Bevacizumab in neoadjuvant treatment of patients with liver metastases from colorectal carcinoma

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SUMMARY

Background: *Liver metastases are the leading cause of death in patients with colorectal cancer. Despite advances in chemotherapy, surgical resection of hepatic metastases is still considered the only curative options. However, the majority of patients have inoperable disease at presentation. Perioperative chemotherapy is the most successful way for improved selection of patients for resection. The aim of the study was to demonstrate if and to what extent does bevacizumab, introduced in chemotherapy, increase response rates, and development of liver metastases.*

Methods: *Our study included 50 patients who were divided in two groups. The experimental group included patients who were treated with bevacizumab plus chemotherapy, and the control group included patients who were treated with chemotherapy only.*

Results: *The comparison showed that the patients who were treated with bevacizumab became candidates for resection of liver metastases in higher percentage (85%:52%). In addition, distribution of patients regarding the development of metastases resulted in statistically significant difference. Ratio between the patients with good response from the experimental and the control group was 67%:39%. Ratio of patients with stable disease was 26%:48%, and of patients with progressive disease, it was 7%:3%. The estimate of margin after resection was statistically insignificant.*

Conclusion: *Bevacizumab in combination with chemotherapy in therapy of liver metastases from primary colorectal cancer improves and increases response rates and development of liver metastases.*

Key words: *Colorectal Neoplasms; Neoplasm Metastasis; Liver Neoplasms; Chemotherapy, Adjuvant; Antibodies, Monoclonal*

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INTRODUCTION

Colorectal carcinoma is one of three most frequent malignant diseases in both sexes (1). Each year, there are 1,025,152 new cases of this malignant disease worldwide, out of which 528,978 people die (2).

In more than 50% of colorectal carcinoma patients' metastases occur in liver parenchyma, 25% synchronic, i.e. detected either at the same time when the primary diseases itself or diagnosed intraoperatively. Further 25% are developed within the period of two years since the operation of the primary colorectal carcinoma (3). The most sensitive diagnostic examinations for detection of metastatic changes in liver are ultrasound, CT (computed tomography), and MRI (magnetic resonance) of abdomen. Besides these, PET-CT can be used in diagnostics as well as liver biopsy. Hematology and blood chemistry tests can also be used in detection of the disease.

Metastatic disease of liver is a leading cause of death from colorectal carcinoma. If patients with liver metastases of colorectal carcinoma stay untreated, they have a very low survival rate. An average survival in untreated patients is 6 to 12 months (4).

In spite of progress in chemotherapy, surgical resection of liver metastases is still considered the only option for healing, with five-year long survival in 28% to 39% (5) of cases. Unfortunately, only 20% of total number of patients with metastatic disease in liver parenchyma is primary resectable. The methods for increase of patients' respectability are based on specific surgical techniques and neoadjuvant chemotherapy (6). The results of numerous studies conducted in large world centers, confirm that neoadjuvant chemotherapy improves response rates and the transfer of unresectable patients into potential candidates for surgical resection and thus for their healing.

Until the 90's of the 20th century, the choice of treatment of patients with advanced carcinoma was limited to 5-fluorouracil (5-FU) with tumor response rate (RR) of 15% and the addition of leucovorin (LV) increased the response to 25%. In the last 10 years, some new cytostatic agents were introduced, such as irinotecan (FOLFIRI) and oxaliplatin (FOLFOX), which justified their usage by better tumor response (56% FOLFIRI and 54% FOLFOX), by increase of number of patients eligible for operative treatment and by survival with average survival time of about 20 months (7). In the last several years, certain randomized studies were published, in which, an even greater step forward was enabled by approval of some biological agents like bevacizumab and cetuximab, or by introduction of the third cytostatic agent (8). *Bevacizumab*, a monoclonal antibody against vascular endothelial growth factor (VEGF), in combination with chemotherapy achieves a median survival of 25 months (9).

Neoadjuvant chemotherapy in patients with liver metastases gives the possibility for potential elimination of micrometastatic disease, and the possibility of tumor regression (downsizing) with a greater probability for complete resection and thus, possible healing (10). It reduces the scope of liver resection, represents the test of tumor tissue chemosensitivity, identifies a more aggressive form of the disease, and prolongs the period without relapse, i.e. relapse free survival (RFS). Further, the response to neoadjuvant therapy is stressed out as a potential prognostic factor for survival and evaluation of patients' eligibility for resection (11).

