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PERIOPERATIVE BEVACIZUMAB IN THE TREATMENT OF COLORECTAL CANCER IN PATIENTS WITH LIVER METASTASES

PERIOPERATIVNO LEČENJE BEVACIZUMABOM PACIJENATA SA KOLOREKTALNIM KARCINOMOM I METASTAZAMA U PARENHIMU JETRE

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Summary

Introduction. Patients with colorectal cancer with metastases in the liver parenchyma may benefit from perioperative chemotherapy with biological agents and operative liver resection. **Material and Methods**. This prospective, multicenter, non-interventional study included 191 previously untreated patients with metastatic colorectal cancer and potentially resectable or initially unresectable liver metastases who received bevacizumab plus chemotherapy. The safety profile, as well as progression-free-survival, response rate and conversion rate of initially unresectable metastases to resectable were assessed. **Results.** A total of 40 adverse events were reported in 29/191 patients (15.2%), of which 31 were serious adverse events. Among the serious adverse events, 14 were related to the use of bevacizumab therapy, of which 4 were fatal due to serious adverse events, but only one could be related to bevacizumab therapy. The median progression-free period was 9 months (1 - 28). A high rate of response to the applied therapy, 34.5% and 49%, was recorded in both groups of patients: with initially unresectable and potentially resectable metastases in the liver parenchyma. A significant part of patients with metastatic colorectal cancer and metastases only in the liver parenchyma had a clinical benefit from intensive chemotherapy with bevacizumab (disease control rate of 70%). **Conclusion.** This study confirmed a favourable safety profile and tolerability in terms of the incidence and severity of adverse and serious adverse events. High rates of resectability in both groups of patients, initially unresectable and potentially resectable, reflect the heterogeneity of criteria in decision making about liver resection and emphasize the need for establishing multisciplinary oncology teams and following the generally accepted criteria.

Key words: Bevacizumab; Perioperative Care; Colorectal Neoplasms; Neoplasm Metastasis; Liver Neoplasms; Drug Therapy; Risk Assessment; Treatment Outcome; Antineoplastic Combined Chemotherapy Protocols; Drug-Related Side Effects and Adverse Reactions

Sažetak

Uvod. Pacijenti oboleli od kolorektalnog karcinoma sa metastazama u parenhimu jetre imaju korist od primene perioperativnih hemioterapija uz biološku terapiju i operativne resekcije metastaza u parenhimu jetre. **Materijal i metode.** U ovu prospektivnu, multicentričnu, neintervencijsku studiju uključen je 191 prethodno nelečeni pacijent sa metastatskim karcinomom kolorektuma i potencijalno resektabilnim ili inicijalno neresektabilnim metastazama u jetri koji su primili perioperativno bevacizumab uz hemioterapiju. Bezbednosni profil kao i period bez progresije bolesti, odgovor na primenjenu terapiju kao i konverzija incijalno neresekabilnih metastatskih promena u jetri u resektabilne su takođe procenjivani. **Rezultati.** Zabeleženo je ukupno 40 neželjenih događaja 29/191 (15,2%), od toga 31 ozbiljan neželjeni događaj. Među ozbiljnim neželjenim događajima 14 je bilo u vezi sa primenom bevacizumab terapije od kojih su četiri bila smrtna ishoda, od toga samo se jedan mogao povezati sa terapijom bevacizumabom. Srednji period bez progresije bolesti bio je devet meseci (1–28). Visoka stopa odgovora na primenjenu terapiju, 34,5% i 49% zabeležena je u obe grupe pacijenata sa inicijalno neresektabilnim i potencijalno resektabilnim metastazama u parenhimu jetre. Značajan deo pacijenata sa kolorektalnim karcinomom sa metastazama i metastazama samo u parenhimu jetre, imali su kliničku korist od sprovedene intenzivne hemioterapije bevacizumabom (stopa kontrole bolesti od 70%). **Zaključak.** Ova studija je potvrdila povoljan sigurnosni profil i podnošljivost u pogledu učestalosti neželjenih i ozbiljnih neželjenih događaja. Visoke stope resektibilnosti u obe grupe pacijenata, inicijalno neresektabilnih i potencijalno resektabilnih, odražavaju heterogenost kriterijuma u donošenju odluka o resekciji jetre i naglašavaju potrebu za uspostavljanjem multidisciplinarnih timova i praćenjem opšteprihvaćenih kriterijuma.

