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BEVACIZUMAB COMBINED WITH IRINOTECAN, 5- FLUOROURACIL AND LEUCOVORIN AS THE FIRST- LINE TREATMENT IN PATIENTS WITH METASTATIC COLORECTAL CARCINOMA

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SUMMARY:

Objective: Bevacizumab improved survival when added to chemotherapy for patients with metastatic colorectal cancer (mCRC). The aim of this study was to explore the efficacy and safety of Bevacizumab containing chemotherapy regimen in the treatment of patient with mCRC.

Methods: From January 2010 to March 2012 twenty two consecutive patients with inoperable mCRC entered the study. Treatment schedule consist of intravenous Irinotecan 180 mg/m2 on day 1, Leucovorin 200 mg/m2 administered as intravenous infusion on day 1 and 2 and 5- Fluorouracil 400 mg/m2 bolus and Bevacizumab 5 mg/kg as an intravenous infusion with repetition every two weeks.

Results: Overall response rate was 31,9% with one complete response and six partial responses achieved. The overall survival time was 16,6 months. The main toxicities observed were leukopenia and diarrhea.

Conclusions: That data suggest that chemotherapy with Irinotecan/ 5- Fluorouracil/ Leucovorin and Bevacizumab remain reasonable regimen for the treatment of patients with mCRC.

Key words: Bevacizumab, Chemotherapy, Metastatic colorectal cancer, Survival

INTRODUCTION

Colorectal cancer (CRC) is currently the third most diagnosed cancer in men and the second in women worldwide, with an estimate of over 1,2 million new cases and 608,700 deaths in 2008 [1]. Although surgery is potentially curative, about 50% of patients with stage III cancer and 20% of patients with stage II cancer are destined to develop distant metastases [2]. Prognosis in these patients is poor although palliative chemotherapy is more effective than the best supportive care in improving survival as well as the quality of life. 5- Fluorouracil (FU) is the most commonly used agent for treatment of metastatic CRC (mCRC) in last 45 years [3]. 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 to thymidylate synthase, thereby increasing the inhibition of DNA synthesis and enhancing the antitumor 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 versus 11,5 months with FU/LV. Owing to the limited response of FU/FA treatment obtained in mCRC patients, other therapeutic agents with different mechanisms were considered. Irinotecan, a potent topoisomerase I inhibitor (an enzyme required for unwinding of DNA during replication), offers mechanism of action completely different from those of FU. Irinotecan and its metabolites bind to a complex of DNA and topoisomerase I, inducting DNA strand breaks and consequent tumor death [4]. Irinotecan has shown antitumor activity in patients with mCRC when administered alone as first- line therapy or as second- line therapy after FU failure. Despite these improvements, nearly all patients with mCRC will die from their disease.

In the past decade, significant improvements have been performed in response rate (RR), progression- free survival (PFS) and overall survival (OS) in patients with mCRC. New therapeutic agents targeting molecular events involved in colorectal carcinogenesis have been developed, including Bevacizumab, a recombinant humanized monoclonal antibody, which binds to the vascular endothelial growth factor (VEGF) with a high specificity and prevents its interaction with receptors on endothelial cells. VEGF plays a key role in angiogenesis, which is involved in the development of carcinogenesis, tumor growth and malignant dissemination. Therefore, Bevacizumab inhibits the activation of VEGF- receptor mediated signaling pathways and resultant biological effects [5]. This antiangiogenic agent, added to a FU/LV ± Irinotecan- based chemotherapy as first- line treatment, has been shown to improve RR and survival of mCRC patients when compared to the chemotherapy alone [6-8].

The aim of our study is to evaluate the activity and safety of Bevacizumab combined with chemotherapy with FU/LV and Irinotecan as first- line therapy in patients with mCRC.

PATIENTS AND METHODS

Twenty- two patients with mCRC, treated in the period 2010-2012 in Department of Medical Oncology, UMHAT "Dr Georgi Stranski", Medical University- Pleven entered the study. Eligibility criteria included age between

18 and 75 years, 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 mcrmol/L) and hepatic function (serum bilirubin level < 21 mmol/L), and absence of active infections. Measurable disease was assessed by computed tomography scan. This study required that previous adjuvant FU/LV- based therapy to be completed at least 6 months prior start of treatment.

Exclusion criteria included bowel obstruction or ileus, thromboembolism that required therapeutic anticoagulation, central nervous system metastasis and major surgery within 6 weeks, nonhealing wounds, uncontrolled hypertension, pregnant or lactating women, bleeding diathesis, active or recent cardiovascular disease or cerebrovascular accident.