The aim of this research was to determine the bevacizumab efficiency in improvement of response to chemotherapy and evaluation of resectability in patients with colorectal carcinoma with metastatic disease in liver.

PATIENTS AND METHODS

Our research included 50 patients with colorectal carcinoma with both potentially resectable and resectable metastases in liver parenchyma, treated at the Oncology Institute of Vojvodina in Sremska Kamenica, at the Internal Oncology Clinic, Gastroenterology Department, from July 2007 to April 2010. The patients were divided into two groups, experimental and control. The experimental group included 27 patients, 16 men and 11 women, who, during the chemotherapy received bevacizumab. In the control group, there were 23 patients, 13 men and 10 women, who were treated with chemotherapeutical regimen only, without bevacizumab. The data were obtained from the medical records and the informational system BIRPIS at the Oncology Institute of Vojvodina.

The usual neoadjuvant chemotherapeutical regimen for patients with metastatic disease is FOLFOX (Oxaliplatin 85mg/m2 on day 1, Leucovorin 200mg/m2 days 1 and 2, 5-Fluorouracil 400mg/m2 in bolus on days 1 and 2, 5-Fluorouracil 400mg/m2 on days 1 and 2). Chemotherapeutical regimen was given at two weeks, in the form of intravenous infusion. Bevacizumab (Avastin®), if it was added to therapy, was added to a standard protocol in the dose of 5mg/kg of the body weight.

Disease staging, prior to chemotherapy, was done based on the abdomen and chest CT/MRI scans. After 4 cycles, a control examination was performed. Restaging was done by the same technique as the staging of the disease.

Data were processed by Excel program from MS office program package. Statistically significant difference between the tested characteristics was determined by the software package SPSS, version 16. The level of significance in all applied methods was 0.05.

The results were presented descriptively, in tables, and graphically.

RESULTS

Among 27 patients who received bevacizumab, 16 were men and 11 women, while in the control group, of 23 patients, 13 were men and 10 women. Statistically significant difference in number of male and female patients in the observed groups does not exist (c^2 =0, 813; p>0, 05) (Figure 1).

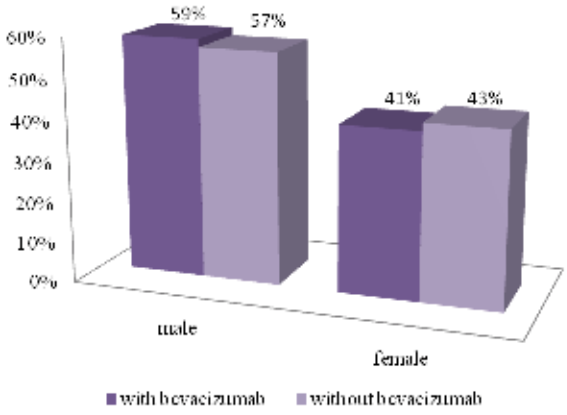

Figure 1. Patients' distribution according to sex in the compared groups

In the experimental group, age was in the range from 33 – 73 years, while the median age was 56.7 years. In the control group, age was in the range from 35 – 76 years with the median age of 58.5 years. The greatest number of patients in both groups was in the category of 51 – 60 years of age. There is no statistically significant difference in relation to age between the two compared groups (c^2 = 0.702; p>0.05) (Figure 2).

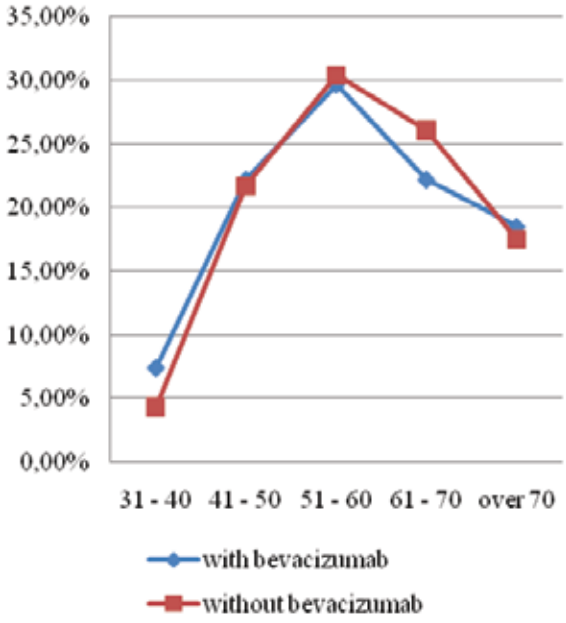

Figure 2. Patients' distribution according to age

Ratio per ECOG stage between the compared groups is given in Figure 3. In the experimental group, there were 22 patients with ECOG 0 and 5 with ECOG 1, and in the control group, there were 19 ECOG 0 and 4 ECOG 1 patients. There is no statistically significant difference (c^2=0.023; p >0.05) (Figure 3).

