Original Study

Evaluation of Bevacizumab in Advanced Small Bowel Adenocarcinoma

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Abstract

Small bowel adenocarcinomas (SBAs) are rarely seen tumors of the gastrointestinal system. Data on the usage of chemotherapy together with bevacizumab in SBAs is limited. We analyzed the results of treatment with bevacizumab with or without chemotherapy in 28 patients with SBAs. Although there was a trend toward a survival benefit, we did not find any statistically significant difference with the addition of bevacizumab to the backbone chemotherapy in SBAs.

Background: Small bowel adenocarcinomas (SBAs) are rarely seen tumors. Data regarding the use of chemotherapy together with bevacizumab in patients with advanced SBA are lacking. The aim of this study was the evaluation of treatment with bevacizumab in advanced SBA. **Materials and Methods:** Twenty-eight patients from 5 centers with a diagnosis of advanced SBA who received first-line treatments with modified FOLFOX6 (mFOLFOX6; oxaliplatin, leucovorin, and 5-fluorouracil) and FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) chemotherapy regimens were involved in the study. All patients were divided into 2 groups; those who received bevacizumab together with these chemotherapy regimens (Chemo+Bev group) and those who did not receive bevacizumab (Chemo group). **Results:** The median progression-free survival (PFS) and overall survival (OS) times of all population were 8.7 months and 16.9 months, respectively. The overall response rate was 43.7% in the Chemo group and 58.3% in the Chemo+Bev group. The median PFSs in the Chemo and Chemo+Bev groups were found to be 7.7 months and 9.6 months, respectively, and the median OSs were 14.8 months and 18.5 months, respectively. There was not a significant difference between the groups in terms of overall response rate, PFS, and OS. **Conclusion:** Although there was no significant difference in any of the outcomes, use of bevacizumab together with chemotherapy is a more effective treatment approach compared with chemotherapy alone, and it does not cause an excess of significant toxicity.

Clinical Colorectal Cancer, Vol. 16, No. 1, 78-83
Keywords: Adenocarcinoma, Advanced, Bevacizumab, Bowel, Small

Introduction

Small bowel tumors are rare tumors of the gastrointestinal tract. Adenocancers, which are the most common histopathologic subtype, together with carcinoid tumors, account for approximately 25% to 40% of all small bowel tumors.[1-3] Nearly 60% of small bowel adenocancers (SBAs) are localized in the duodenum, with a decreasing prevalance towards the distal parts.[4,5] The mean age of diagnosis ranges from 50 to 70 years, and there is a male predominance with a ratio of 3 to 2.[1,3] Diagnosis is troublesome as the disease is rarely seen, and symptoms and signs are not specific to the disease.[3,6] Because symptoms and signs are nonspecific and there are delays in diagnosis, the disease is usually diagnosed at advanced stages that may substantially worsen the survival and negatively affect the response to treatment. About one-third of patients were at

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Submitted: Jan 28, 2016; Revised: Mar 23, 2016; Accepted: Apr 27, 2016; Epub: May 7, 2016

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1533-0028/$ - see frontmatter
http://dx.doi.org/10.1016/j.clcc.2016.04.013

advanced stages at the time of diagnosis and their prognoses were extremely poor.[7] Studies regarding systemic treatment in advanced SBAs are extremely limited, given the rarity of these tumors. Clinicians generally tend to decide treatment based upon the results of studies conducted basically in colorectal and gastric adenocancers. Similarly, the use of bevacizumab (a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibting vascular endothelial growth factor A) in combination with chemotherapy has not been adequately studied. There are currently no standard chemotherapy regimens specifically approved for advanced SBA. Conclusively, there is an unmet medical need regarding the use of systemic chemotherapy and bevacizumab together with systemic chemotherapy in advanced SBAs. Therefore, in this multicenter retrospective study, we aimed to determine the effects of mFOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil) and FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) (Chemo group) alone (which are generally used as standard first-line chemotherapy regimens in advanced colorectal cancers) and the addition of bevacizumab to these regimens (Chemo+Bev group) on overall survival (OS) and progression-free survival (PFS) in patients diagnosed with advanced SBA.

