensive nature of the disease in the majority of

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the patients. The chemotherapy is applied for palliative purposes in the metastatic disease. 5-FU is the time-tested agent for systemic chemotherapy for recurrent or metastatic colorectal cancer (MCRC). For the patients with metastatic disease the standard therapy was, until recently, treatment with 5-FU plus folinic acid, which yielded a median survival time of 10-12 months (8,9). Phase II studies in metastatic colorectal cancer demonstrated an average response rate of 36% (range 15% to 59%) to continuous infusion (CI) of 5-FU (10). Comparison of bolus and continuous infusion FU administration schedules revealed improved response rates with the infusional regimen and a slight improvement in overall survival (11-13). These observations were confirmed by a meta-analysis of six randomized trials including 1219 patients (9). The meta-analysis showed higher response rates for patients who received continuous infusion compared to patients who received bolus 5-FU and continuous infusion was more tolerable than bolus 5-FU. Nevertheless, survival results were not satisfactory with these 5-FU schedules. Therefore, the new agents or combinations are needed for the treatment of MCRC. Irinotecan, raltitrexed, capecitabine and oxaliplatin are frequently used in MCRC (14-22).

Irinotecan is a potent inhibitor of topoisomerase I and exerts its cytotoxicity through the inhibition of DNA replication. The sensitivity of colorectal tumours to irinotecan, combined with a mechanism of action distinct from that of 5-FU, provided the rationale for the combination of these agents in the treatment of patients with advanced disease. Based on phase II and phase III results, irinotecan plus FU/FA regimens were accepted as a standard therapy in the first-line treatment of MCRC. Although irinotecan plus FU/FA were more effective than FU/FA alone, currently, debates about treatment schedule and doses of these agents are going on. The goal of this retrospective analysis was to evaluate the efficacy and toxicity of irinotecan plus bolus FU/FA (Nordic regimen) as a first-line therapy in patients with advanced colorectal cancer.

2. Materials and methods

2. 1. Patients

Patients with histologically confirmed diagnosis of metastatic adenocarcinoma of the colon or rectum were included in this retrospective analysis. Irinotecan plus bolus FU/FA (Nordic regimen) was administred as first line chemotherapy. All patients had at least one measurable metastatic lesion and no potentially resectable metastases. All the patients had adequate performance (ECOG 0-2) status and renal, hepatic and hematological functions. Pre-treatment evaluation included a complete medical history, physical examination, complete blood cell counts, blood chemistry, carcino-embryogenic antigen (CEA), chest X-Ray, ultrasound of the abdomen and computed tomography of the abdomen and/or thorax in cases based on assessable target lesions.

2. 2. Treatment plan

Patients were treated with 210 mg/m^2 irinotecan (dissolved in 500 ml of 5% dextrose or saline solution) as a 30-90 min intravenous infusion on day 1, followed by 5-FU 500 mg/m^2 and FA 60 mg/m^2 bolus on days 1 and 2, every 2 weeks. 5-FU was administered immediately after irinotecan administration and folinic acid was administred 30 min later from 5-FU administration. Before chemotherapy, standard premedication procedures were performed. The next treatment course was given on schedule if there was no evidence of tumor progression and the following criteria were met: hemoglobin ≥9.0 g/dL (after transfusion if necessary), neutrophils ≥1,500/μL, and platelets ≥100,000/μL. Dose reduction for the following course, in 25% decrements, was applied if a patient had manifested any of the following: grade 4 neutropenia with fever or infection or lasting ≥7 days, grade 3 neutropenia lasting beyond day 21, grade 4 thrombocytopenia and grade 3/4 diarrhea or stomatitis. Patients continued with therapy until disease progression (PD) or unacceptable toxicity. Patients with stable disease continued on therapy for at least four courses or until the investigator felt that it was in the patient's benefit to discontinue treatment. Patients with a complete response (CR) or partial response (PR) by World Health Organization criteria were allowed to continue until disease progression.

