

Bevacizumab plus chemotherapy in elderly patients with previously untreated metastatic colorectal cancer: single center experience

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Background. Metastatic colorectal cancer (mCRC) is mainly a disease of elderly, however, geriatric population is underrepresented in clinical trials. Patient registries represent a tool to assess and follow treatment outcomes in this patient population. The aim of the study was with the help of the patients' register to determine the safety and efficacy of bevacizumab plus chemotherapy in elderly patients who had previously untreated metastatic colorectal cancer. **Patients and methods.** The registry of patients with mCRC was designed to prospectively evaluate the safety and efficacy of bevacizumab-containing chemotherapy as well as selection of patients in routine clinical practice. Patient baseline clinical characteristics, pre-specified bevacizumab-related adverse events, and efficacy data were collected, evaluated and compared according to the age categories.

Results. Between January 2008 and December 2010, 210 patients with mCRC (median age 63, male 61.4%) started bevacizumab-containing therapy in the 1st line setting. Majority of the 210 patients received irinotecan-based chemotherapy (68%) as 1st line treatment and 105 patients (50%) received bevacizumab maintenance therapy. Elderly (≥ 70 years) patients presented 22.9% of all patients and they had worse performance status (PS 1/2, 62.4%) than patients in < 70 years group (PS 1/2, 35.8%). Difference in disease control rate was mainly due to inability to assess response in elderly group (64.6% in elderly and 77.8% in < 70 years group, $p = 0.066$). The median progression free survival was 10.2 (95% CI, 6.7–16.2) and 11.3 (95% CI, 10.2–12.6) months in elderly and < 70 years group, respectively ($p = 0.58$). The median overall survival was 18.5 (95% CI, 12.4–28.9) and 27.4 (95% CI, 22.7–31.9) months for elderly and < 70 years group, respectively ($p = 0.03$). Three-year survival rate was 26% and 37.6% in elderly vs. < 70 years group ($p = 0.03$). Overall rates of bevacizumab-related adverse events were similar in both groups: proteinuria 21/22 %, hypertension 25/19 %, haemorrhage 2/4 % and thromboembolic events 10/6 %, for elderly and < 70 years group, respectively.

Conclusions. In routine clinical practice, the combination of bevacizumab and chemotherapy is effective and well-tolerated regimen in elderly patients with metastatic colorectal cancer.

Key words: metastatic colorectal cancer; bevacizumab; chemotherapy; elderly

Introduction

As with many cancers, metastatic colorectal cancer (mCRC) is mainly a disease of elderly population. However, geriatric population is underrepresented in clinical trials. The median age at diagnosis

for patients with CRC is 72 years, while the median age of patients in clinical trials is 63 years.¹ In Slovenia, 44% of colorectal cancer cases were diagnosed in people aged 70 years and over.² Age together with performance status and comorbidities is one of the most important factors when deciding

on treatment regimen.³ Studies show that close to half of the elderly patients with stage III colon cancer do not receive chemotherapy, although most of the studies and meta-analysis have reported similar response rate (ORR), overall survival (OS), time to progression (TTP) and tolerability for elderly and younger patients in adjuvant and metastatic setting.^{4,6}

Addition of bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, to the chemotherapy backbone regimens improves progression-free survival (PFS) and overall survival in first-line and second-line treatment and when continued beyond first progression in mCRC.⁷ Data from large observational studies, subgroup analysis and pooled analysis of randomized trials have suggested that the survival benefits associated with the use of bevacizumab in the first-line treatment are similar in elderly and general population.⁸⁻¹³ With the introduction of bevacizumab as standard of care for mCRC patients in Slovenia¹⁴, our centre has created patient registry to prospectively assess patient selection as well as efficacy and safety of bevacizumab containing chemotherapy in routine clinical practice. This registry enabled data capturing of the mCRC management in geriatric population that is usually excluded in clinical research and comparison of clinical outcomes to their younger counterparts.

The aim of the study was with the help of the patients' register to determine the safety and efficacy of bevacizumab plus chemotherapy in elderly patients who had previously untreated metastatic colorectal cancer.