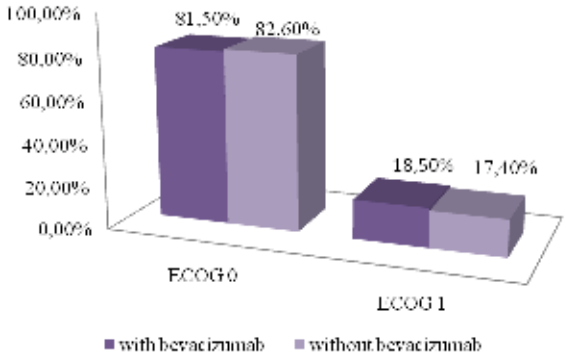

Figure 3. Patients' distribution according to ECOG stage

In the group receiving bevacizumab, there were 23 patients that were candidates for resection and 4, who were not. In the control group, the distribution of resectable and unresectable patients was approximately equal, with 13 patients that were resectable and 10 unresectable ones. There is statistically significant difference regarding the patients' resectability after the administration of chemotherapy (c^2 = 9.03; p< 0.05) (Figure 4).

In the experimental group, we found positive therapeutic response of the metastatic disease (complete response (CR) and partial response (PR)) in 18 (67%) patients and in 9 (43%) patients from the control group. Stable

disease was confirmed in 7 (26%) patients from experimental and in 11 (48%) patients from the control group. Progression was observed in 2 (7%) patients in experimental and in 3 (13%) patients in the control group (Figure 5). There is a statistically significant difference between the compared groups (c^2= 8.6; p< 0.05).

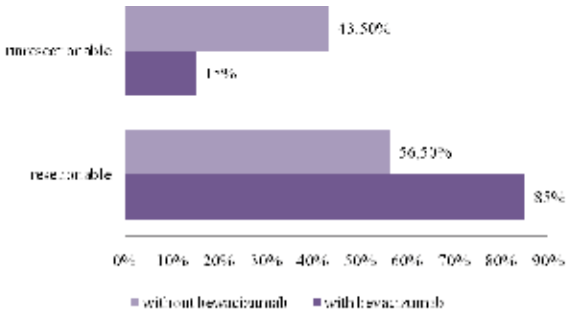

Figure 4. Distribution of resectable and unresectable patients in the groups

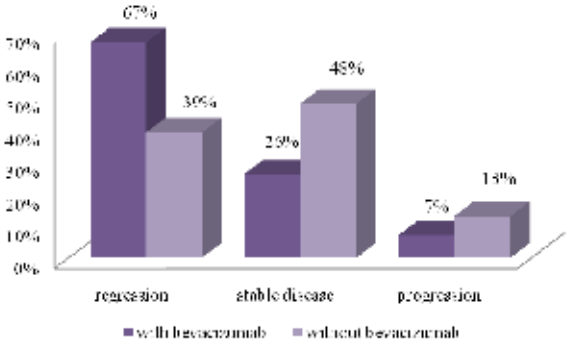

Figure 5. Ratio of the compared groups according to response to therapy

Of all resectable patients, 19 patients from the experimental group and 12 patients from the control group underwent surgery. Patients' distribution after resection is shown in Table 1 and Figure 6. There is no statistically significant difference (c^2=0.518; p>0.05).