Ključne reči: bevacizumab; perioperativna nega; kolorektalne neoplazme; metastaze; neoplazme jetre; farmakoterapija; procena rizika; ishod lečenja; kombinovani antineoplastični hemoterapijski protokoli; neželjeni efekti i neželjene reakcije

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Abbreviations

CRC – colorectal cancer
RR – response rate
PFS – progression free survival
mCRC – metastatic colorectal cancer
CRF – case report form
ITT – intention-to-treat
DFS – disease free survival

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. Approximately 50% of patients suffering from colorectal cancer will develop metastases, usually in the liver, while 25% have metastases at diagnosis [1]. Survival strongly correlates with the extent of the disease. In recent years, perioperative chemotherapy for patients with liver only metastatic colorectal cancer (mCRC) is commonly used in routine clinical practice. The advantages of perioperative therapy include effects on micrometastases, tumor chemo-sensitivity testing (by radiological and pathological methods), which is important in the choice of adjuvant chemotherapy. Furthermore, by assessing the aggressiveness of the disease, perioperative therapy may indicate patients who will not benefit from the resection [2]. It is known that resection of liver metastases is the best chance for cure of these patients [3] with a five-year survival rate of 25 – 40% [4], which may go to 55% or even higher [5, 6]. Reflecting this, conversion to resectability of liver metastases is a very important step in the treatment of mCRC patients.

Bevacizumab (Avastin, Roche) is a biologic therapy that provides statistically significant increase in response rate (RR), overall survival (OS) and progression free survival (PFS), while, in combination with fluoropyrimidine chemotherapy, provides quality survival of mCRC patients [7]. Bevacizumab inhibits vascular endothelial growth factor, leading to normalization of tumor blood vessels and reduction of intratumoral pressure, which improves the delivery of chemotherapeutic agents to tumor cells [8–11]. Based on numerous clinical evidence and worldwide routine clinical practice experience, bevacizumab, in combination with chemotherapy, has become a standard therapy for mCRC.

Data showed that colorectal cancer patients with mCRC may benefit from perioperative chemotherapy with biological agents and liver resection [12, 13]. Resectability rate may be increased by aggressive approach with triplet chemotherapy consisting of doublet chemotherapy and monoclonal antibody.

It is important to select patients with resectable metastases and those with initially unresectable disease in whom the metastases may become resectable after a major response has been achieved with combined chemotherapy. The role of perioperative treatment may therefore be to convert initially unresectable liver metastases of mCRC to resectable and to increase the resectability rate.

Monitoring of bevacizumab efficacy in routine practice with safety monitoring should enable proper dosing and treatment duration. Desired outcomes of perioperative usage of combination of chemotherapy with bevacizumab may lead to higher resectability rate, as well as RR and PFS.

The aim of this study was to demonstrate that in treatment of mCRC, according to local label and local standard of care, bevacizumab represents a valuable perioperative therapy option.

The primary objective was to assess the safety profile of bevacizumab combined with chemotherapy regimens. The secondary objective was to evaluate RR (including rate of conversion from primary unresectable to resectable) and PFS.

Material and Methods

This open-label, multicenter non-interventional phase IV study evaluated the safety and efficacy of bevacizumab in the perioperative treatment of mCRC patients.

Study was conducted at 6 clinical sites in Serbia. The patients were recruited from March 2009 to October 2012. The last subject's last visit was in August 2014.

The target population included previously untreated mCRC patients, aged > 18, eligible for bevacizumab treatment per local label and clinical practice. A total of 191 patients signed informed consent forms for participation in the study. The main exclusion criterion was contraindication to bevacizumab therapy as per locally approved prescribing information.

All study procedures were conducted in accordance with routine clinical practice. Before the initiation of therapy, patients were evaluated in terms of resectability of liver metastases. Assessment of resectability was performed using the following criteria: remnant liver volume ≥ 30%, lesions near and/or invading vascular and/or biliary vessels, and feasibility for removal of all liver lesions. Additionally, the Fong clinical risk score was used to assess the risk of recurrence using the following parameters: involvement of lymph nodes, appearance of metastases within 12 months from primary tumor surgery, carcinoembryonic antigen levels, number of liver metastases, and sites of metastases. Based on the final score, patients were classified as low, medium and high risk patients.

Patients enrolled in the study received preoperative chemotherapy with bevacizumab, every two or three weeks.