The treatment schedule consists of Irinotecan 180 mg/m2 administered in 500 mL normal saline or dextrose as a 2- hours intravenous infusion on day 1. LV (40 mg/m2) was administered as 1 -hours intravenous infusion on day 1 and day 2, immediately followed by FU (400 mg/m) given as a bolus. Bevacizumab administration always followed chemotherapy. Bevacizumab was given at 5 mg/kg as an intravenous infusion. The first infusion of Bevacizumab was given over 90 min, the second over 60 min, and if both were well tolerated, subsequent infusions were given over 30 min. No premedication was given. Treatment was administered every 2 weeks until the disease progressed, unacceptable toxic effects developed, or the patient refused further treatment. Dose modifications of Irinotecan or FU were made for hematological or non- hematological toxicity, on the basis of the most severe grade of toxicity that occurred during the previous cycle. Treatment was delayed until the absolute number of neutrophils was > 1,5x10^9/L, platelets were > 100x10^9/L, and recovery occurred from mucositis, diarrhea, or skin toxicity to grade 1 or less. The FU dose was reduced after the occurrence of National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 diarrheas, stomatitis or dermatitis. For toxicity of grade 3 or higher, a dose reduction of irinotecan by 20% was prescribed. Bevacizumab was retained for uncontrolled hypertension or proteinuria of > 2g in 24 hours. Bevacizumab was discontinued for grade 3 or 4 bleeding, thromboembolic events that required full dose anticoagulation, or any grade 4 toxicity.

Patients were evaluated for tumor response after third and sixth course of chemotherapy. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors [9]. 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 four weeks apart. PR was defined as at least a 30% decrease in the sum of the longest diameter of a target lesions, taking as a reference point the baseline sum's longest diameter. In addition, there could be no appearance of any new lesions or progression of any known lesion(s). Objective tumor response included both confirmed CR and PR. Meanwhile, PD was defined as at least of 20% increase of the sum of the longest diameter of the target lesions, taking as a reference the smallest sum of the longest diameter recorded before the patient started to receive treatment. The latter could also be indicated if identification of one or more new lesions were made. A SD was defined as neither having sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for a PD.

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]. Safety was assessed using NCI-CTC version 2, in which events are categorized as mild (grade 1), moderate (grade 2), serious (grade 3) or life- threatening (grade 4).

RESULTS

From January 2010 to March 2012 twenty two consecutive patients with advanced or mCRC entered the study. Table 1 lists demographic data, baseline disease and pretreatment characteristics for all patients. The median age of patients was 63 years, ranging from 42 to 74 years. There were 17 male and 5 female patients. Ten patients had a WHO performance status of 0, eight had a WHO status of 1 and four had a WHO performance status of 2. Nine and thirteen patients had rectal and colon cancers, respectively. The most common metastases sites were the liver and lung. Fourteen of patients had received adjuvant chemotherapy with 5-FU/ FA. A total of 104 treatment courses were provided. The median follow- up period for the entire group was 12,5 months.

Tumor response

The resulting antitumor effects are presented in Table 2. All twenty two patients were evaluable for response. The overall response rate was 31,9% including one CR and six PR (27,3%) achieved. Eight patients (36,4%) showed SD, and seven patients (31,9%) had PD. The tumor control rate were 68,3% (16 patients). The median time to response was 5,1 months and the median duration of response was 4,2 months. The median PFS was 8,6 months. Median survival time was 16,6 months. Sixteen patients (72,7%) were alive at one year.

Toxicity

All twenty two patients and all 104 treatment chemotherapy courses were evaluated for toxicity. Hematologic toxicity (grade 3 or 4) is summarized in Table 3. The most common adverse event was leukopenia without fever and febrile neutropenia, which were experienced by four and two patients (18,2% and 9,1%), respectively. The incidence of this side effect was reduced after FU dose reduction in these patients. Thrombocytopenia was

rare and a platelet count below $25x10^9$/L was observed in only one patient (4,6% of all treated). Anemia grade 3- 4 was not observed.

Non-hematologic toxicity is displayed in Table 4. No gastrointestinal perforation occurred. There were only two bleeding events occurred, both mild and not require permanent discontinuation of Bevacizumab treatment. There were also four deep venous thromboembolic events and only one required treatment with Heparin. Grade 3 and grade 4 diarrhea occurred in seven and one patients (31,6% and 4,6%) respectively, with two patient requiring rehydratation. Nausea or vomiting of grade 3 or 4 was observed in four and two patients (18,2% and 9,1%) respectively. No treatment- related deaths were observed.

