JBUON 2016; 21(5): 1242-1249
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Evaluation of prognostic factors and treatment in advanced small bowel adenocarcinoma: report of a multi-institutional experience of Anatolian Society of Medical Oncology (ASMO)

Dincer Aydin[1], Mehmet Ali Sendur[2], Umut Kefeli[3], Olcun Umut Unal[4], Didem Tastekin[5], Murat Akyol[6], Eda Tanrikulu[7], Aydin Ciltas[8], Basak Bala Ustaalioglu[9], Didem Sener Dede[10], Onur Esbag[11], Ali Inal[12], Cemil Bilir[13], Ahmet Bilici[14], Hakan Harputlu[15],Veli Berk[16], Alper Sevinc[17], Nuriye Yildirim Ozdemir[2], Emre Yildirim[1], Alper Sonkaya[3],Mehmet Ali Ustaoglu[1], Mahmut Gumus[18]

[1]Department of Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul; [2]Department of Medical Oncology, Numune Education and Research Hospital, Ankara; [3]Department of Medical Oncology, School of Medicine, Kocaeli University, Kocaeli; [4]Department of Medical Oncology, Faculty of Medicine, Dokuz EylulUniversity, Izmir; [5]Department of Medical Oncology, Faculty of Medicine, Selcuk University Meram, Konya; [6]Department of Medical Oncology, Faculty of Medicine, Katip Celebi University, Izmir; [7]Department of Medical Oncology, Faculty of Medicine, Marmara University, Istanbul; [8]Department of Medical Oncology, Faculty of Medicine, Gazi University, Ankara; [9]Department of Medical Oncology, Haydarpasa Education and Research Hospital, Istanbul; [10]Department of Medical Oncology, Faculty of Medicine, Yildirim Beyazit University, Ankara; [11]Department of Medical Oncology, Ankara Oncology Education and Research Hospital, Ankara; [12]Department of Medical Oncology, Faculty of Medicine, Dicle University, Diyarbakir; [13]Department of Medical Oncology, Faculty of Medicine, Karaelmas University, Zonguldak; [14]Department of Medical Oncology, Faculty of Medicine, Medipol University, Istanbul; [15]Department of Medical Oncology, Faculty of Medicine, Inonu University, Malatya; [16]Department of Medical Oncology, Faculty of Medicine, Erciyes University, Kayseri; [17]Department of Medical Oncology, Faculty of Medicine Gaziantep University, Gaziantep; [18]Department of Medical Oncology, Faculty of Medicine, Bezmialem University, Istanbul, Turkey

Summary

Purpose: *Small bowel adenocarcinoma (SBA) is a rare tumor of the gastrointestinal system with poor prognosis. Since these are rarely encountered tumors, there are limited numbers of studies investigating systemic treatment in advanced SBA. The purpose of this study was to evaluate the prognostic factors and systemic treatments in patients with advance SBA.*

Methods: *Seventy-one patients from 18 Centers with advanced SBA were included in the study. Fifty-six patients received one of the four different chemotherapy regimens as first-line therapy and 15 patients were treated with best supportive care (BSC).*

Results: *Of the 71 patients, 42 (59%) were male and 29 (41%) female with a median age of 56 years. Median follow-up duration was 14.3 months. The median progression free survival (PFS) and overall survival (OS) were 7 and 13 months, respectively (N=71). In patients treated with FOLFOX (N=18), FOLFIRI (N=11), cisplatin-5-fluorouracil/5-FU (N=17) and gemcitabine alone (N=10), median PFS was 7, 8, 8 and 5 months, respectively, while median OS was 15, 16, 15 and 11 months, respectively. No significant differences between chemotherapy groups were noticed in terms of PFS and OS. Univariate analysis revealed that chemotherapy administration, de novo metastatic disease, ECOG PS 0 and 1, and overall response to therapy were significantly related to improved outcome. Only overall response to treatment was found to be significantly prognostic in multivariate analysis (p= 0.001).*

Conclusions: *In this study, overall response to chemotherapy emerged as the single significant prognostic factor for advanced SBAs. Platin and irinotecan based regimens achieved similar survival outcomes in advanced SBA patients.*