Patients and methods

Patient clinical baseline characteristics, pre-specified bevacizumab-related adverse events, and efficacy data were prospectively collected within local patient registry from 210 mCRC patients who started bevacizumab-containing chemotherapy in the 1st line setting. Patient clinical characteristics (primary tumour treatments, an Eastern Cooperative Oncology Group [ECOG] performance status [PS], metastatic burden), rate of bevacizumab-related toxicities, metastasectomy rate, ORR, PFS and OS were evaluated.

The study was done in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and was approved by national ethics committee. All patients provided written informed consent for data collection.

Statistical analysis

Statistical analyses were performed on the intent-to-treat (ITT) population e.g. patients who received at least one dose of bevacizumab. Patient characteristics and toxicity data were summarized descriptively by the age group. Proportions of categorical variables were compared using the chi-square test. Survival analyses were performed using the Kaplan-Meier method, which provided medians and 95% confidence intervals (CIs). The differences in survival were evaluated using the log rank test; the follow-up time for this comparison was limited to 3 years, which is the minimum period available for all the patients.

Results

Patient characteristics

The data from 210 patients (median age 63, males 61.4%) treated with bevacizumab-containing chemotherapy (B-CTX) in the 1st line setting in routine clinical practice were included in the evaluation. The patients with mCRC started B-CTX treatment between January 2008 and December 2010 and were followed for outcomes at our centre until December 2013. The ECOG PS at baseline was 0 in 58%, 1 in 38% and 2 in 4% of all patients. Subgroup Elderly patients (≥ 70 years, $n = 48$) presented 22.9% of all patients and they had worse performance status (PS1/2 62.4%) than patients in < 70 years group (PS1/2 35.8%). Patient characteristics are described in Table 1. Metastatic disease was the first diagnosis in 63% of patients < 70 years old, while in the elderly patients only 45.8% had mCRC as the first diagnosis of CRC.

Treatment

Bevacizumab 5 mg/kg every two weeks or 7.5 mg/kg every three weeks was administered in combination with chemotherapy (CTX) to the patients with mCRC. Majority of 210 patients received irinotecan-based chemotherapy (68%) as 1st line treatment and 105 patients (50%) received bevacizumab maintenance therapy. The patients in < 70 years group received mainly irinotecan-based chemotherapy (66%) - capecitabine plus irinotecan (XELIRI) 58.6%, capecitabine plus oxaliplatin (XELOX) 27.8%, leucovorin, fluorouracil plus irinotecan (FOLFIRI) 6.8%, leucovorin, fluorouracil plus oxaliplatin (FOLFOX) 4.9%, monotherapy capecitabine or irinotecan 1.8%. Median duration

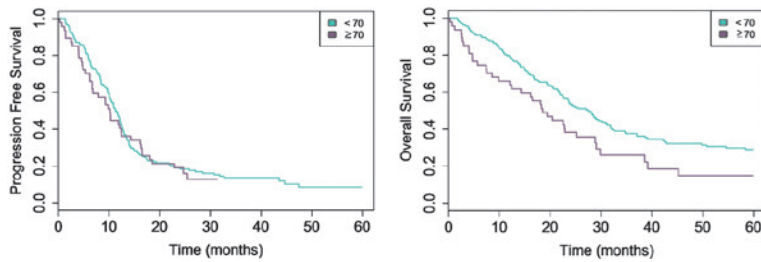


FIGURE 1. Kaplan-Meier survival curves for Progression Free Survival and Overall Survival in patients aged < 70 years and ≥ 70 years.