DISCUSSION:

Bevacizumab- containing regimes are a standard treatment for first and second- line therapy in patients with mCRC. Multiple clinical trials have proven the use of Bevacizumab results in an improvement in PFS and OS. In a phase III trial Hurwitz H. et al. explored 813 consecutive patients with previously untreated mCRC. They randomly assigned 402 patients to receive Irinotecan, FU, and LV plus Bevacizumab (5 mg/kg intravenously every two weeks) and 411 to receive the same chemotherapy regimen plus placebo. The overall PR was 44,8% with median OS and PFS 20,3 months and 10,6 months respectively [6]. The BICC-C trial was initially designed to evaluate modified Irinotecan, FU and LV (mIFL), FOLFIRI or Capecitabine with IFL with or without Celecoxib in 430 patients with mCRC [11]. The trial was later amended to evaluate FOLFIRI or mILF with or without Bevacizumab in 117 patients. Addition of Bevacizumab to each of the chemotherapy regimens resulted in improved PFS of 11,2 months in the FOLFIRI arm (vs. 7,6 months for FOLFIRI alone) and 8,3 months in the mIFL arm (versus 5,9 months for mIFL alone). Further support for the use of Bevacizumab in combination with FOLFIRI comes from a single- arm phase II trial in which 43 patients had a median PFS of 12,5 months and 1- year survival rate of 95% [12]. These studies clearly demonstrate that Bevacizumab is effective when added to chemotherapy with an improved PFS and OS.

The aim of our study was to explore the efficacy and safety of Bevacizumab when added to standard chemotherapy regimen as first- line treatment in patients with mCRC. Our results are similar to those reported by Hurwitz et al. We observed median OSS of 16,6 months, PFS of 8,6 months and ORR 31,9 %. Our results are also similar to the results Fuchs et al, which find OS of 22,6 months and RR of 57,9% for the arm Irinotecan/ FU/LV/Bevacizumab. The incidence of grades 3- 4 toxicities are similar to those reported too. The main hematological toxicity neutropenia was observed in 18,2% of our patients compared with 28,8% of patients in Fuchs study and 37,1% of patients in Hurwitz trial. The non- hematological toxicity was mild to moderate with only two bleeding events occurred and four deep vein thromboses.

In conclusions, antiangiogenic therapy with Bevacizumab plus FOLFIRI is an effective and well- tolerated regimen for the first- line treatment of patients with mCRC. Available data suggest that Bevacizumab combined with FOLFIRI should be considered as the therapy of choice for the treatment of patients with mCRC.

Table 1. Patient characteristics

Patient characteristics	Number of patients - 22
Age (years)	42 - 74
Sex	
Males	17 (77,3%)
Females	5 (22,7%)
Primary tumor site	
Colon	9 (40,9%)
Rectum	13 (59,1%)
Dominant site of metastasis	
Liver	11 (50,0%)
Lung	3 (13,6%)
Lymph nodes	2 (9,1%)
Peritoneum	2 (9,1%)
Local relaps	4 (18,2%)
Performance status WHO	
0	10 (45,5%)
1	8 (36,4%)
2	4 (18,1%)
Previous treatment	
Surgery	6 (27,3%)
Surgery+ radiotherapy	2 (9,1%)
Surgery+ adjuvant chemotherapy	14 (63,6%)

Table 2. Objective responses

Patients/Response	CR	PR	NC	PD	ORR %
22	1	6	8	7	34,6 %

CR - Complete response; PR - Partial response; NC - No change; PD - Progressive disease; ORR - Overall response rates (ORR= CR + PR)

Table 3. Hematological toxicity- grade 3- 4

Adverse drug reactions	Number of patients
Leukopenia	4 (18,2%)
Febrile neutropenia	2 (9,1%)
Thrombocytopenia	1 (4,6%)
Anemia	0 (0 %)

Table 4. Non-hematologic toxicity- grade 3- 4

Adverse drug reactions	Number of patients
Gastrointestinal perforation	0 (0 %)
Deep vein thromboses	1 (4,6%)
Bleeding	0 (0 %)
Diarrhea	8 (36,4%)
Nausea	4 (18,2%)
Vomiting	2 (9,1%)

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