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Optimal duration of therapy in the first line treatment of metastatic colorectal cancer: single-center study

Optimalno trajanje terapije u prvoj liniji tretmana kod metastatskog kolorektalnog karcinoma

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Abstract

Background/Aim. Standard treatment options for the first-line treatment of metastatic colorectal carcinoma (mCRC) are 5-fluorouracil, folinic acid, oxaliplatin (FOLFOX4)/capecitabine (CapOx), plus bevacizumab (bev) and 5-fluorouracil, folinic acid and irinotecan (FOLFIRI) plus bev. The aim of this study was to compare overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with mCRC who were treated in the first line with FOLFIRI/bev vs. FOLFOX4/bev. At the same time, the aim was also to compare the safety profile in the observed groups of patients and to investigate optimal treatment duration and characteristics of patients who had the best treatment outcomes. **Methods.** The retrospective-prospective study included patients with mCRC treated with chemotherapy protocols for the first line in combination with bev (FOLFOX4/bev, respectively, FOLFIRI/bev). Treatment efficacy was evaluated on the basis of ORR, PFS, and OS, and the safety of treatment was evaluated by monitoring adverse drug reactions (ADR). **Results.** ORR was 70% in the FOLFIRI/bev group and 50% in the FOLFOX4/bev group. Median PFS for FOLFIRI/bev (n = 30) and for FOLFOX4/bev (n = 30) was 15.6 months and 12.1 months, respectively [hazard ratio (HR) 0.85; 95% confidence interval (CI) 0.47–1.53; p = 0.5591]. Median OS for FOLFIRI/bev and for FOLFOX4/bev was 24.7 months and 19.9 months, respectively (HR 0.67; 95% CI 0.37–1.23; p = 0.1552). In both patient groups, the patients who received more than 9 cycles of induction therapy had better treatment response compared with patients who received less than 9 cycles of therapy. In the FOLFOX4/bev group, PFS was 16.9 vs. 9.7 months, and OS was 22.1 vs. 17.6 months, respectively. In the FOLFIRI/bev group, PFS was 9 months for patients who received less than 9 cycles of therapy vs. 18.8 months for patients who received more than 9 cycles, and OS was 18.0 months vs. 27.7 months, respectively. ADR grade 3 and 4 had 7% of the patients in the FOLFIRI/bev group vs. 27% in the FOLFOX4/bev group. **Conclusion.** Patients who received FOLFIRI/bev compared to those treated with FOLFOX4/bev had better ORR (70% vs. 50 %, respectively), PFS (15.6 months vs. 12.1 months, respectively), and OS (24.7 months vs. 19.9 months, respectively). In both patient groups, the patients who received induction therapy for 4–6 months (more than 9 cycles of therapy) had a better treatment response.

Key words:
clinical protocols; colorectal neoplasms; drug-related side effects and adverse reactions; duration of therapy; folfox protocol; ifl protocol; neoplasm metastasis; survival.

Apstrakt

Uvod/Cilj. Standardne opcije u prvoj liniji lečenja metastatskog karcinoma debelog creva (mCRC) su 5-fluorouracil, folinska kiselina i oksaliplatin (FOLFOX4)/kapecitabin, oksaliplatin (CapOx) uz dodatak bevacizumaba (bev) i 5-fluorouracil, folinska kiselina i irinotekan (FOLFIRI) uz dodatak bev. Cilj rada bio je da se uporedi ukupni odgovor (*overall response rate* – ORR), period do progresije bolesti (*progression-free survival* – PFS) i ukupno preživljavanje (*overall survival* – OS) u grupama bolesnika sa mCRC koji su u prvoj liniji primali FOLFIRI/bev vs. FOLFOX4/bev. Takodje, cilj je bio i da se uporedi sigurnosni profil u ovim grupama bolesnika, kao i da se ispita optimalna dužina lečenja i karakteristike bolesnika koji su imali najbolje ishode lečenja. **Metode.** Retrospektivno-prospektivnim ispitivanjem obuhvaćeni su