TABLE 2. Efficacy outcomes

Outcomes	Age < 70 y (n = 162)	Age ≥ 70 y (n = 48)
Best response, n (%)		
Complete	9 (6)	4 (8)
Partial	60 (37)	13 (27)
Stable disease	57 (35)	14 (29)
Progressive disease	21 (13)	6 (13)
Not evaluable	7 (4)	6 (13)
Overall response rate, % (95% CI)	69 (43)	17 (35)
Disease-control rate, % (95% CI)	126 (78)	31 (65)
Progression free survival, months		
Median (95% CI)	11.3 (10.2–12.6)	10.2 (6.7–16.2)
Overall survival, months		
Median (95% CI)	27.4 (22.7–31.9)	18.5 (12.4–28.9)
Metastasectomy, n (%)		
	32 (21.2)	6 (15)

CI = confidence interval

of B-CTX was 24 weeks (range 3 to 36) and the median number of treatment cycles was 8 (range 1 to 16). In this group of patients, maintenance bevacizumab was administered to 83 patients (51%), with median number of cycles 6 (range 1 to 70). The backbone chemotherapy in patients aged ≥ 70 years was also mostly irinotecan (75%) - XELIRI 60.4%, XELOX 14.6%, FOLFIRI 10.4%, FOLFOX 6.2%, monotherapy capecitabine or irinotecan 8.4%. Median duration of B-CTX in elderly was 17 weeks (range 3 to 36) and the median number of treatment cycles was 6 (range 1 to 12). Twenty one patients (44%) received maintenance bevacizumab with median number of cycles 5 (range 1 to 51).

Treatment interruption was reported in 20.4% of patients in < 70 years group and 14.6% of patients ≥ 70 years group. Two main reasons for bevacizumab discontinuation in < 70 years group were disease

TABLE 1. Patient characteristics at baseline

Characteristics	Age < 70 y (n = 162)	Age ≥ 70 y (n = 48)
Gender, n (%)		
Men	96 (60)	33 (70)
Women	64 (40)	14 (30)
Age		
Median, years	59	72
Range, years	24–69	70–81
ECOG performance status, n (%)		
0	104 (64)	18 (38)
1	52 (32)	27 (56)
2	6 (4)	3 (6)
3	0	0
Site of metastatic disease, n (%)		
Liver	112 (69)	35 (73)
Lung	39 (24)	12 (25)
Lymph nodes	42 (26)	12 (25)
Bones	6 (4)	3 (6)
Other	64 (40)	13 (27)
Primary tumour location, n (%)		
Colon only	106 (65)	31 (65)
Rectum only	56 (35)	16 (33)
Colon and rectum	0	1 (2)
Adjuvant chemotherapy, n (%)		
	50 (31)	18 (38)
Previous radiotherapy, n (%)		
	30 (19)	9 (19)
Surgical resection, n (%)		
	132 (82)	42 (88)

progression (49% of all patients that discontinued) and adverse events (25%). In ≥ 70 years group bevacizumab was discontinued due to disease progression (35%) and adverse events (20%), but 15% of patients were lost to follow-up.

Efficacy

Efficacy data are summarized in Table 2. Difference in disease control rate (DCR) was mainly due to inability to assess response in elderly group (64.6% in elderly and 77.8% in < 70 years group).

ORR and DCR did not differ significantly between the two groups ($p = 0.375$ and $p = 0.066$, respectively). The median PFS was 10.2 (95% CI, 6.7–16.2) and 11.3 (95% CI, 10.2–12.6) months in elderly and < 70 years group, respectively ($p = 0.58$) (Figure 1). The median OS was 18.5 (95% CI,

12.4–28.9) and 27.4 (95% CI, 22.7–31.9) months for elderly and <70 years group, respectively ($p = 0.03$) (Figure 1).

Metastasectomy was performed in 6 (15%) of elderly patients and 32 (21.2%) patients in <70 years group. Three-year survival rate was 26% (95% CI, 15.3–44.2) and 37.6% (95% CI, 30.7–46.1) in elderly *vs.* <70 years group ($p = 0.03$).

In elderly patients, 15 patients received second-line therapy, all of them receiving bevacizumab in combination with subsequent chemotherapy. In patients aged <70 years, 101 patients received second-line therapy, out of which 76% contained bevacizumab.