Table 1. Evaluation of a margin after resection

	WITH BEVACIZUMAB		WITHOUT BEVACIZUMAB	
	No.	%	No.	%
R0	15	78.9	8	66.7
R1	3	15.8	3	25
R2	1	5.3	1	8.3

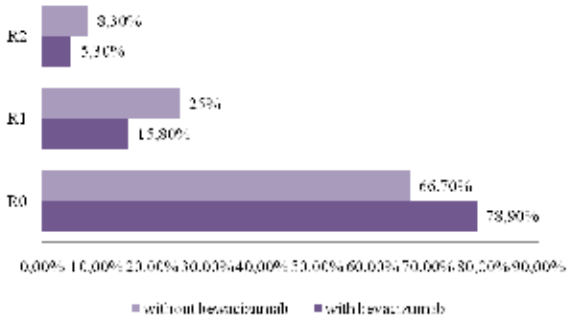

Figure 6. Patients' ratio according to margin evaluation after resection

DISCUSSION

In patients with colorectal carcinoma, liver metastases resection is the only option of treatment, which may enable permanent healing (12, 13). Patients who do not have extrahepatic metastases, with a preserved liver function, with a good general status are eligible for resection. Classic contraindications, like more than 4 metastases, extrahepatic disease, resectional margin larger than 4 cm, were revised during the previous years. It is suggested that the absolute contraindications should include unresectable extrahepatic disease, liver involvement greater than 70% (6 segments), liver insufficiency, and bad general status of a patient (14).

Phases II and III of clinical trials have shown that the addition of bevacizumab to a standard chemotherapy significantly improves response rates (RR), the progression free survival (PFS), and the overall survival (OS) in comparison to the standard chemotherapy treatment (15, 16).

In the study, where two groups of patients were compared, among who there was no statistically significant difference in relation to sex, age and ECOG stages, one group received bevacizumab together with chemotherapy, while the other group received chemotherapy without bevacizumab, i.e. placebo. The results have shown that PFS was prolonged from 6.2 to 10.6 months, OS from 15.6 to 20.3 months, and RR was increased from 34.8% to 44.8 % (16).

In a recently published study, the combination of bevacizumab and neoadjuvant protocol FOLFOX or XELOX resulted in a significantly better PFS in comparison to the standard protocol (17).

VEGF, known as the key mediator of angiogenesis is expressed in about 50% of colorectal cancers. An increase of the serum level of VEGF is significantly related to the lymph nodes status, tumor aggressiveness, high rate of relapse and bad prognosis (18-20). VEGF receptors were found in large numbers in liver metastases of primary colorectal carcinoma (19). The mechanism by which bevacizumab increases the activity of chemotherapy is not entirely clarified, but the reduction of vascular permeability of tumor may reduce interstitial pressure and relatively normalize the blood flow through the tumor, which improves the introduction of cytostatics into the tumor tissue (21).

A research, which monitored the efficiency and safety of bevacizumab administration, confirmed that the liver metastases resection after the therapy with bevacizumab is feasible and safe. The percentage of R0 resection, which was achieved in such patients, justified the usage of this biological agent prior to resection (22).

Joint analyses of the results of 3 randomized clinical studies (two in phase II and one in phase III) on the administration of the bevacizumab combined with chemotherapy in 1,236 patients with metastatic colorectal carcinoma confirm the improved outcomes in the treated patients (23).

Half-life of bevacizumab is relatively long, about 20 days (11 to 50 days) and it is accepted that the safe period for operative treatment is 6 weeks after the last administration of bevacizumab, which is in correlation with the double duration of the drug half-life (24). The results obtained in the research of neoadjuvant therapy (XELOX + bevacizumab) in 32 patients, 15 of who underwent operative treatment, show that bevacizumab can be safely administered up to 5 weeks prior to resection. This therapy does not increase the number of postoperative complications and does not affect the liver parenchyma regeneration after the resection (25).

In our research, out of 23 patients who were eligible for resection, 19 patients treated with bevacizumab underwent operative treatment. A complete response was achieved in one patient who did not undergo surgery. Three patients refused surgical treatment. Twelve patients from the control group underwent surgery, while only 1 patient achieved complete response. There was no statistically significant difference between the groups in the evaluation of margins after resection.

In the BEAT study, which included 1,914 patients, who received chemotherapy combined with bevacizumab added, the results showed that, R0 resection of liver metastases was performed in 76.9% out of total number of operated patients (22). The similar results were obtained in our research.

CONCLUSION

Patients who were treated with bevacizumab achieved resectability of liver metastases in significantly higher percent than patients treated with neoadjuvant therapy without bevacizumab. Furthermore, we found a significant difference between the patients of the two observed groups in relation to the response of liver metastatic disease to the administered chemotherapy:

– Positive therapeutic response occurs in higher percent in patients treated with bevacizumab,
– Stable disease and disease progression occur to larger extent in patients treated with chemotherapy only, without bevacizumab.

Based on our results we believe that there is a significant benefit from bevacizumab in improvement of neoadjuvant chemotherapy efficacy.

Conflict of interest

We declare no conflicts of interest.

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