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bolesnici sa mCRC, lečeni primenom hemioterapijskog protokola za prvu liniju terapije, u kombinaciji sa bev (FOLFOX4/bev, odnosno, FOLFIRI/bev). Efikasnost lečenja procenjena je na osnovu ORR, PFS i OS, a bezbednost lečenja praćenjem neželjenih reakcija. **Rezultati.** Parametar ORR bio je 70% u FOLFIRI/bev grupi i 50% u FOLFOX4/bev grupi. Medijana PFS za FOLFIRI/bev grupu (n = 30) iznosila je 15,6 meseci, odnosno 12,1 meseci za FOLFOX4/bev grupu (n = 30) [*hazard ratio* (HR) 0,85; 95% interval poverenja (IP) 0,47–1,53; $p = 0,5591$]. Medijana OS iznosila je 24,7 meseci u FOLFIRI/bev grupi i 19,9 meseci u FOLFOX4/bev grupi (HR 0,67; 95% IP 0,37–1,23; $p = 0,1552$). U obe grupe bolesnika bolji terapijski odgovor imali su bolesnici koji su primili više od 9 ciklusa indukcione terapije u poređenju sa bolesnicima koji su primili manje od 9 ciklusa. U FOLFOX4/bev grupi, PFS je iznosio 16,9 meseci, a OS 22, 1 mesec za bolesnike koji su primili više od 9 ciklusa, u odnosu na 9,7 meseci (PFS) i 17,6 meseci (OS) za bolesnike koji su primili manje od devet ciklusa terapije. U FOLFIRI/bev grupi, PFS je iznosio 9 meseci za bolesnike koji su primili manje od devet ciklusa terapije u odnosu na 18,8 meseci za bolesnike koji su primili više od 9 ciklusa, dok je OS iznosio 18,0 meseci u odnosu na 27,7 meseci u tim grupama bolesnika. Neželjenih dejstava gradusa 3 i 4 imalo je 7% bolesnika u FOLFIRI/bev grupi, a u FOLFOX4/bev grupi 27%. **Zaključak.** Bolesnici koji su primili FOLFIRI/bev protocol, u odnosu na one lečene FOLFOX4/bev protokolom, imali su bolji ORR (70% vs. 50%), PFS (15,6 meseci vs. 12,1 meseci) i OS (24,7 meseci vs. 19,9 meseci). U obe grupe bolesnika bolji ishod imali su bolesnici koji su primali indukcionu terapiju 4–6 meseci (9 do 12 ciklusa).

Ključne reči:
protokoli, klinički; kolorektalne neoplazme; lekovi, neželjeni efekti i neželjene reakcije; lečenje, trajanje; protokol, folfox; protokol, ifl; neoplazme, metastaze; preživljavanje.

Introduction

According to Global Cancer Observatory (GLOBOCAN) 2018, the estimated number of new cancer cases in Bosnia and Herzegovina was 14,385 (7,666 men and 6,719 women). The most common cancers in Bosnia and Herzegovina are lung cancer (2,424 new cases or 16.9%), colorectal cancer (CRC) (1,818 new cases or 12.6%), and breast cancer (1,386 new cases or 9.6%). CRC in Bosnia and Herzegovina ranked second in incidence in both men and women: 772 cases or 11.5% in women and 1,046 cases or 13.6% in men. The total number of cancer deaths from rectal cancer in 2018 in Bosnia and Herzegovina was 585 and 489 deaths from colon cancer [1].

At the time of diagnosis, approximately 80% of patients with CRC have resectable disease [2], but 30–50% of patients who undergo curative surgery experience disease recurrence and die of metastatic diseases [3]. The addition of targeted agents to standard chemotherapy has broadened treatment options. This affected the overall survival (OS). Bevacizumab (bev) is a humanized recombinant monoclonal antibody that blocks all isoforms of vascular endothelial growth factor-A (VEGF-A). Bev, in combination with chemotherapy (CHT), improves progression-free survival (PFS) or OS [4–10].

The aim of this study was to compare overall response rate (ORR), PFS, and OS in the groups of patients with metastatic CRC (mCRC), treated in the first line with FOLFIRI (5-fluorouracil, folinic acid, irinotecan) vs. FOLFOX4 (5-fluorouracil, folinic acid, oxaliplatin) both in combination with bev (FOLFIRI/bev vs. FOLFOX4/bev). At the same time, the safety profile and optimal treatment duration in the observed groups of patients were investigated, as well as the characteristics of patients who had the best treatment outcomes.

Methods

In this retrospective-prospective study, 60 patients with mCRC were treated using FOLFIRI/bev or FOLFOX4/bev protocol. All patients were divided into two groups. Male to female ratio was similar. The first group of patients (n = 30) received the FOLFOX4/bev protocol. The second group of patients (n = 30) received the FOLFIRI/bev protocol. All patients had metastatic disease, with primary tumor histologically confirmed and located in the colon or the rectum. Some patients received adjuvant or neoadjuvant CHT that ended 6 months prior to this study. The patient enrollment period was from January 1, 2014, until December 31, 2016, and patients were followed up until June 15, 2018. The study was conducted at the Oncology Clinic of the University Clinical Center of the Republic of Srpska, Banjaluka, Bosnia and Herzegovina and was approved by the local Ethics Committee from December 23, 2013 (No. 01-9-384.2/13).

Induction therapy protocols were FOLFOX4+bev and FOLFIRI+bev. Patients received induction therapy for a minimum of six and a maximum of 12 cycles.

Post-operative adjuvant therapy was capecitabin + oxaliplatin (XELOX) protocol.

