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IRINOTECAN, FLUOROURACIL AND LEUCOVORIN IN PATIENTS WITH METASTATIC COLORECTAL CANCER

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RESUME:

Background: Irinotecan is a topoisomerase I inhibitor that prolongs survival as second- line therapy in patients with metastatic colorectal cancer, treated with Fluorouracil and Leucovorin only. **Aim:** The aim of this study was to evaluate the efficacy and toxicity of the combination Irinotecan, Fluorouracil and Leucovorin. **Methods:** In the period 2006- 2007 34 patients with metastatic colorectal cancer entered the study. The treatment schedule consists of Irinotecan 180 mg/m2 day 1, Fluorouracil 400 mg/m2 day 1 and 2 and Leucovorin 200 mg/m2 day 1 and 2 every 14 days. **Results:** Overall response rate was 36,7% with three complete remissions. Median survival was 20,3 months. Diarrhea, vomiting and mucositis were most common side effects. **Conclusions:** That data suggest that the addition of Irinotecan to Fluorouracil and Leucovorin will offer opportunity to treat patients with metastatic colorectal cancer.

Key words: Irinotecan, Colorectal cancer, Treatment, Survival

INTRODUCTION

Colorectal cancer /CRC/ is the third most common cause of cancer death and the second most lethal cancer overall /1/. Although surgery is potentially curative, about one- third of all newly diagnosed patients presents with inoperable metastatic disease. Palliative chemotherapy is more effective than the best supportive care in improving survival as well as the quality of life in advanced CRC /2/. 5- Fluorouracil /FU/ is the most commonly used agent for treatment of metastatic CRC in last 45 years /3/. A fluorinated pyrymidine, FU acts by inhibiting thymidylate synthase, an enzyme necessary for the production of thymidine nucleotides required for DNA synthesis. FU is usually given in combination with leucovorin /LV/, a biomodulating agent that increases the binding of FU with to thymydilate synthase, thereby increasing the inhibition of DNA synthesis and enhancing the antitumour effect of FU. This approach has increased response rate from 11% for FU alone to 23% with FU/LV but has provided no meaningful survival benefit - median survival 11.0 months with FU alone vs. 11,5 months with FU/LV /4/.

Irinotecan, a topoisomerase I inhibitor, offers mechanism of action completely different from those of FU in the treatment of CRC. Irinotecan and its metaboites bind to a complex of DNA and topoisomerase I /an enzyme required for unwinding of DNA during replication/, inducting DNA strand breaks and consequent tumour death /4/. Irinotecan has shown antitumour activity in patients with CRC when administered alone as first- line therapy or as second- line therapy after FU failure. In two randomized phase III studies in patients who experienced failure of first–line therapy with FU, Irinotecan was compared with either best supportive care or with intensive FU based infusional therapy. Both studies showed a statistically significant survival benefit for patients treated with Irinotecan /5/. The activity of Irinotecan against untreated and FU-resistant colorectal cancer led to studies of this agent in combination with FU/LV as first- line therapy for this disease /6,7/.

The aim of this study was to evaluate the efficacy and toxicity of the combination Irinotecan, Fluorouracil and Leucovorin in patients with metastatic colorectal cancer.

PATIENTS AND METHODS

Thirty-four patients with metastatic colorectal cancer, treated in the period 2006- 2007 in Medical university-Pleven, Oncological center, Department of chemotherapy entered the study. Participants needed to be between 18 and 75 years of age. Eligibility criteria included histologically documented adenocarcinoma of the colon or rectum, progressive measurable metastatic disease, life expectancy of minimum three months, World Health Organisation /WHO/ performance status 0 to 2, no prior chemotherapy for metastatic disease, adequate bone marrow function / absolute granulocyte count $>1,5x10^9$/L, platelet count $> 140x10^9$/L/ as well as normal renal /serum creatinine level < 1,5 jmol/L/ and hepatic function /serum bilirubin level < 21 jmol/L/, absence of active infections, no overt cardiac disease and at least one measurable tumour lesion. Measurable disease was assessed by computed tomography scan. This study required that previous adjuvant FU- based therapy be completed at least 6 months prior start of

treatment. Patients with central nervous system metastases, bowel obstruction or ileus were excluded from the study. The treatment schedule consists of Irinotecan 180 mg/m2 day 1, Fluorouracil 400 mg/m2 day 1 and 2 and Leucovorin 200 mg/m2 day 1 and 2. Treatment was administered every 2 weeks until progression. Patients were evaluated for tumour response before treatment and after third and sixth course of chemotherapy. Tumour response was evaluated according to WHO response criteria /8/. Response was defined as complete response (CR), partial response (PR), no change (NC), or progressive disease (PD).