Patients and Methods

Twenty-eight patients from 5 different centers with diagnosis of advanced SBA between August 2003 and May 2014 who had an Eastern Cooperative Oncology Group Performance Status of 0 to 1 and who received mFOLFOX6 and FOLFORI chemotherapy regimens as first-line chemotherapy were involved in our study. Patients were divided into 2 groups, as ones who received bevacizumab together with these chemotherapy regimens (Chemo+Bev group) and ones who did not receive bevacizumab (Chemo group). Clinical information, such as age, gender, histopathologic grade, localization, previous treatments, metastatic site of tumors, treatment responses, toxicities, and survey of patients, were obtained from patient files. The staging of the patients was carried out by using the 2010 American Joint Committee on Cancer (seventh edition) system according to pathologic, clinical, and radiologic findings on the date of diagnosis.[8] Patients were followed every 3 to 4 months in the first 2 to 3 years, every 6 months in the subsequent 2 years, and yearly thereafter.

Chemotherapy Regimens

Twenty-eight advanced SBA patients received 1 of the 2 different regimens as first-line chemotherapy. These regimens involve the mFOLFOX6 regimen (oxaliplatin 85 mg/m^2, at day 1; leucovorin 200 mg/m^2 over 2 hours, at day 1; fluorouracil 400 mg/m^2 bolus, at day 1, followed by 2400 mg/m^2 over 46 hours, cycled in every 14 days)[9] and the FOLFIRI regimen (irinotecan 180 mg/m^2, at day 1; leucovorin 200 mg/m^2 over 2 hours, at day 1; fluorouracil 400 mg/m^2 bolus, at day 1, followed by 2400 mg/m^2 over 46 hours, cycled in every 14 days).[10] Sixteen of 28 patients received only chemotherapy, whereas 12 patients received bevacizumab (5 mg/kg, at day 1, cycled in every 14 days) combined with chemotherapy.

Statistical Analysis

The data were analyzed to determine the clinical characteristics, treatment patterns, outcomes, and prognostic factors of SBA. Statistical calculations were performed using IBM SPSS statistics 17.0 (SPSS, Inc, Chicago, IL). Descriptive analyses were presented using means and standard deviations for normally distributed variables. The significance of the differences between the mean values was determined by the Mann-Whitney *U* test. The difference in the distribution of ordinal variables was evaluated with the χ^2 test or the Fisher exact test. The survival analysis and curve were compared using the log-rank test by the Kaplan-Meier method. PFS and OS were defined as the duration between the first chemotherapy dose and the date of disease progression or death, and the duration between the first chemotherapy dose and death or loss of follow-up or current date, respectively. Univariate and multivariate analyses (Cox proportional hazards model) were used to calculate hazard ratios with 95% confidence intervals (CIs). A 2-sided *P*-value of $< .05$ was considered a statistically significant difference.

Results

Patient Characteristics

The median age of the 28 patients with advanced SBA involved in the study was 52.4 years (range, 27-69 years), and about 57% of them were male. The primary localization of tumor was the duodenum in 57%, the jejunum in 25%, and the ileum in 18%. At diagnosis, 89% of the patients were metastatic, and 11% of them were at the locally advanced stage. De novo metastatic disease was detected in 57% of patients. More than half of the patients (57%) had liver metastases. Eleven (43%) patients previously had a curative resection and then progressed to an advanced stage. Seven of 11 patients who were resected curatively received adjuvant chemotherapy.

As first-line chemotherapy, 17 (60%) patients received an mFOLFOX6 regimen, and 11 (40%) received a FOLFIRI regimen. Sixteen patients received only chemotherapy (Chemo group), whereas 12 patients received bevacizumab together with chemotherapy (Chemo+Bev group). In the Chemo group, 68% of the patients received an mFOLFOX6 regimen and 32% of them received a FOLFIRI regimen; in the Chemo+Bev group, half of them received an mFOLFOX6 regimen and the other half received a FOLFIRI regimen. The median number of chemotherapy cycles was 12 (range, 4-14). There was no significant difference between groups in terms of patient characteristics. The distribution of patient features according to all patients and treatment groups is shown in Table 1.

Response to Treatment

The overall response rate (ORR) obtained with chemotherapy in the whole population was 50%, a complete response was observed in 3 patients, a partial response was observed in 11 patients, and stable disease was seen in 6 patients. According to treatment groups, the ORR was 58.3% in the Chemo+Bev group and 43.7% in the Chemo group, which was statistically insignificant (Table 2).