After induction therapy, patients received maintenance therapy: capecitabin (monotherapy) or capecitabin + bev (AVAX).

Statistical analysis

Toxicity and safety were assessed in terms of toxicity and evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 3.0. Survival analysis (PFS and OS) was estimated by the Kaplan-Meier method using MedCalc software.

Results

Out of the 60 patients enrolled in the study, 6 were still alive in the FOLFIRI/bev group, and 9 were still alive in the FOLFOX4/bev group at the end of the follow-up (Table 1).

Table 1

Baseline patient demographic and clinical characteristics

Characteristics	FOLFIRI/bev (n = 30)	FOLFOX4/bev (n = 30)
Age (years)	51.5 (41–62)	56.0 (39–73)
Sex		
male	20 (67.0)	17 (57.0)
female	10 (33.0)	13 (43.0)
Site of primary tumor		
right colon	6 (20)	5 (16)
left colon	24 (80)	25 (84)
Adjuvant chemotherapy	10 (33.3)	4 (13.3)
capecitabine/oxaliplatin	3 (10.0)	0 (0.0)
capecitabine/oxaliplatin/radiotherapy	2 (6.7)	0 (0.0)
capecitabine	2 (6.7)	2 (6.7)
5-FU/folinic acid	2 (6.7)	2 (6.7)
cisplatina/5-FU	1 (3.3)	0 (0.0)
Number of metastatic sites		
1	18 (60.0)	8 (26.7)
2	8 (26.7)	14 (46.7)
3	4 (13.3)	8 (26.7)
Palliative radiotherapy	1 (3.3)	8 (26.7)
Induction chemotherapy		
6 cycles received	2 (6.7)	4 (13.3)
12 cycles received	15 (50.0)	5 (16.7)
Maintenance therapy	13	13
AVAX	2–30 cycles	2–37 cycles
FOLFOX4	1	0
capecitabine	0	1
Dose reduction	0 (0.0)	5 (16.7)
Therapy delayed	3 (10.0)	5 (16.7)
Therapy stopped	1 (3.3)	1 (3.3)
Resection of primary tumor	28/30 (93.3)	23/30 (76.7)
Second look surgery	10/30 (33.3)	7/30 (23.3)
curative	5 (16.7)	3 (10.0)
palliative	5 (16.7)	4 (13.3)

All values are expressed as number (percentage) of patients or median (range). AVAX – bevacizumab+capecitabine; FOLFIRI/bev – folinic acid, 5-fluorouracil (5-FU), and irinotecan/bevacizumab; FOLFOX4/bev – folinic acid, 5-fluorouracil (5-FU), and oxaliplatin/bevacizumab.

Localization of metastases

It is shown that in the FOLFIRI/bev group, there was a significantly higher number of patients with metastases in the liver alone, as opposed to the patients in the FOLFOX4/bev group (Figure 1).

Second surgical resection

Ten patients underwent a second surgery in the FOLFIRI/bev group. Out of these 10 patients, 5 patients underwent palliative surgery, and 5 patients underwent curative surgery: 4 patients underwent curative liver surgery without

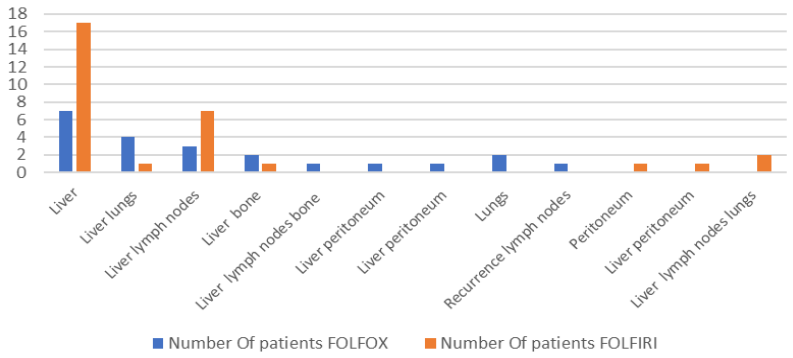


Fig. 1 – Localization of metastases in patients with colorectal cancer treated with FOLFIRI or FOLFOX4 protocol in combination with bevacizumab. FOLFIRI: folinic acid, 5-fluorouracil, and irinotecan; FOLFOX4: folinic acid, 5-fluorouracil, and oxaliplatin.

therapy, and 1 patient underwent curative liver surgery and received 6 cycles of XELOX CHT.

Seven patients underwent a second surgery in the FOLFOX4/bev group. Out of these 7 patients, 4 patients underwent palliative surgery and 3 patients underwent curative surgery: one patient underwent curative liver surgery and received 4 cycles of FOLFOX4/bev chemotherapy, one patient underwent metastasectomy and received XELOX, and one patient underwent curative liver surgery and received 4 cycles of capecitabine.