Toxicity

Adverse events related to bevacizumab were reported in 123 (75.9%) and 38 (79.2%) patients in <70 years and ≥ 70 years group, respectively. Adverse events of special interest to bevacizumab are summarized in Table 3 (epistaxis excluded). A case of vesico-rectal fistula was reported in the patient aged <70 years (rectal cancer with previous radiotherapy). One case of acute myocardial infarction was reported in each group. One patient on capecitabine monotherapy from elderly group presented with adverse event with an outcome death (heart failure).

The incidence of adverse event that led to bevacizumab discontinuation was 19% in both age groups. The incidence of adverse event that led to bevacizumab dose interruption was 10.5% and 10% in patients aged <70 and ≥ 70 years, respectively.

Discussion

Randomized studies, subgroup and pooled analysis, along with large observational studies suggest that bevacizumab containing first-line chemotherapy is efficacious and safe in elderly patients with mCRC. Randomized phase II trial of bevacizumab or placebo added to 5-FU in elderly patients not suitable for irinotecan treatment reported significantly longer PFS in patients who received bevacizumab *versus* placebo (9.2 months *versus* 5.5 months, respectively, hazard ratio, 0.5; $p = 0.0002$).¹⁵ Furthermore, results from phase III trial AVEX showed that in patients over age of 70 years and non-fit for oxaliplatin or irinotecan-based chemotherapy, PFS was significantly longer in the group of patients who received bevacizumab plus capecitabine *versus* the capecitabine alone group

TABLE 3. Targeted adverse events

Adverse event	No. of patients (%)				Total
	Grade1	Grade2	Grade3	Grade4	
< 70 years (n = 162)					
Hypertension	11 (6.8)	15 (9.3)	5 (3.1)	0 (0)	30 (18.5)
Thromboembolism	1 (0.6)	4 (2.5)	4 (2.5)	0 (0)	9 (5.6)
Proteinuria	23 (14.2)	11 (6.8)	2 (1.2)	0 (0)	36 (22.2)
Hemorrhage	4 (2.5)	1 (0.6)	0 (0)	1 (0.6)	6 (3.7)
Infection	4 (2.5)	1 (0.6)	4 (2.5)	0 (0)	8 (4.9)
> 70 years (n = 48)					
Hypertension	3 (6.2)	6 (12.5)	2 (4.2)	0 (0)	12 (25)
Thromboembolism	0 (0)	1 (2.1)	2 (4.2)	2 (4.2)	5 (10.4)
Proteinuria	7 (14.6)	3 (6.2)	0 (0)	0 (0)	10 (20.8)
Hemorrhage	0 (0)	0 (0)	1 (2.1)	0 (0)	1 (2.1)
Infection	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (2.1)

(9.1 *versus* 5.1 months, $p < 0.0001$).¹⁶ The subanalysis of the BICC-C study (bevacizumab + FOLFIRI or mFL) reported no difference in efficacy and safety for mCRC patients >70 years compared with patients ≤ 70 years (PFS 7.6 months compared to 10.7 months, $p = 0.14$, with FOLFIRI/Bev ORR 57% >70 years and 58% ≤ 70 years).¹¹ Pooled analysis of four randomized trials (three first-line and one second-line treatment, $n = 3,007$), where patients were treated with fluoropyrimidine-based chemotherapy with or without bevacizumab, showed that addition of bevacizumab to CTX significantly prolonged PFS in older and younger patients with similar magnitude of PFS benefit (hazard ratios were 0.59, 0.58 and 0.54 in patients aged <65 years, ≥ 65 years and ≥ 70 years, respectively). In addition, OS in both older and younger patients was statistically significantly prolonged by addition of bevacizumab to CTX (median OS was 19.9 months in patients aged <65 years, 17.9 months in patients ≥ 65 years and 17.4 months in those aged ≥ 70 years).¹³ Recent results from phase II study BECOX suggest that bevacizumab plus XELOX is effective and well tolerated in elderly mCRC patients with time to progression of 11.1 months, median OS of 20.4 months and ORR of 46%.¹⁷

Bevacizumab-containing CTX outcomes from routine clinical practice were monitored and/or reported in mCRC patients registries such as prospective US BRiTE registry ($n = 1,953$)⁹ or retrospective Czech ($n = 3,187$) and French ($n = 1,322$) registries.^{10,18} These large first-line setting registries confirmed similarity of clinical benefit between

younger and older patients, previously reported in randomized clinical trials and pooled analysis.