Bevacizumab was administered as an intravenous infusion at a dose of 5 mg/kg once every 2 weeks, up to maximum 10 cycles. Standard chemotherapy regimens were used: FOLFOX4, (oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2, fluorouracil IV bolus 400 mg/m^2, then fluorouracil continued infusion for 22 hours 600 mg/m^2), FOLFIRI (irinotecan 180 mg/m^2 on day 1, leucovorin 200 mg/m^2, fluorouracil bolus 400 mg/m^2, then fluorouracil

continued infusion for 22 hours 600 mg/m^2), XELOX (oxaliplatin 130 mg/m^2 on day 1, capecitabine 1000 mg/m^2, 1 – 14 days), XELIRI (irinotecan at 175 mg/m^2 on day 1, capecitabine 1000 mg/m^2, 1 – 14 days). After four cycles of bevacizumab-containing regimens, tumor assessments were performed. In the majority of cases, radiology evaluation was done using computed tomography, while magnetic resonance imaging and positron emission tomography and computed tomography were used on demand. Radiology assessment was performed as per local standard of care, using Response Evaluation Criteria in Solid Tumors 1.1.

Clinical assessments included RR evaluation, evaluation of resectability, PFS and safety monitoring according to routine practice. Patients whose status did not convert to resectable could continue with therapy for up to 10 cycles. Patients who were evaluated as resectable underwent surgery after mminimum 4 weeks following the last dose of bevacizumab. After surgery, patients could have received chemotherapy, but without bevacizumab, as per local regulations.

All patients were followed until progression of the disease, unacceptable toxicity, lost to follow up, death of any cause, or withdrawal of informed consent. The following data were analyzed: baseline patient characteristics, previous treatment, and current treatment, duration of treatment, conversion to resectability, RR and therapy outcome, PFS, and frequency and grade of adverse events/severe adverse events.

All patient data were recorded in paper case report forms (CRF) and in a timely manner validated by the responsible specialist. Data entered in the CRF were matched with data entered in the medical history of each patient. Statistical analysis was performed based on clinical database for this study. All analyses were performed in intention-to-treat (ITT) population.

Descriptive statistical analysis was performed including all baseline patient characteristics. All subjects enrolled in the study who received at least one dose of study medication were included in analysis. Categorical data were analyzed using a chi-square test and Fisher's exact test, as appropriate.

The incidence and severity of adverse events were assessed in order to determine the safety and tolerability of bevacizumab. Sample size was calculated according to gathered data about the safety and tolerability of bevacizumab.

The analysis of ITT population included all patients who received at least one dose of the study drug and had subsequent post baseline assessment. All adverse events reported during the observational period were included in the analysis of the safety data.

Results

Baseline characteristics are presented in **Tables 1** and **2**. At initial presentation, metastatic disease was found in 41.9% of patients. Previous adjuvant treatment was received by 63 patients (33%). Disease free survival (DFS) in patients who were initially diagnosed as Dukes B or C was 12 months **(Table 3)**. Mean sum of the longest diameters of liver metastases was 7.7 cm. In the study, 95% of

Table 1. Demographic characteristics of patients
Tabela 1*. Demografske karakteristike pacijenata*

Baseline characteristics/*Osnovne karakteristike*	No./Br. = 191 (%)
Gender/*Pol*	
Male/*Muški*	120 (62.8)
Female/*Ženski*	71 (37.2)
Age/*Uzrast*	
Mean/*Srednja vrednost*	59.31 ± 10.23
Median/*Medijana*	61
Minimum/*Minimum*	27
Maximum/*Maksimum*	78

Table 2. Performance status and initial stage of patients at diagnosis
Tabela 2*. Performans status i inicijalni stadijum pacijenata u momentu dijagnoze*

ECOG Performance status/*Opšte stanje pacijenta*	
0	149 (78%)
1	40 (21%)
Unknown/*Nepoznato*	2 (1%)
Stage at initial diagnosis/*Stadijum kod inicijalne dijagnoze*	
Dukes B	43 (22.5)
Dukes C	67 (35.1)
Dukes D	80 (41.9)
Carcinoma in situ	1 (0.5)

Legend: ECOG – Eastern Oncology Cooperative Group/*Legenda: ECOG – Istočna kooperativna onkološka grupa*

Table 3. Disease free survial
Tabela 3. *Prikaz vremena bez bolesti kod pacijenata*

DFS (months)/*Vreme bez bolesti (meseci)*	
Mean/*Srednja vrednost*	15.84 ± 14.7
Median/*Medijana*	12
Minimum/*Minimum*	1
Maximum/*Maks*imum	96
Age distribution (years)/*Starosna distribucija (godine)*	N = 191 (%)
Age (years)/*Starost*	
18 - 64	126 (66%)
65 - 84	65 (34%)
85 years and over/*85 godina i stariji*	0 (0)

patients received oxaliplatin-based regimen, mostly FOLFOX4 or XELOX, only 5% received irinotecan-based chemotherapy.