Evaluation of therapeutic response

Evaluation of response to therapy was performed according to the RECIST criteria, using ultrasonography, hematological and biochemical analyses, computed tomography, magnetic resonance imaging, and tumor markers CEA and CA 19-9. The results are shown in Tables 2 and 3. In both observed groups, the highest number of patients had a partial response to therapy (60.0% in the FOLFIRI/bev group and 46.7% in the FOLFOX4/bev group).

Kaplan-Meier survival estimates of PFS and OS for the FOLFIRI/bev group and FOLFOX4/bev group are presented in Figures 2 and 3, respectively.

PFS and OS were evaluated using: the number of cycles, localization of the primary tumor, and liver-limited dis*ease (LLD).*

Patients who received less than 9 cycles of therapy in both groups were compared to patients who received 9 and more cycles of induction chemotherapy. In both patient groups, significantly higher values of both PFS and OS were observed in patients who received more than 9 cycles of induction CHT with bev. The difference is more noticeable in the FOLFIRI/bev group. Patients with left-sided tumors had better PFS and OS in both patient groups. The difference is more noticeable in the FOLFOX4/bev group. Patients who

Table 2

Response of the patients to the treatment applied

Therapeutic response	FOLFIRI/bev	FOLFOX4/bev
Complete	3 (10.0)	1 (3.3)
Partial	18 (60.0)	14 (46.7)
Stable disease	4 (13.3)	8 (26.7)
Progressive disease	5 (16.7)	7 (23.3)

All values are expressed as number (percentage) of patients.
FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab;
FOLFOX4/bev – bolnic acid, 5-fluorouracil, and oxaliplatin/bevacizumab.

Table 3

Efficacy parameters of the treatment applied

Therapeutic response	FOLFIRI/bev	FOLFOX4/bev
PFS (months)	15.6 (95% CI: 11.7–19.5)	12.1 (95% CI: 8.9–15,4)
OS (months)	24.7 (95% CI: 20.7–28.7)	19. 9 (95% CI: 15.2–24.5)
ORR (%)	70	50
PFS and OS not reached	6 (4 pts with 37 months)	9 (1 pts with 37 months)

FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab; FOLFOX4/bev – folnic acid, 5-fluorouracil, and oxaliplatin/bevacizumab; PFS – progression free survival; OS – overall survival; ORR – overall response rate; CI – confidence interval; pts – patients.

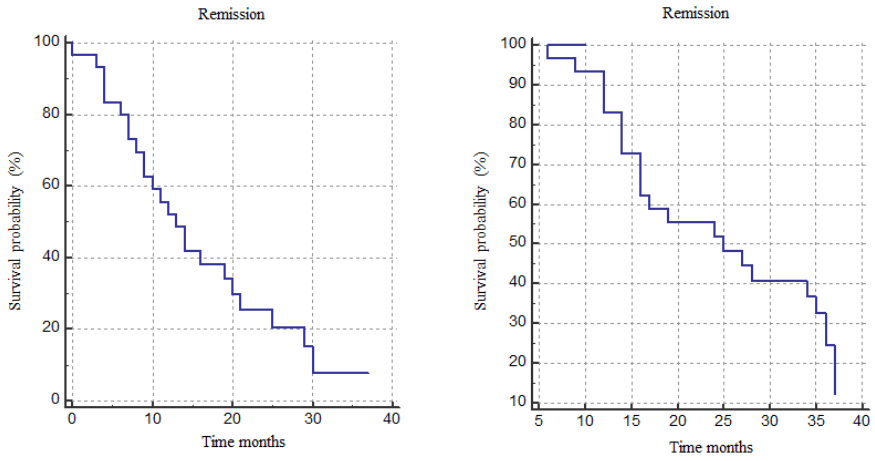


Fig. 2 – Kaplan-Meier survival estimates of PFS (left) and OS (right) for FOLFIRI/bev treatment. PFS – progression free survival; OS – overall survival; FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab.