Safety profile for all these studies is generally similar in older and younger patients, except for thromboembolic events, which were more common in the older group.

Within local registry of patients with metastatic colorectal cancer, we have assessed efficacy and safety of bevacizumab in combination with various chemotherapy regimens and compared data between two age groups - patients aged below and over 70 years.

While other registries as backbone chemotherapy reported use of primarily oxaliplatin-based first line chemotherapy (FOLFOX followed by XELOX or FOLFIRI) with trend of increased monotherapy use in elderly population, in our centre backbone chemotherapy was in majority of patients (68%) irinotecan-based. Specifically, bevacizumab was administered mainly with XELIRI (58.6% in <70 years group and 60.4% in ≥70 years group) followed by XELOX (27.8% in <70 years group and 14.6% in ≥70 years group) with low rate of monotherapy use (1.8% and 8.4% for <70 years and ≥70 years, respectively). Although median duration of B-CTX in elderly was 17 weeks and in patients aged <70 years was 24 weeks, maintenance with bevacizumab was well tolerated in both groups with median number of cycles 6 and 5 for <70 years (51% of patients) and ≥70 years group (44% of patients), respectively. ORR and DCR did not differ significantly between the two groups ($p = 0.375$ and $p = 0.066$, respectively) which is in concordance with other studies. The median PFS of 10.2 and 11.3 months in elderly and <70 years group, respectively ($p = 0.58$) is also comparable to findings in other studies. In BRiTE registry, even after adjusting for significant baseline covariates such as ECOG PS or site and surgical resection of primary tumour, decreasing median OS in older age cohorts was observed.⁹ Similarly, in our study median OS was 18.5 and 27.4 months for elderly and <70 years group, respectively ($p = 0.03$). This can be partially explained by worse PS in elderly (PS1/2 62.4%) than patients in <70 years group (PS1/2 35.8%). Selection bias and influence of comorbidities and presence of synchronous metastasis that were not captured cannot be excluded.

In the registry, only bevacizumab-associated adverse event information was collected. A disadvantage of our registry was lack of data for chemotherapy induced adverse events. This was not in scope of the registry, as in an earlier retrospective study from our group, where we compared XELIRI/

bevacizumab to FOLFIRI/bevacizumab (age range 31–77 years), we have reported similar efficacy and safety data between two chemotherapy regimens, but with more grade 3/4 neutropenia in FOLFIRI/bevacizumab combination, and more grade 3/4 diarrhoea in XELIRI/bevacizumab, findings confirmed also by other studies.^{19,20}

The rates of most bevacizumab-targeted adverse events in the older patient group were similar to rates in the patients aged <70 years. They were also comparable to previously reported overall rates of adverse events.^{9,13,15} The most common bevacizumab-associated adverse events were hypertension and proteinuria, with hypertension being slightly more observed in elderly (25% *vs.* 18.5%). No grade 4 or 5 hypertensive events were recorded. Thromboembolic events were reported in 10.4% of elderly patients compared to 5.6% in patients aged <70 years. The increase of arterial thromboembolism in elderly treated with bevacizumab, but no change in venous thromboembolic events, was previously reported in pooled analysis of four randomized trials as well as in large patient registry.^{9,13}

Conclusions

Our single centre experience present new set of data confirming PFS and OS benefit of bevacizumab containing, predominantly irinotecan-based first-line chemotherapy in mCRC patients in routine clinical practice. This benefit was observed in both elderly and patients aged <70 years with manageable safety profile. Proper selection of patients with mCRC can result in a safe and beneficial B-CTX treatment results in older patients with similar outcomes to their younger counterparts, therefore, chronological age does not present exclusion to treatment with bevacizumab.

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