All patients underwent complete physical examination and assessment of toxicity (including blood counts and biochemical parameters) every 14 days. Radiological assessment was repeated at every 4 cycles of therapy.

2. 3. Response evaluation

Primary efficacy criteria were response rate and progression free survival, secondary efficacy criteria were duration of response and overall

Table 1. Patients' characteristics

No. of patients	43
Median age (year)	56 (29-76)
Male [No. (%)]	29 (67)
Female [No. (%)]	14 (33)
Median performance status (ECOG)	1
Rectum carcinoma [No. (%)]	22 (51)
Colon carcinoma [No. (%)]	21 (49)
No. assessable for clinic-radiologic response (%)	43 (100)
No. assessable for CEA response (%)	25 (58)
No. assessable for toxicity (%)	43 (100)
Stage at the time of the diagnosis [No. (%)]	
I	0
II	5 (12)
III	15 (35)
IV	23 (53)
Histologic type [No. (%)]	
Adeno Carcinoma	43 (100)
Cellular differentiation [No. (%)]	
good	1 (2)
Intermediate	25 (58)
poor	6 (14)
unknown	11 (26)
Localization of metastasis [No. %]	
Liver	30 (70)
Periton	8 (19)
Lung	11 (26)
Lymph node	4 (9)
Bone	2 (4)
Spleen	1 (2)
Prior curative surgery [No. (%)]	20 (46)
Prior palliative surgery [No. (%)]	13 (30)
Prior adjuvant chemotherapy [No (%)]	17 (39)
Prior adjuvant radiotherapy [No (%)]	8 (17)

survival. Response was assessed by both clinical and serological parameters (CEA). Tumour response was assessed according to WHO criteria [complete response (CR), partial response (PR), minor response, stable disease and progressive disease. A complete clinical response was defined as the complete disappearance of all known disease, including return of CEA to normal limits for at least 4 weeks. A partial clinical response was defined as a 50% or greater decrease of measurable lesions. A partial CEA response was defined as a 50% decrease in serum CEA levels. The overall response rate was defined as the percentage of patients with CR or PR. The duration of response was calculated from the date of first infusion to the first date of documented progression. A clinical progressive disease was defined as a 50% or greater increase of

measurable lesions. Serologically progressive disease was defined as a 50% or greater increase in serum CEA levels. Stable disease was defined as disease that did not fulfill the criteria for partial clinical response or clinically progressive disease. Serologically stable disease was defined as disease that did not fulfill the criteria for serological partial response or progressive disease. Serological and clinical disease control rates were defined as the complete or partial response plus stable disease.

2. 4. Survival analysis

Progression free survival (PFS) was calculated from the date of treatment allocation to the first objective evidence of tumour progression and overall survival (OS) was calculated from the date of treatment allocation to the death due to progression. PFS and OS were calculated with Kaplan-Meier method. SPSS (Statistical Package for Social Sciences) v.11.5 software was used for statistical analysis.

2. 5. Toxicity

Patients were evaluated for hematological and non-hematological toxicities and were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria.

3. Results

3. 1. Patients

A total of 43 patients with metastatic colorectal cancer admitted to Ege University School of Medicine Department of Medical Oncology and SSK Izmir Hospital, Department of General Surgery between August 2003 and August 2004 were included in this retrospective analysis. Twenty-nine (67%) patients were male and 14 (33%) patients were female. Twenty-two (51%) patients were diagnosed with rectum adenocarcinoma and 21 (49%) patients were diagnosed with colon adenocarcinoma. Median patient age was 56 (range 29-76). Patients received 330 cycles of irinotecan-Nordic regimen (median: 8, range 2-18). Forty-three patients were assessable for clinical response, 25 patients were assessable for serological response and 43 patients were assessable for toxicity. All the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (mean 1). Seventeen (39%) patients previously received adjuvant chemotherapy and 8 (17%) patients previously received adjuvant radiotherapy. Twenty (46%) patients had curative surgery and 13 (30%) patients had palliative surgery. Histopathologically, all the patients had adenocarcinoma. Liver (70%), lung (26%), periton (19%), lymph node (9%) were most frequently affected sites. Patients' characteristics are illustrated in table I.