In regard to resectability evaluation, 89% of patients were evaluated as potentially resectable with remnant liver volume of ≥ 30%. In 79% of patients, potential resection could be done with microscopically negative margins (R0) and 5.8% of patients had metastases surrounding important vascular and biliary vessels. In terms of prognostic parameters, assessment was done in 98% of patients: 45% were classified as low risk, 52% as medium, and 1% of patients were classified as high risk.

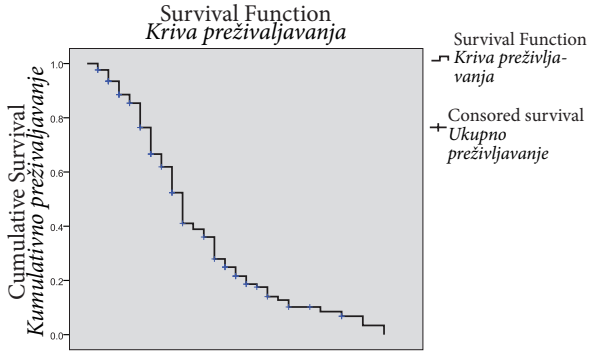
Based on these parameters, all included patients were classified as potentially resectable (162 patients) and initially unresectable (29 patients), that could be converted to resectable.

Patients with initially unresectable liver metastases of mCRC

The mean number of initial bevacizumab cycles was 4 (1 – 8). Complete remission was achieved in 7%, partial response in 31%, stable disease (SD) in 31%, and progressive disease was recorded in 13.8% of patients, while the response was not assessed or data were missing in 17.2% of patients. Four patients (13.8%) continued bevacizumab therapy after the first evaluation, but on second evaluation they were confirmed as unresectable. Ten patients (34.5%) had undergone liver resection. A microscopically negative margins resection was performed in 4 patients (40%, or 13.8% of all unresectable patients), without recorded perioperative complications, and 2 patients continued therapy after resection.

Patients with potentially resectable liver metastases of mCRC

The mean number of initial bevacizumab cycles was 4.5 (1 – 12). A complete remission was achieved in 5.6%, PR in 25.3%, SD in 42%, and disease progression was recorded in 17.9 of patients, while the response was not assessed or data were missing in 9.2% of patients. Thirty-four patients (21%) continued bevacizumab therapy after the first evaluation, but on second evaluation only 1 patient was considered for liver resection, after the 7th cycle. Eighty patients (49.4%) had undergone liver resection. A microscopisally negative margins resection was performed in 61 patients (76%), transitional perioperative complications were recorded in 4 patients, and 21 patients continued therapy after resection. In terms of PFS, median PFS in ITT population was 9 months (1 – 28) **(Graph 1)**.



Graph 1. Median disease free survival in intention-to-treat population
Grafikon 1. *Medijana vremena bez progresije bolesti kod populacije sa namerom lečenja*

Adverse events

In this study, adverse events were reported in 29/191 patients (15.2%). Of 40 reported adverse events, 31 were serious **(Table 4)** and 9 non-serious **(Table 5)**. A detailed description of all adverse events is listed below. Among serious adverse events, 14 were designated as related to bevacizumab therapy, of which the majority (7/14) were vascular disorders, which all resolved with recovery. There were four fatal outcomes due to serious adverse events. One fatal outcome occurred in a patient with febrile neutropenia that was not related to bevacizumab treatment. The second fatal outcome occurred in a patient with multiple serious adverse events (diarrhea, fatigue, fever, abdominal pain, acute renal failure), and this outcome was reported as related to bevacizumab treatment. The third fatal event was sudden death, not related to bevacizumab treatment. The fourth fatal outcome

Table 4. Summary of serious adverse events
Tabela 4. *Pregled ozbiljnih neželjenih efekata*

