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OUR EXPERIENCE WITH IRINOTECAN AND BOLUS FLUOROURACIL / LEUCOVORIN IN THE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER

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RESUME:

Background: Irinotecan is a topoisomerase I inhibitor that prolongs survival as first- line therapy in patients with advanced or metastatic colorectal cancer **Aim:** The aim of this study was to evaluate the efficacy and toxicity of Irinotecan combined with bolus Fluorouracil and Leucovorin. **Methods:** In the period 2006- 2008 38 consecutive patients with metastatic colorectal cancer entered the study. The treatment schedule consists of Irinotecan 180 mg/m^2 i.v. day 1, Fluorouracil i.v. bolus 450 mg/m^2 days 2- 5 and Leucovorin i.v. bolus 35 mg/m^2 day 2- 5 with repetition every 21 days. **Results:** Overall response rate was 34,2% with two complete remissions. Median survival was 15,4 months. Diarrhea, nausea, vomiting and mucositis were most common side effects. **Conclusions:** The combination of Irinotecan with bolus Fluorouracil / Leucovorin as first- line therapy for patients with metastatic colorectal cancer offer consistently improved tumour control and prolonged survival.

Key words: Metastatic colorectal cancer, First- line reatment, Irinotecan, Response rate

INTRODUCTION

Colorectal cancer /CRC/ is the third in the league cancer death worldwide with more than 204 000 deaths in Europe each year /1/. Approximately 25% of CRC patients presents with overt metastases, and an additional 25- 35% of patients will develop metastases during the course of their disease /2/. Significantly between 20% and 30% of patients with advanced CRC have liver only metastases, while approximately 50% of recurrences following resection of primary tumour are localized to the liver /3/. Liver resection offers the only chance of cure for such patients, with five-year survival rates following resection range between 25% and 40% compared with between 0% and 5% for patients who did not undergo liver resection /4/. However, approximately 85% of patients with stage IV CRC have metastatic liver disease which is considered to be unresectable at presentation /5/. Palliative chemotherapy is more effective than the best supportive care in improving survival as well as the quality of life in such patients /6/. 5-Fluorouracil /FU/ is the most commonly used agent for treatment of metastatic CRC for over 50 years /7/. A

fluorinated pyrymidine, FU acts by inhibiting thymidylate synthase, an enzyme necessary for the production of thymidine nucleotides required for DNA synthesis. There are preclinical in vitro, as well as clinical in vivo, data that suggest that FU had a schedule- dependent mechanism of action. When the agent is delivered by a short- duration bolus, it mainly inhibits RNA synthesis. When FU is delivered by long- term infusion lasting days to weeks, it mainly inhibits DNA synthesis /8/. 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 /9/.

In the 1990s, two additional agents, Irinotecan and Oxaliplatin, was found to have activity against advanced CRC. 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 /10/. Irinotecan has demonstrated antitumorogenic activity in patients with CRC when administered alone and in combinations with FU/FA. In the first- line setting of metastatic CRC two randomized multicenter phase III clinical trials demonstrated synergistic activity of Irinotecan with both bolus and infusional FU/FA regimens. In both studies, combinations of Irinotecan and FU/FA were superior to the control arms, Irinotecan alone or FU/FA, specifically in regard to response rate, progression- free and overall survival/11/.

The aim of this study was to evaluate the efficacy and toxicity of the combination Irinotecan and bolus Fluorouracil/ Leucovorin in patients with metastatic CRC.

PATIENTS AND METHODS

Thirty- eight patients with metastatic colorectal cancer, treated in the period 2006- 2008 in Medical University- Pleven, Oncological center, Department of chemotherapy, entered the study. Participants needed to be between 18 and 75 years of age. To be eligible, patients had to have 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 μmol/L/ and hepatic function /serum bilirubin level < 21 μmol/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 12 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 i.v. day 1, Fluorouracil i.v. bolus 450 mg/m^2 days 2- 5 and Leucovorin i.v. bolus 35 mg/m^2 day 2- 5 with repetition every 21 days 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 /12/. 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.

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 /13/.

RESULTS

A total of 38 patients were enrolled in the study over a 36- months period. Data were collected for an additional 12 months after accrual ended, with data on survival collected through March 2009. All patients, regardless of their length of treatment, were included in analysis. Antitumour effects were evaluated for all 38 cases. Some patient's characteristics are listed in Table 1. The safety was assessed in all 38 patients. Median duration of treatment was 6,5 months. The median follow- up period was 18,5 months.

Efficacy

The resulting antitumour effects are presented in Table 2. Two complete and eight partial remissions were obtained. The overall response rate /ORR/ was 34,2 % (13 of 38), showing that chemotherapy had induced a significant efficacy. Median time to disease progression was 7,5 months. A one- year survival rate was 71,5 %. Median survival was 15,4 months.

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 bolus Fluorouracil and Leucovorin as first- line chemotherapy for metastatic CRC. Irinotecan- containing regimes have been the most commonly used chemotherapy protocols for metastatic colorectal cancer. Response rate- 34,2% 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 75% of patients with survival duration- 15,4 months and is similar to other reports /14,15/

In the majority of patients the chemotherapy regimen was well tolerated. Both haematological and non-haematological 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 15,4 months and low toxicity.

Table 1. Patient characteristics

Patient characteristics	Number of patients
Age (years)	38 – 74
Sex	
Males	23 (60,5%)
Females	15 (39,5%)
Primary tumour site	
Colon	14 (36,8%)
Rectum	24 (63,2%)
Dominant site of metastasis	
Liver	23 (60,5%)
Lung	12 (31,6%)
Peritoneum	3 (7,9%)
N of metastatic sites	
1	26 (68,4%)
2	9 (23,7%)
3	3 (7,9%)
Previous treatment	
Surgery	14 (36,8%)
Surgery+ radiotherapy	6 (15,7%)
Surgery+ chemotherapy	18 (47,5%)
Performance status	
0	13 (34,2%)
1	17 (44,7%)
2	8 (21,1%)

Table 2. Objective responses

Patients/ Response	CR	PR	NC	PD	ORR%
38	2	11	19	6	34,2%

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
Acute diarrhea	6 (15,7 %)
Delayed diarrhea	3 (7,8 %)
Mucositis	3 (7,8 %)
Nausea	6 (15,7 %)
Fever	1 (2,6 %)
Obstipatio	2 (5,2 %)
Alopezia	2 (5,2 %)
Abdominal pain	2 (5,2 %)

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

Adverse drug reactions	Number of patients
Leucopenia	6 (15,7 %)
Thrombocytopenia	3 (7,8 %)
Anaemia	2 (5,2 %)

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