3. 2. Response evaluations

Twenty-five of 43 patients were evaluated for CEA response and all patients were evaluated for clinical response. Response rates were 72% as a CEA level and 45% as a clinic evaluation. Disease control rates were 76% as a CEA level and 80% as a clinic evaluation. Median duration of response was 5,8 (2-9) months as a clinic evaluation and 6,6 (2-11) months as a CEA level. Table II describes the clinical and serological response results.

Table 2. Clinical and serological response results

Clinical response (no:43)	no (%)	Serological response (no:25)	no (%)
CR	2 (5)	CR	5 (20)
PR	17 (40)	PR	13 (52)
SD	15 (35)	SD	1 (4)
PD	9 (20)	PD	6 (24)

CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease

3. 3. Survival analysis

Median follow-up was 12 (3-18) months. Progression free survival curve is shown in figure I and overall survival curve is shown in figure II. Median progression free interval was 9 (2-13) months (95% CI 6.74; 11,26) and median overall survival was 16 (3-18) months (95% CI 14,51; 17.49). Progression free survival was 21% at 12^{th} month and overall survival was 73% at 12^{th} month and 30% at 18^{th} month.

3. 4.Toxicity analysis

A total of 330 cycles with a median of 8.0 cycles (range: 2-18) were administered to the patients. Grade 3-4 neutropenia occured in 30% of the patients. Neutropenic fever was only seen 3 (7%) of 43 patients. There was no treatment-related toxic death. No patients needed erytrocyte and platelet support. Fifteen (35%) of 43 patients used colony stimulating factor (G-CSF) due to severe neutropenia. Two (5%) patients had their dose reduced (25% dose reduction) because of

Table 3. Treatment related toxicity results

	G1-2 [No. (%)]	G3 [No. (%)]	G4 [No. (%)]
Leucopenia	13 (30)	7 (16)	1 (2)
Neutropenia	10 (23)	10 (23)	3 (7)
Thrombocytopenia	3 (7)	0	0
Anemia	7 (16)	0	0
Nausea	16 (37)	2 (5)	0
Vomiting	4 (9)	1 (2)	0
Stomatitis	8 (19)	2 (5)	0
Diarrhea	15 (35)	6 (14))	0
Weakness	19 (44)	1 (2)	0
Anorexia	14 (32)	1 (2)	0
Dispepsia	1 (2)	0	0
Alopesia	7 (19)	3 (7)	-
Acute colinergic sendrom	4 (9)	0	0
Liver toxicity	3 (7)	0	0

heamatologic toxicity. In twenty two (7%) of 330 cycles, chemotherapy were delayed for one week because of heamatologic and nonheamatologic toxicity. Nonhaematologic toxicities were mild. Most frequently non-hematologic toxicities were diarrhea (49%), weakness (46%), nausea (42%), anorexia (34%), alopecia (26%) and stomatitis (24%). Grade III/IV non-haematological adverse events were uncommon and included diarrhea (14% of patients), alopecia (7% of the patients), nausea (5% of patients) and stomatitis (5% of patients). Hepatic tolerance was excellent. All side effects were reversible and manageable. Table III describes the treatment related toxicity results.