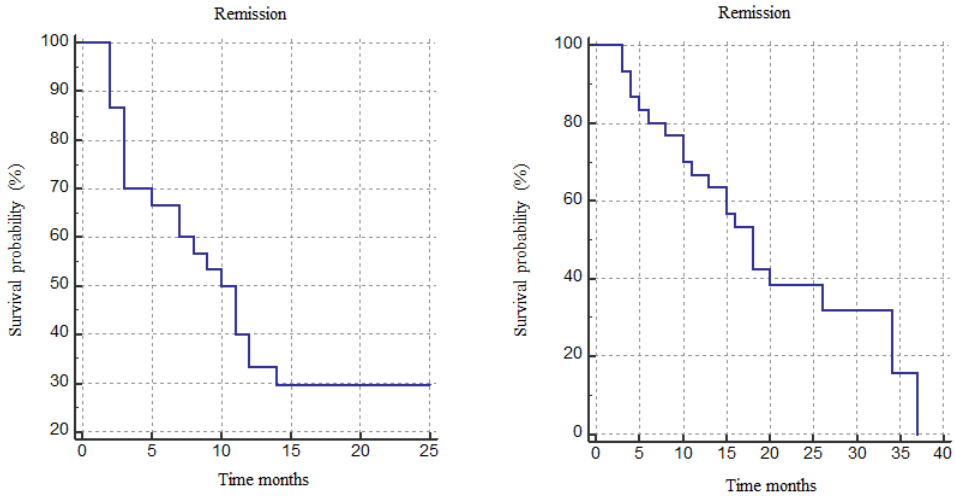


Fig. 3 – Kaplan-Meier survival estimates of PFS (left) and OS (right) for FOLFOX4/bev treatment. PFS – progression free survival; OS – overall survival; FOLFOX4/bev – folinic acid, 5-fluorouracil, and oxaliplatin/bevacizumab;

had LLD were compared to the patients who had metastases in the liver and other organs. Patients who had only liver metastases had better PFS and OS. The difference was more significant in the FOLFOX4/bev group (Table 4).

Delayed therapy

In the FOLFOX4/bev group, therapy was discontinued or delayed in a total of 5 patients due to adverse reactions (ADRs) as described below.

Bev was discontinued due to the occurrence of grade 4 pulmonary embolism. Complete therapy was delayed by 7 days due to the onset of grade 2 leukopenia and pancytopenia. Complete therapy was delayed by 10 days due to the onset of diarrhea, fatigue, and grade 2 pain. Complete therapy was delayed by 7 days due to the onset of grade 2 leukopenia and neutropenia, grade 1 thrombocytopenia, and grade 1 pulmonary embolism. Complete therapy was delayed by 15 days due to the onset of grade 3 leukopenia, grade 2 diarrhea, and grade 2 Hand-Foot Syndrome (HF Sy).

In the FOLFIRI/bev group, therapy was discontinued or delayed in a total of 3 patients. Complete therapy was discontinued in one patient due to grade 4 ileus. Complete therapy was delayed in one patient by 7 days due to the onset of grade 2 neutropenia and by 7 days in one patient due to grade 1 nausea and vomiting.

Adverse drug reactions in a group of patients treated with FOLFOX4/bev

ADRs in the FOLFOX4/bev group are given in Table 5.

The most commonly reported ADRs were hypertension (26.7%), leukopenia (23.3%), neutropenia (16.7%), and proteinuria (16.7%).

Grade 4 of ADRs were leukopenia, fistula, ileus, subileus, leukopenia, neutropenia, and pulmonary thromboembolism. The total percentage of grade 3 and grade 4 ADRs was 27%.

Adverse drug reactions in a group of patients treated with FOLFIRI/bev

ADRs in the FOLFIRI/bev group are given in Table 6.

The most commonly reported ADRs were diarrhea (36.7%), hypertension (30.0%), alopecia (23.3%), and nausea and vomiting (23.3%). Grade 4 ADRs were diarrhea and ileus. The total percentage of ADRs in grades 3 and 4 was 7%.

Table 4

Difference in PFS and OS in patients with mCRC (metastatic colorectal carcinoma) treated with FOLFOX4/bev and FOLFIRI/bev depending on treatment duration, site of primary tumor, and liver metastases

Parameter	FOLFOX4/bev						FOLFIRI/bev					
	PFS	HR	*p*	OS	HR	*p*	PFS	HR	*p*	OS	HR	*p*
Number of cycles												
≤ 9	9.7	0.34 (95% CI 0.14–0.82)	0.0305	17.6	0.51 (95% CI 0.20–0.29)	0.1958	9.0	0.36 (95% CI 0.13–1.03)	0.0084	18.0	0.36 (95% CI 0.13–1.03)	0.0075
> 9	16.9	2.92 (95% CI 1.22–6.96)		22.1	1.95 (95% CI 0.78–4.90)		18.8	2.76 (95% CI 0.97–7.90)		27.7	2.76 (95% CI 0.97–7.83)	
Site of primary tumor												
right	5.8	0.39 (95% CI 0.10–1.54)	0.0432	15.4	0.62 (95% CI 0.19–1.98)	0.3203	10.5	0.57 (95% CI 0.18–1.88)	0.2440	20.3	0.68 (95% CI 0.22–2.07)	0.4113
left	13.4	2.56 (95% CI 0.65–10.05)		21.2	1.62 (95% CI 0.51–5.16)		16.7	1.74 (95% CI 0.53–5.70)		25.8	1.47 (95% CI 0.48–4.50)	
Liver metastases												
yes	11.1	0.77 (95% CI 0.28–2.13)	0.6280	17.3	0.44 (95% CI 0.18–1.07)	0.0946	14.8	0.92 (95% CI 0.41–2.09)	0.8477	23.4	0.95 (95% CI 0.42–2.14)	0.8907
no	13.8	1.29 (95% CI 0.47–3.55)		27.1	2.29 (95% CI 0.94–5.62)		15.9	1.08 (95% CI 0.48–2.45)		25.5	1.06 (95% CI 0.47–2.38)	

FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab; FOLFOX4/bev – folinic acid, 5-fluorouracil, and oxaliplatin/bevacizumab; PFS – progression free survival; OS – overall survival; HR – hazard ratio; CI – confidence interval; pts – patients.