Survival Analysis

The median duration of follow-up was 16.3 months (range, 3.7-33.1 months) and all patients died of the disease. One- and 2-year PFS rates in the whole population were 11% and 0%, respectively, and 1- and 2-year OS rates were 79% and 10%, respectively. The median PFS and OS times for all patients were 8.7 months (SE, 0.6;

Table 1 Baseline Characteristics of Patients

Characteristics	All Patients n (%) n = 26	Type of Chemotherapy		*P* Value
		Chemo+Bev n (%) n = 12	Chemo n (%) n = 16	
Age (years)				.22
Median age (range)	52.4 (27-69)	51.6 (27-68)	52.9 (33-69)	
<60	20 (71)	10 (83)	10 (62)	
≥60	8 (29)	2 (17)	6 (38)	
Gender				.12
Female	12 (43)	3 (25)	9 (56)	
Male	16 (57)	9 (75)	7 (44)	
Grade				.18
Gr 1	6 (22)	4 (33)	2 (13)	
Gr 2	18 (64)	5 (42)	13 (81)	
Gr 3	4 (14)	3 (25)	1 (6)	
Localization				.54
Duodenum	16 (57)	6 (50)	10 (62)	
Jejunum	7 (25)	3 (25)	4 (25)	
Ileum	5 (18)	3 (25)	2 (13)	
De novo metastatic disease				.36
Yes	16 (57)	6 (50)	10 (62)	
No	12 (43)	6 (50)	6 (38)	
Localization of metastasis				.22
Liver	16 (57)	7 (58)	9 (56)	
Lung	1 (3)	0 (0)	1 (6)	
Peritoneal metastasis	8 (29)	3 (25)	5 (32)	
Locally relapsed	3 (11)	2 (17)	1 (6)	
Chemotherapy regimens				.51
mFOLFOX6	17 (60)	6 (50)	11 (68)	
FOLFIRI	11 (40)	6 (50)	5 (32)	
Number of cycles				.41
Mean	10	10.4	9.7	
Median (range)	12 (4-14)	12 (6-14)	12 (4-12)	
Second-line chemotherapy				.49
Yes	15 (54)	7 (58)	8 (50)	
No	13 (46)	5 (42)	8 (50)	

Abbreviations: Chemo = Chemotherapy; Chemo+Bev = chemotherapy + bevacizumab; FOLFIRI = leucovorin, 5-fluorouracil, and irinotecan; mFOLFOX6 = oxaliplatin, leucovorin, and 5-fluorouracil.

95% CI, 7.6-9.8 months) and 16.9 months (SE, 1.7; 95% CI, 13.3-20.1 months), respectively. The median PFSs in the Chemo and Chemo+Bev groups were 7.7 months (SE, 1.0; 95% CI, 5.7-9.7 months) and 9.6 months (SE, 0.5; 95% CI, 8.6-10.5 months), respectively, and the median OS times were 14.8 months (SE, 1.2; 95% CI, 12.4-17.3 months) and 18.5 months (SE, 1.6; 95% CI, 15.4-21.6 months), respectively. There was not a significant difference between the groups in terms of ORR, PFS, and OS. PFS and OS times of patients according to treatment are shown in Figure 1.

Toxicity

Patients were evaluated in terms of treatment-related toxicity. In 5 patients who received the mFOLFOX6 regimen and in 4 patients who received the FOLFIRI regimen, grade 3 to 4 toxicity developed. Most of the grade 3 to 4 toxicities were hematologic. The majority of hematologic toxicities were neutropenia (63%) and thrombocytopenia (29%). Two patients developed oxaliplatin-related neurotoxicity, and 1 patient developed irinotecan-related diarrhea. In the Chemo+Bev group, because of the use of bevacizumab, 1 patient developed grade 3 to 4 hypertension, and 1 patient experienced nasal bleeding. None of the patients died of toxicity, and there was no significant difference between treatment groups in terms of grade 3 to 4 toxicity.

Second-Line Chemotherapy

Second-line chemotherapy was administered to 15 (54%) patients, 7 (58%) of whom were in the Chemo+Bev group and 8

Table 2 Tumor Response According to Treatment

Patient With Measurable Disease	Treatment		*P* Value
	Chemo + Bev n (n = 12)	Chemo n (n = 16)	
Complete response	2	1	
Partial response	5	6	
Stable disease	3	3	
Disease progression	2	6	
Overall response rate (%)	58.3	43.7	.44

Abbreviations: Chemo = Chemotherapy; Chemo+Bev = chemotherapy + bevacizumab.