System Organ Class/*Klasa sistema organa*	Treatment Group/*Grupa na terapiji* No./*Br.* = 191				
Preferred Term/*Odabrani termin*	n (%)	Number of Events/*Broj neželjenih dejstava*			
		Total	TR	Fatal	TR Fatal
Number of subjects with at least one SAE *Broj pacijenata sa bar jednim ozbiljnim neželjenim dejstvom*	23 (12)	31	14	4*	1
Infections and infestations/*Infekcije i infestacije*					
Tuberculosis/*Tuberkuloza*	1 (0.5)	1	0	0	0
System Organ Class *Klasa sistema organa*	Treatment Group N = 191/*Grupa na terapiji* No./*Br. = 191*				
Preferred Term/*Odabrani termin*	n (%)	Number of Events/*Broj neželjenih dejstava*			
		Total	TR	Fatal	TR Fatal
Blood and lymphatic system disorders/*Poremećaji krvi i limnog sistema*					
Febrile neutropenia/*Febrilna neutropenija*	1 (0.5)	1	0	1	0
Neutropenia/*Niski leukociti*	5 (2.6)	5	1	0	0
Thrombocytopenia/*Niski trombociti*	1 (0.5)	1	0	0	0
Vascular disorders/*Vaskularni poremećaji*					
Deep vein thrombosis/*Duboka venska tromboza*	1 (0.5)	1	0	0	0
Embolism/*Embolija*	1 (0.5)	1	1	0	0
Hypertension/*Povišen krvni pritisak*	3 (1.5)	3	3	0	0
Peripheral artery thrombosis/*Periferna arterijska tromboza*	1 (0.5)	1	1	0	0
Thrombophlebitis/*Upala vena*	1 (0.5)	1	1	0	0
Respiratory, thoracic and mediastinal disorders/*Respiratorni poremećaji*					
Pleural effusion/*Pleuralni izliv*	1 (0.5)	1	0	0	0
Pulmonary embolism/*Plućna embolija*	1 (0.5)	1	1	0	0
Respiratory failure/*Respiratorna insuficijencija*	1 (0.5)	1	0	0	0
Gastrointestinal disorders/*Gastrointestinalni poremećaji*					
Abdominal pain/*Bol u trbuhu*	1 (0.5)	1	1	1	1
Diarrhea/*Proliv*	2 (1)	3	1	1	1
System Organ Class/*Klasa sistema organa*	Treatment Group N = 191/*Grupa na terapiji No./Br. = 191*				
Preferred Term/*Odabrani termin*	n (%)	Number of Events/*Broj neželjenih dejstava*			
		Total	TR	Fatal	TR Fatal
Gastrointestinal necrosis/*Gastrointestinalna nekroza*	1 (0.5)	1	1	0	0
Ileus/*Ileus*	1 (0.5)	1	0	0	0
Renal and urinary disorders/*Poremećaji urogenitalnog trakta*					
Acute kidney injury/*Akutna bubrežna insuficijencija*	1 (0.5)	1	1	1	1
General disorders and administration site conditions/*Opšti poremećaji i stanja na mestu primene*					
Fatigue/*Umor*	2 (1)	2	1	1	1
Impaired healing/*Ne zarastanje rana*	1 (0.5)	1	0	0	0
Sudden death/*Iznenadna smrt*	1 (0.5)	1	NR**	1	NR**
Investigations/*Ispitivanja*					
High body temperature/*Povišena telesna temperatura*	1 (0.5)	1	1	1	1
Injury, poisoning and procedural complications *Povrede, trovanja i proceduralne komplikacije*					
Post procedural complication *Komplikacije nakon procedure*	1 (0.5)	1	0	1	0

Legend: *1 fatal is without reported relationship with bevacizumab; **NR – Not reported; N = number of subjects at risk; n = number of subjects with an event; TR – treatment related; Fatal – Number of events with fatal outcome; TR Fatal – Number of treatment-related events with fatal outcome

*Legenda: *1 smrtni ishod bez prijavljene veze sa bevacizumabom; **NR – Nije prijavljeno; N = broj rizičnih subjekata; n = broj subjekata sa neželjenom reakcijom; TR – povezano sa lečenjem; Fatal – Broj reakcija sa smrtnim ishodom; TR Fatal – Broj reakcija u vezi sa lečenjem sa smrtnim ishodom*