Table 5

Most frequent treatment-related adverse events per patient in a group of patients treated with FOLFOX4/bev, classified by grades

Adverse events	grade 1	grade 2	grade 3	grade 4	Total
	number of patients				n (%)
Alopecia	1				1 (3.3)
Anemia	2	1			2 (10.0)
Fatigue	2	1			3 (10.0)
Diarrhea	1	2	1		4 (13.3)
Epistaxis	3				3 (10.0)
Fever		1			1 (3.3)
Fistula				1	1 (3.3)
Anorexia	1				1 (3.3)
Hematuria		1			1 (3.3)
HF Sy.	2	2			4 (13.3)
Hypertension	5	3			8 (26.7)
Ileus				3	3 (10.0)
Leucopenia			3	4	7 (23.3)
Nausea and vomiting		1			1 (3.3)
Neuropathy	2				2 (6.7)
Neutropenia		4		1	5 (16.7)
Pancytopenia		1			1 (3.3)
Pulmonary Thromboembolism	1			2	3 (10.0)
Proteinuria	5				5 (16.7)
Rhinitis	1				1 (3.3)
Subileus				1	1 (3.3)
Epiphora		1			1 (3.3)
Thrombocytopenia	2		1		3 (10.0)

FOLFOX4/bev – folnic acid, 5-fluorouracil and oxaliplatin/bevacizumab; HF Sy – Hand-Foot Syndrome.

Table 6

Most frequent treatment-related adverse events per patient in a group of patients treated with FOLFIRI/bev, classified by grades

Adverse events	grade 1	grade 2	grade 3	grade 4	Total
	number of patients				n (%)
Alopecia	7				7 (23.3)
Anemia	1	1			2 (6.7)
Anorexia	1				1 (3.3)
Fatigue	5	1			6 (20.0)
Diarrhea	4	6		1	11 (36.7)
Dyspepsia	1				1 (3.3)
Lower Extremity Embolism	1				1 (3.3)
Epistaxis	5	1			6 (20.0)
HF Sy.		2			2 (6.7)
Hypertension	5	3	1		9 (30.0)
Ileus				1	1 (3.3)
Leucopenia		1			1 (3.3)
Nausea and vomiting	5	2			7 (23.3)
Neutropenia		1	2		3 (10.0)
Obstipation	1				1 (3.3)
Pancytopenia	1				1 (3.3)
Pneumonia		1			1 (3.3)
Proteinuria	3	1			4 (13.3)
Stomatitis	2	1			3 (10.0)
Subileus	1				1 (3.3)
Thrombocytopenia		2			2 (6.7)
Thrombophlebitis	2				2 (6.7)

FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab; HF Sy – Hand-Foot Syndrome.

Adverse drug reactions depending on the treatment duration

Table 7 shows the number of adverse drug events depending on the number of cycles of therapy classified by grade in patients treated with FOLFOX4/bev.

Table 8 shows the number of the reported ADRs depending on the number of cycles of therapy classified by grade in patients treated with FOLFIRI/bev.

Table 7

Total number of adverse drug events depending on the treatment duration classified by grade in patients treated with FOLFOX4/bev

Number of cycles	grade 1	grade 2	grade 3	grade 4
< 9 (n = 21 patients)	9	14	2	7
≥ 9 (n = 9 patients)	19	7	5	0

FOLFOX4/bev – folnic acid, 5-fluorouracil and oxaliplatin/bevacizumab.

Table 8

Total number of adverse drug events depending on the treatment duration classified by grade in patients treated with FOLFIRI/bev

Number of cycles	grade 1	grade 2	grade 3	grade 4
< 9 (n = 10 patients)	13	9	1	2
≥ 9 (n = 20 patients)	32	14	2	0

FOLFIRI/bev – folinic acid, 5-fluorouracil, and irinotecan/bevacizumab.

Characteristics of the survived patients

In our study, at data cut-off time, 6 patients were alive in the FOLFIRI/bev group and 9 patients in the FOLFOX4/bev group. All these patients had left-sided tumors. Radical surgery of the primary tumor was performed on 10 out of 15 living patients. Two patients in the FOLFIRI/bev group received adjuvant CHT. Ten out of fifteen patients received induction CHT for 9–12 cycles (4–6 months), and 8 of them received subsequent maintenance CHT with bev. Three patients in the FOLFIRI/bev group and 2 patients in the FOLFOX4/bev group underwent curative liver resection (second look surgery). After the liver surgery, both patients in the FOLFOX4/bev group and 1 patient in the FOLFIRI/bev group received CHT.