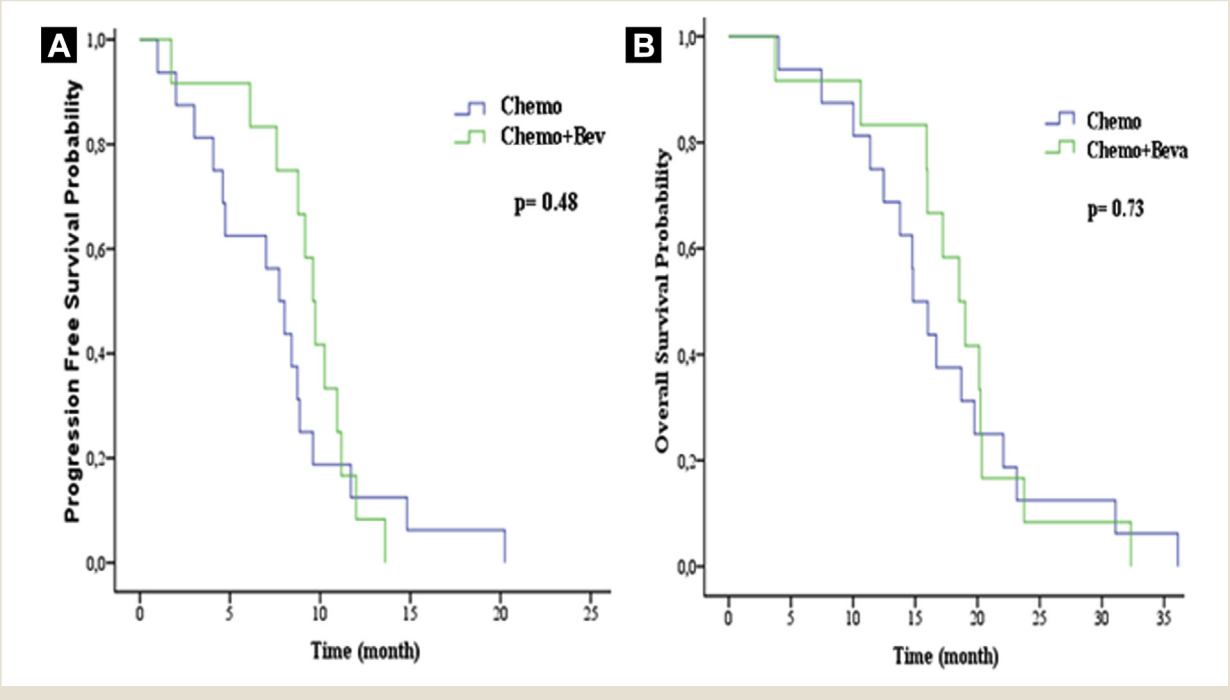
(50%) of whom were in the Chemo group. Patients who progressed on first-line mFOLFOX6 or on FOLFIRI regimens were followed by an alternate sequence in the second-line setting. None of the patients received a biologic or targeted agent as part of the second-line treatment.

Discussion

Because of the absence of randomized studies that compare different chemotherapy protocols in advanced SBAs, given the rarity of disease and difficulties in diagnosis, there is not a standard first-line chemotherapy regimen. Therefore, chemotherapy protocols applied in advanced SBAs in most of the oncology clinics are given upon the basis of protocols particularly used in the treatment of advanced colorectal cancers. Currently, FOLFOX and FOLFIRI regimens are standard first-line chemotherapy regimens that are used in advanced colorectal cancers.[10,11] Both agents have a similar effectiveness as the first-line chemotherapy in advanced colorectal adenocancers.[12,13] There are a limited number of studies that evaluated the effectiveness of oxaliplatin- and irinotecane-based regimens in advanced SBA; these are mostly retrospective. In a single-center, prospective, phase II study conducted by Owerman et al including 31 patients diagnosed with advanced or inoperable small bowel and ampullary adenocarcinoma (which was one of the rare prospective studies), a CAPOX regimen (capecitabin 750 mg/m^2 twice daily on days 1 through 14 and oxaliplatin 130 mg/m^2 on day 1, every 21 days) was evaluated in 25 patients with metastatic disease.[14] The objective response rate was found to be 52%. Time-to-progression and median OS were reported as 9.4 months and 15.5 months, respectively. In an another multicenter phase II study conducted by Xiang et al including 32 patients diagnosed with unresectable and metastatic small bowel adenocancers, a modified FOLFOX regimen was evaluated.[15] With a modified FOLFOX6 regimen, the objective response rate was found to be 49%. The median time-to-progression and median OS were reported as 7.8 months and 15.2 months, respectively. Results in other prospective and retrospective studies regarding oxaliplatin apart from the prospective studies mentioned above also support these results.[16,17]

In addition to the low number of prospective studies, there are retrospective studies evaluating various chemotherapy regimens in

Figure 1 The Curves of Progression-Free Survival (A) and Overall Survival (B) According to Treatment



Abbreviations: Chemo = Chemotherapy; Chemo+Bev = chemotherapy + bevacizumab.

advanced SBA.[16,18-20] One of these retrospective studies was performed by the MD Anderson Cancer Center and included 80 patients who had been diagnosed with metastatic SBA and received various chemotherapy regimens.[18] Twenty patients received FU and platinum (mostly cisplatin), 41 received platinum-free FU-dependent chemotherapy, and 10 received non—FU-involving chemotherapy. The response rates and the median PFS time of platinum plus FU regimens were significantly better compared with other regimens (46% vs. 16% and 8.7 months and 3.9 months, respectively). However, this result did not affect the median OS time (14.8 months vs. 12 months, respectively).