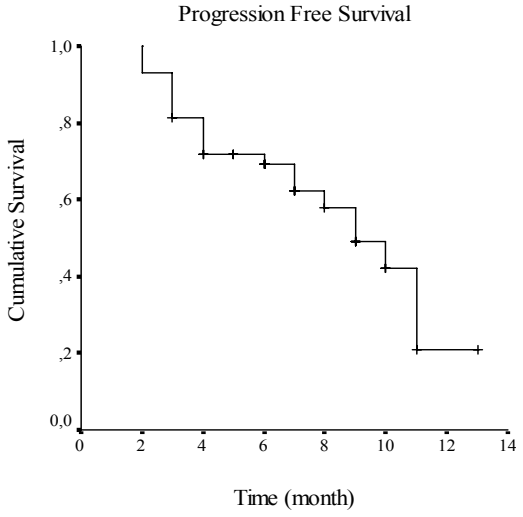

Fig. 1. Progression free survival (Kaplan-Meier).

4. Discussion

After phase II trials, initially, irinotecan was used as second-line therapy in MCRC (23,24). Based on the results of phase II trials, two randomized phase III trials conducted the use of irinotecan in combination with 5-FU/FA in the first-line treatment of MCRC (14,25). Although irinotecan plus 5-FU/FA were more effective than 5-FU/FA alone, currently, debates about treatment schedule (weekly or biweekly and bolus regimens or infusional regimens) and doses of this agents are on going.

The two phase III trials described above, enrolling a total of 1070 patients, provide overwhelming support for the use of irinotecan + 5-FU/FA in the first-line treatment of MCRC.

In Douillard study (25), the response rate was 49% in the irinotecan group, compared with 31% in the no-irinotecan group ($p<0{\cdot}001$). Overall response rates were 33% in irinotecan-de Gramont arm and %39 in irinotecan-AIO arm. Median progression free intervals were 6.5 months in irinotecan-de Gramont arm and 7.2 months in irinotecan-AIO arm. Overall survivals were 66.7% in irinotecan-de Gramont arm and 75% in irinotecan-AIO arm at 12^{th} month. Grade 3 or 4 neutropenia and leucopenia were significantly more frequent in the irinotecan group than in the no-irinotecan group. With the 2-weekly regimen, diarrhea was more frequent in the irinotecan group than in the no-irinotecan group, and the difference was close to significance in the weekly regimen. This adverse effect occurred more frequently with the weekly

than with the corresponding 2-weekly regimen in the two treatment groups. Among patients receiving the weekly regimen, diarrhea led to hospital admission for 17 (31·5%) in the irinotecan group and five (11·6%) in the no-irinotecan group. For the 2-weekly regimen, 16 (11·0%) patients in the irinotecan group and two (1·4%) in the no-irinotecan group were admitted for diarrhea. Diarrhea was the main reason for dose reduction or discontinuation of treatment in the weekly regimen, and neutropenia was the main reason for dose delay in the 2-weekly regimen.

In Saltz study (14), overall response rate was 39%, and median progression free intervals were 7 months in irinotecan-bolus 5-FU/FA arm. Median overall survival was 14.8 months in irinotecan-bolus 5-FU/FA arm. Grade 3 (severe) diarrhea was more common during treatment with irinotecan, fluorouracil, and leucovorin than during treatment with fluorouracil and leucovorin, but the incidence of grade 4 (life-threatening) diarrhea was similar in the two groups (<8 percent). Grade 3 or 4 mucositis, grade 4 neutropenia, and neutropenic fever were less frequent during treatment with irinotecan, fluorouracil, and leucovorin.

These studies evaluated irinotecan combined with either bolus (Saltz) or infusional 5-FU/LV (Douillard) in previously untreated patients with metastatic colorectal cancer. Both studies demonstrated statistically significant clinical benefits with the irinotecan/5-FU/LV combinations, including improved tumor control and prolonged survival. In both studies, approximately 23% of patients treated with the combination irinotecan/5-FU/LV regimens experienced grade 3-4 diarrhea compared with approximately 10% to 14% of patients receiving 5-FU/LV alone. Of note, grade 3-4 mucositis was quite infrequent with irinotecan-based therapy, occurring in <4% of patients receiving combination therapies. By contrast, the Mayo Clinic schedule commonly employed as first-line therapy in North America was associated with a much higher frequency of severe, grade 3-4 mucositis (17%) (26).