Discussion

Decisions for the optimal treatment of patients with mCRC should be made by a multidisciplinary team.

Most of the patients have metastatic disease that is not initially resectable. However, it is important to select patients with initially unresectable disease and in whom metastases may become suitable for resection after achieving a good response to combination CHT. The goal of treating this group of patients is to convert initially unresectable mCRC into resectable CRC.

Published results in international journals show the advantage of introducing angiogenesis inhibitors into standard CHT protocols for first-line treatment of mCRC [11].

Patients who received FOLFIRI/bev had better results than the patients treated with FOLFOX4/bev. Potential reasons are that the patients were younger, and the average age was 51. A significantly higher number of patients received adjuvant CHT, and also a higher number of patients had primary tumor resection. More patients in this group received induction CHT for a longer period of time, and a significantly higher number of patients had metastases in the liver alone.

ORR in both observed groups was high and statistically significantly higher in the FOLFIRI/bev group (70%) compared to the FOLFOX4/bev group (50%). ORR in the FOLFIRI/bev group was also higher compared to protocols for oligometastatic disease in the literature [12].

The assumption is that it was directly related to the fact that in both observed groups of patients, there was a large number of patients with left-sided colon tumors and that in the FOLFIRI/bev group, more patients had primary tumor resection and additionally, 56.6% of patients had liver metastases only. The high ORR is also supported by the fact that the average age of patients is lower (FOLFIRI/bev group – 51 years, FOLFOX4/bev group – 56 years). In the Bevacuzimab regimens investigation of treatment effects (BRiTE) study, the OS was 26.0 months in patients under the age of 65 [13].

Right-sided colon tumors are more common in women and have a higher stage at the time of diagnosis. They are mucinous, immunogenic, microsatellite unstable, more commonly RAS and BRAF genes mutated, and as such, have a worse prognosis. Left-sided colon tumors are more likely to have chromosomal instability, epidermal growth factor receptor (EGFR) expression, and higher VEGF-A expression.

In both patient groups, there was a significantly higher number of left-sided tumors (FOLFIRI/bev group 24/30 and FOLFOX4/bev group 25/30). Patients in both groups received bev leading to high ORR. Consequently, both PFS and OS were high.

The impact of localization of the primary tumor as a prognostic factor is known from earlier studies. The importance of localization in the efficacy of bev treatment was pointed out by Jordan et al. [14] in an analysis published in 2018, where 1,080 patients were monitored between 2003 and 2016. Patients with a tumor on the left side were compared with patients with a tumor on the right side, and their response to therapy was analyzed. Patients were divided into two groups: the

group of patients receiving bev and CHT (CHT/bev) and the group of patients receiving CHT only. OS for patients with left-sided tumors in the CHT/bev group was 31.5 months vs. 18.4 months for patients who received CHT only.

In contrast to patients with left-sided tumors, in patients with right-sided tumors, OS was 21.09 months in the CHT/bev group and 18.5 months in the CHT-only group. This indicates that the addition of bev to the treatment of patients with mCRC has a significant effect on the OS in patients with left-sided tumors. That is not the case in patients with right-sided tumors.

A meta-analysis by You et al. [15] published in Frontiers in Oncology showed improved survival when bev was added to chemotherapy in patients with left-sided mCRC.

Analysis by Jordan et al. [14] also showed that there was no benefit when bev was added to the treatment of patients with right-sided tumors regardless of the liver resection. In contrast, the addition of bev to the treatment of patients with left-sided tumors resulted in benefits even in patients who did not undergo resection of the liver metastases. The addition of bev affected the operability of the liver metastases. In the group of patients treated with CHT and bev, 25.3% of patients underwent liver resection in contrast to 18.6% of patients who received CHT only.

The efficacy and safety of bev in combination with CHT vs. CHT alone were analyzed in the meta-analysis published in BMC Cancer 2016 by Botrel et al. [12]. The analysis included 3,914 patients from 9 studies who received first-line treatment for mCRC. Patients who received CHT/bev had better ORR, PFS, and OS. Slightly better outcomes were seen in patients treated with irinotecan-containing protocols. In that meta-analysis, HR for PFS was 0.69 and for OS 0.87.

Median PFS was 15.6 months in the FOLFIRI/bev group (n = 30) and 12.1 months in the FOLFOX4/bev group (n = 30) (HR, 0.85; 95% CI 0.47–1.53; $p = 0.5591$). Median OS was 24.7 months in the FOLFIRI/bev group and 19.9 months in the FOLFOX4/bev group (HR, 0.67; 95% CI 0.37–1.23; $p = 0.1552$).