A CR was defined by the disappearance of all known disease, confirmed by two observations not less than 4 weeks apart. PR was defined as a decrease in tumour size of 50% or more (either measured or estimated in the case of measurable or assessable disease). In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumour response included both confirmed CR and PR.

Safety was assessed using the WHO toxicity criteria /9/.

The duration of response was calculated from the day of the start of treatment to disease progression; overall survival was measured from study entry to death. The time to disease progression was calculated from study entry until the day of the first evidence of disease progression. The actuarial survival was estimated by the method of Kaplan and Meyer /10/.

RESULTS

A total of 34 patients were entered in the study over a 24- months period. All patients, regardless of their length of treatment, were included in analysis. Antitumour effects were evaluated for all 34 cases. Some patient's characteristics are listed in Table 1. The safety was assessed in all 34 patients. Median treatment period was 5,5 months. The median follow-up period was 16,5 months.

Antitumour effects

The resulting antitumour effects are presented in Table 2. Three complete and eight partial remissions were obtained. The overall response rate /ORR/ was 36,7 % (11 of 34), showing that chemotherapy had induced a significant efficacy. Median time to disease progression was 6,5 months. A one- year survival rate was 79.5%.

Safety

Table 3 and 4 presents the incidence of haematological and nonhaematological adverse drug reactions that occurred in entire group. The highest incidence was gastrointestinal, haematology and mucositis. Most of these symptoms were rated as grade II or I and chemotherapy was not stopped or delays. Grade III- IV gastrointestinal and haematology toxicity was observed in 16,4 % of the patients and never was fatal.

DISCUSSION

In the current study we evaluated efficacy and safety of the combination of Irinotecan with Fluorouracil and Leucovorin as first- line chemotherapy for metastatic colorectal cancer. Irinotecan- containing regimes have been the most commonly used chemotherapy protocols for metastatic colorectal cancer. Response rate- 36,7% is promising. These results are comparable with previously published data . In these studies response rate were 40-56% with time to progression of 6-8 months. Tumour control /CR= PR+ SD/ was achieved in 85% of patients with survival duration- 20,3 months and is similar to other reports /11,12/

In the majority of patients the chemotherapy regimen was well tolerated. Both haematological and nonhaematological toxicity was mild to moderate and chemotherapy was not stopped because of toxicity. Gastrointestinal toxicity or mucositis never was fatal. Delayed diarrhea, a well-known side effect of Irinotecan was generally managed with loperamide, which was administered to approximately one third of patients.

In conclusion, the results of the present study indicate that this combination appears promising with of survival rate of 20,3 months and low toxicity.

Table 1. Patient characteristics

Patient characteristics	Number of patients
Age (years)	39 – 72
Sex	
Males	19
Females	15
Primary tumour site	
Colon	16 (47,1%)
Rectum	18 (52,9%)
Dominant site of metastasis	
Liver	19 (55,8%)
Lung	9 (26,4%)
Local relapse	4 (11,9%)
Peritoneum	2 (5, 9%)
N of metastatic sites	
1	24 (70,4%)
2	8 (23,5%)
3	2 (6,1%)
Previous treatment	
Surgery	14 (41,1%)
Surgery+ radiotherapy	5 (14,7%)
Surgery+ chemotherapy	15 (44,2%)
Performance status	
0	13 (39,2%)
1	18 (52,8%)
2	3 (8.0%)

Table 2. Objective responses

Patients/Response	CR	PR	NC	PD	ORR%
34	3	8	18	5	36,7%

ORR= CR + PR .

CR - complete response; PR - partial response; NC - no change; PD - progressive disease; ORR - overall objective response rates;

Table 3. Adverse drug reactions by symptoms: grade 3 and 4 non-hematological toxicities

Adverse drug reactions	Number of patients
Nausea	8 (23,5 %)
Acute diarrhea	2 (5,8 %)
Delayed diarrhea	4 (11,7 %)
Mucositis	6 (11,7 %)
Fever	1 (2,9 %)
Obstipatio	2 (5,8 %)
Alopezie	2 (5,8 %)
Abdominal pain	2 (5,8 %)

Table 4. Adverse drug reactions by symptoms: grade 3 and 4 haematological toxicities

Adverse drug reactions	Number of patients
Leucopenia	5 (14,7 %)
Thrombocytopenia	4 (11,2 %)
Anaemia	2 (5,8 %)

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