Glimelius et al (27) evaluated the efficacy and safety of irinotecan combined with the Nordic bolus schedule of 5-FU/FA as first-line therapy in patients with advanced colorectal cancer. In this phase II trial, overall response rate and tumour growth control rate were reported 39% and 84%, respectively. Median survival time and median time to progression were reported 15,6 months and 6.4 months respectively. Neutropenia was the main adverse event with NCI-CTC grade 3–4 toxicity occurring in 66% of patients and 17.5% of cycles. Two patients (3%) experienced febrile neutropenia and six patients (8%) had grade 3 and grade 4 infections with grade 3–4 neutropenia. No

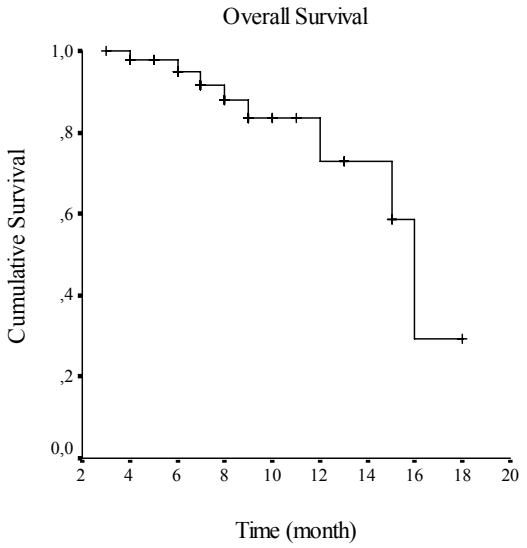

Fig. 2. Overall survival (Kaplan-Meier).

patient experienced severe anemia or thrombocytopenia. Overall non-haematologic toxicities, grade 3–4 adverse events were uncommon and included diarrhea (16% of patients and 1.7% of cycles), nausea (11% of patients and 1.2% of cycles), vomiting (9% of patients and 0.9% of cycles), pain, anorexia or constipation (3% of patients and 0.3% of cycles), stomatitis or fatigue (3% of patients and 0.2% of cycles). Hepatic tolerance was excellent. Grade 3 toxicity was observed for bilirubin increase in two patients (3%). Twenty-seven patients (36%) experienced grade 2 alopecia.

In our retrospective analysis, response rates were 72% as a CEA level and 45% as a clinic evaluation. Disease control rates were 76% as a CEA level and 80% as a clinic evaluation. Median duration of response was 5,8 (2-9) months as a clinic evaluation and median duration of response was 6,6 (2-11) months as a CEA level. Median progression free interval was 9 (2-13) months and median overall survival was 16 (3-18) months. Irinotecan-Nordic regimen was effective and this regimen can be accepted alternative regimen in MCRC. The predominant toxicity observed with irinotecan plus Nordic regimen is neutropenia. However, treatment related myelosupression in generally noncumulative, reversible, and predictable. Febrile neutropenia is infrequent. In our retrospective analysis, grade 3-4 neutropenia occurred in 30% of the patients. Neutropenic

fever was seen only 3 (7%) of 43 patients. There was no drug-related toxic death. Thirty-five percent of 43 patients required colony stimulating factor (G-CSF). Two (5%) patients had their dose reduced (25% dose reduction) because of heamatologic toxicity. Irinotecan-Nordic regimen were uncommon.

In conclusion, irinotecan plus bolus 5-FU/FA (Nordic regimen) is an effective regimen as a first-line chemotherapy in MCRC. Alternative schedules may provide higher tumor response rates and less myelosupression compared with the irinotecan-Nordic regimen. Neverthless, randomized controlled studies are necessary to directly compare these alternative regimens with Nordic regimen.

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