The Baraniskin et al. [16] meta-analysis published online in the European Journal of Cancer in November 2018 included 7 randomized trials analyzing the addition of bev to CHT in the first-line treatment of mCRC. Patients who received bolus 5-fluorouracil (5-FU) were excluded from the study. The addition of bev affected the prolongation of PFS in all studies except for the group of patients who received only 5-FU continuous infusion with bev. Extension in OS was not observed. This meta-analysis has its limitations in different study designs and objectives as well as different molecular subgroups of patients.

Incidence of ADR, as well as the severity of ADR in both patient groups (FOLFOX4/bev and FOLFIRI/bev), corresponds to the literature data [17, 18].

The difference was observed only for gastrointestinal (GI) perforations (13.3% in the FOLFOX4/bev group and 6.7% in the FOLFIRI/bev group). In the WJOG4407G trial, the incidence of GI perforations was 4% in the FOLFIRI/bev group and 3% in the FOLFOX4/bev group [19].

There were no GI perforations in TRIBE and OLIVIA trials. The reason for this, especially when it comes to the FOLFOX4/bev group, lies in the fact that the resection of the primary tumor was not performed. In the FOLFOX4/bev group, 23 out of 30 patients were operated on, while in the FOLFIRI/bev group, 27 out of 30 patients were operated on. There was less grade 3 and grade 4 ADR in both observed groups compared with the literature data [17, 20].

The incidence of ADR grades 1–3 was higher in the subgroup of patients who received 9 and more FOLFOX4/bev cycles, but the incidence of severe grade 4 ADR was significantly higher in the subgroup of patients who received less than 9 cycles of CHT.

A significant difference in the incidence between the two observed subgroups within the FOLFOX4/bev group was observed for leukopenia (3.3% vs. 20.0%) and proteinuria (3.3% vs.13.3%).

The incidence of grade 1–3 ADRs was higher in the subgroup of patients who received 9 and more FOLFIRI/bev cycles, but the incidence of severe grade 4 ADRs was significantly higher in the subgroup of patients who received less than 9 cycles of CHT.

No ADRs were observed in 5 patients, with 4 patients receiving 12 cycles and 1 receiving 7 cycles of FOLFIRI/bev CHT.

A significant difference in the incidence between the two observed subgroups within the FOLFIRI/bev group was observed for hypertension (0.0% vs. 30.0%), fatigue (0.0% vs. 20.0%), and proteinuria (0.0% vs. 13.3%).

ADRs generally occur within the first three months of treatment. A response to a significantly lower rate of grade 3 and 4 ADRs in both patient groups should be sought in a relatively small sample, as well as in a specific patient population and a significantly younger overall patient population in both groups. Better tolerance in younger patients was confirmed in the previous trials [21].

Patients experienced more nausea and vomiting in the FOLFIRI/bev group, and in the FOLFOX4/bev group, more leukopenia, neuropathies, and more grade 3 and 4 ADRs. In the FOLFIRI/bev group, fatigue, proteinuria, and hypertension occurred only in patients who received 9 to 12 cycles of induction therapy.

About 30% of patients with mCRC have LLD. These patients also die with liver metastases only. Resection of metastases in this subgroup of patients is a significant treatment option. The 5-year survival in patients who underwent resection was 55.2%, compared to 19.5% in patients who were unsuitable for resection. A 10-year survival was reported in 25.0% of patients who underwent resection. In our study, liver resection was performed in 16.7% of patients in the FOLFIRI/bev group and 10% in the FOLFOX4/bev group. Liver resection significantly influenced the increase in ORR in the FOLFIRI/bev group (70.0%).

Following curative resections of liver metastases, clinical studies support the use of bev with CHT (HEPATICA study). In this study, the two-year disease-free period for pa-

tients receiving CAPOX/bev was 70% compared to those receiving CAPOX alone (52%).

In our study, liver metastases alone were present in 17 patients (56.7%) in the FOLFIRI/bev group and in 7 patients (23.3%) in the FOLFOX4/bev group. This difference also resulted in better treatment results in the FOLFIRI/bev group compared to the FOLFOX4/bev group (higher PFS, OS, and ORR).

Limitations of the study

The limitations of this study are relatively small groups of patients. Moreover, the existence of a control group of patients who would receive only chemotherapy would give more information and more comprehensive conclusions. Doing molecular testing of RAS and BRAF genes would be advisable as well.

Conclusion

Patients from both groups received standard first-line CHT with the addition of bev, and the patients who received induction therapy for 4–6 months (9 to 12 cycles of therapy) had better treatment response. Those were the younger patients who had left-sided colon tumors, LLD, and who had their primary tumor resected. The consensus molecular subtypes classification and tumor microenvironment analysis of these patients could give us more information about these results. Those investigations could be the subject of future research.

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