Table 5. Non-serious adverse events
Tabela 5. *Ostali neželjeni efekti*

System organ classification *Klasa sistema organa*	Non serious adverse events *Ostali neželjeni efekti*	n (%) *n (%)*	No. of Events *Br. neželjenih efekata*	Grade (N) NA *Stepen (N)*		
				1	2	3
Blood and lymphatic system disorders *Poremećaji krvi i limnog sistema*	Neutropenia *Neutropenija*	1 (0.5)	1		1	
	Thrombocytopenia *Trombocitopenija*	1 (0.5)	1		1	
Vascular disorders *Vaskularni poremećaji*	Hypertension *Hipertenzija*	1 (0.5)	1			1
General disorders and administration site conditions *Opšti poremećaji i stanja na mestu primene*	Disease progression *Progresija bolesti*	1 (0.5)	1			1
Gastrointestinal disorders *Gastrointestinalni poremećaji*	Constipation *Konstipacija*	1 (0.5)	1		1	
	Diarrhea *Dijareja*	2 (1)	2	1	1	
Renal and urinary disorders *Poremećaji urogenitalnog trakta*	Proteinuria *Proteinurija*	2 (1)	2	1	1	

occurred as a consequence of post procedural complication and was not reported as related to bevacizumab therapy.

Discussion

Preoperative chemotherapy is increasingly used in real-life clinical practice prior to surgical resection of liver mCRC [12, 13]. A large number of published papers pointed out the benefits of neoadjuvant chemotherapy in these patients in terms of potential downstaging and conversion to resectable disease, leading to metastases resection and potential cure. On the other hand, chemotherapy can cause damage to the liver: blue liver (oxaliplatin) and steatohepatitis or yellow liver (irinotecan), which is associated with perioperative morbidity and even mortality in patients undergoing surgery [14]. The addition of bevacizumab to preoperative chemotherapy regimens does not increase the morbidity or mortality related to liver resection and significantly prolongs survival in patients with mCRC [15]. Therefore, to a large extent, bevacizumab is used in combination with chemotherapy regimens in patients with potentially resectable liver metastases [16].

On the other hand, as an angiogenesis inhibitor, bevacizumab has its own side effects - hemorrhage, hypertension, wound healing complications, bowel perforation, arterial thromboembolism, which in turn can delay surgery or increase postoperative morbidity and mortality.

The primary and secondary objectives of this study were achieved. Bevacizumab demonstrated a favourable safety and tolerability in regard to the incidence and severity of adverse and serious adverse events reported during the course of the study. There were no new safety signals recorded in this study. This observational study confirmed a high percentage of patients who achieved a clinical benefit (70% of disease control rate) after beginning of aggressive triplet therapy, including bevacizumab, for patients with liver only mCRC (both initially unresectable and resectable/potentially resectable). High resectability rate, 34.5% and 49%, both in initially unresectable and potentially resectable patients, shows heterogeneous criteria in decision making about liver resection, and highlights the need for establishing and following generally accepted criteria. The role of specially trained and educated surgeons remains very important. Overall, bevacizumab confirmed that it is a valuable perioperative therapy option for mCRC patients.

In addition, bevacizumab demonstrated PFS and RR which are in line with doses recorded in other studies. Our results are in agreement with the results of already published studies on the treatment of mCRC. In the study by T. Gruenberger and associates [17] the overall RR was obtained in 59% of cases, a stable disease was achieved in 38%, while 3% of patients had a disease progression. On the other hand, Wong and colleagues found an objective RR in 78% of cases, stable disease was achieved in 16%, while disease progression occurred only in 7% of cases [18]. Encouraging are also the results of a large observational cohort study (BRITE), which included 46 centres and a total of 1953 patients, who received bevacizumab in the first line therapy for mCRC. In this study, complete remission was achieved in 12.3% of patients, partial response in 35.8%, stable disease was found in 30.5% of patients, while disease progression occurred in 21.3% of patients [19]. Comparing our results with the results of the BRITE study, we noticed similarity in terms of stable disease and disease progression, while in our country slightly higher rate of partial response and lower rate of complete remission were reported.

Limitations

Heterogeneous resectability criteria between centres may lead to diverse classification of patients between potentially resectable and unresectable.

Conclusion

Overall, bevacizumab confirmed that it is a valuable perioperative therapy option for metastatic colorectal cancer patients. Based on the results of studies conducted so far, and based on the results of our trial, we can conclude that the combination of bevacizumab with standard chemotherapy regimens increases the resectability rate of metastatic colorectal cancer with high probability. Given that we are in the era of biological target therapy, its use offers new possibilities and modalities of cancer treatment.

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