There are also retrospective studies supporting the efficacy of irinotecan and gemcitabine, excluding platinum regimens.[19,21,22] However, both retrospective and prospective trials evaluating irinotecan- and gemcitabine-based regimens are relatively few compared with those evaluating platin-based regimens, particularly oxaliplatin-including regimens. In one of these rare trials, irinotecan- and gemcitabine-based regimens were retrospectively evaluated in 44 patients with advanced SBA.[21] Of the 44 patients, 12 were treated with irinotecan-based palliative chemotherapy (6 FOLFIRI, 2 capecitabine plus irinotecan, 4 single agent irinotecan), and the rate of overall response was stated as 41.6% with these regimens.[21] In the same trial, 17 of 44 patients received gemcitabine-based chemotherapy (9 single agent gemcitabine, 4 gemcitabine plus FU, 4 gemcitabine plus capecitabine), and the corresponding overall response rate was found to be 41.1%.[21]

In our study, the overall response rate, median PFS, and median OS times in 16 patients that received only mFOLFOX6 or FOLFIRI were consistent with those reported in the literature. Although there is no randomized study regarding this issue, retrospective studies of varying numbers support that patients with unresectable SBAs who received chemotherapy have an advantage on survival compared with those who did not.[15,19,21,23] Regarding chemotherapy selection, FOLFOX seems to be superior to other chemotherapy regimens[16,19,23]; however, FOLFIRI is another regimen of choice in terms of effectiveness and tolerability.[20,21] The results of first-line treatment are not satisfactory in advanced SBA, despite the improvements in outcome suggested by published studies. As is known, the benefit of adding bevacizumab (a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A) to an irinotecan-based regimen in the first-line treatment of advanced colorectal adenocancers was demonstrated in a phase III study published in 2004 that included 813 patients.[24] The addition of bevacizumab significantly improved ORR (45% vs. %35), median PFS (10.6 vs. 6 months), and median OS (20 vs. 16 months). The effectiveness of addition of bevacizumab to regimens including irinotecan as well as oxaliplatin was also demonstrated.[25] However, data regarding the effectiveness of bevacizumab in advanced SBA was extremely rare. Reports were limited to case presentations, but the results were promising.[26-28] In our study of 12 patients who received bevacizumab combined with mFOLFOX6 or FOLFIRI, 2 developed complete response, and 5 developed partial response. With the addition of bevacizumab to chemotherapy, the ORR (58.3% vs. 43.7%), median PFS (9.6 vs. 7.7 months), and median OS (18.5 vs. 14.8 months) were improved, although none of them were statistically significant. This is probably related to the low statistical power of the study. Whereas the addition of bevacizumab improved survival, it does not appear to increase the incidence of the grade 3 to 4 toxicity.

Conclusions

There is no study available that evaluated the effectiveness of bevacizumab combined with chemotherapy except for data from a few case reports. Our study, to our knowledge, is the first to evaluate the use of bevacizumab together with chemotherapy and is therefore valuable. Although there was no significant difference in any of the outcomes, the use of bevacizumab together with chemotherapy is a more effective treatment approach compared with chemotherapy alone, and it does not cause an excess of significant toxicity. However, due to the nonrandomized and retrospective nature of this study, along with the small sample size and nonoptimal homogeneity between treatment groups, the power of the current study is low. Multicenter prospective studies including sufficient amount of patients for the determination of first-line chemotherapy and the effectiveness of bevacizumab in advanced SBA patients are required. We hope that this study will help contribute to designs of future prospective studies.

Clinical Practice Points

- There is no study available that evaluated the effectiveness of bevacizumab combined with chemotherapy in patients with advanced SBA except for a few case reports.
- With the addition of bevacizumab to chemotherapy, the ORR, median PFS, and median OS were improved, although none of them were statistically significant.
- We believe our data support that the use of bevacizumab together with chemotherapy is a more effective treatment approach compared with chemotherapy alone.

Disclosure

The authors have stated that they have no conflicts of interest.

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