Key words*: advanced, chemotherapy, prognostic factors, small bowel adenocarcinoma*

Correspondence to: Dincer Aydin, MD.Dr. Lutfi Kirdar Kartal Training and Research Hospital, Department of Medical Oncology, Semsi Denizer Street, 34890, Kartal, Istanbul, Turkey. Tel: +90 5072751746, Fax: +90 2164422947, E-mail: dinceraydin79@yahoo.com
Received: 16/01/2016; Accepted: 01/02/2016

Introduction

Malignant tumors in small bowel compose a rarely seen disease group. Although the small bowel represents 75% of the length and 90% of surface area of gastrointestinal tract, only 3% of gastrointestinal system tumors originate from small bowel [1,2]. Adenocarcinoma, which is the most common histopathological subtype along with carcinoid tumors, is responsible for one-third of the small bowel tumors [2]. These two histological subgroups are followed by lymphoma and sarcoma [3-5]. SBA is most frequently localized in the duodenum and its incidence decreases in distal parts of the small bowel [6,7].

SBA frequently affects men aged between 50 and 70 years. Although there are various risk factors and predisposing conditions, the etiology of most SBA is unknown [2,8]. The clinical presentation of SBA is nonspecific, with the most frequent symptom being abdominal pain. Diagnosis of disease is pretty difficult due to its rarity and non-specific signs and symptoms [9,10]. The mean duration between the onset of symptoms and diagnosis is about 8 months due to difficulties and inaccessibility of diagnostic methods [5]. The diagnosis of disease is generally delayed as a result of non-specific signs and symptoms and wasting time during diagnostic work-up. This condition negatively affects response to therapy. As in nearly all malignancies, early diagnosis and surgical resection are the only curative methods for the management of SBA [9]. However, about one-third of patients have advanced stage SBA at diagnosis [11]. Achieving cure for advanced SBA is unlikely with any of the treatment modalities. SBA has a poor prognosis and the rate of 5-year disease-specific survival is 4% in advanced stage [11]. Besides, the rate of 5-year disease-specific survival in patients with primary duodenal adenocarcinoma is lower in comparison to jejunum and ileum primaries [11-14].

There is a limited number of studies regarding systemic chemotherapy in advanced SBA due to its low incidence rate. Clinicians tend to administer chemotherapy according to studies performed on adenocarcinomas of colorectal, gastric and ampullary Vater origin. Information regarding systemic chemotherapy in advanced SBA is still inadequate. Therefore, the purpose of the present study was to define clinicopathologic parameters, the effect of chemotherapy on OS and PFS and potential prognostic factors in patients diagnosed with advanced SBA.

Methods

A total of 108 patients diagnosed with SBA in 18 different cancer centers in Turkey between July 2005 and May 2013, were retrospectively evaluated. Thirty-seven patients who underwent complete tumor resection and achieved remission were excluded from the study. Therefore, 71 patients with advanced SBA were included in this study. Of these, 15 could not receive chemotherapy due to poor performance score and were followed with BSC. SBA included tumors of the duodenum, ileum, and jejunum but excluded ampullary Vater cancers or double primary cancers. Clinical information including age, sex, ECOG PS, previous treatments, toxicities, treatment responses, patient follow-up and histopathological grade, localization, prior curative resection, and metastatic sites of tumors were obtained from the patient files. The stage of patients was evaluated according to pathological, clinical and radiological findings by using American Joint Committee on Cancer (AJCC) system (7th Edn, 2010) [15]. Patients were followed every 3–4 months in the first 2–3 years, every 6 months in the subsequent 2 years, and yearly thereafter. Serum CEA levels were obtained from the patient charts before treatment and during routine follow-up.

Chemotherapy regimens

As first-line therapy, 56 patients received one of the following four different chemotherapy regimens. These regimens involved: (1): modified FOLFOX6 (mFOLFOX6) (Oxaliplatin 85 mg/m^2, day 1; Leucovorin 200 mg/m^2 over 2 hrs, day 1; 5-FU 400 mg/m^2 bolus, day 1, followed by 2400 mg/m^2 over 46 hrs, cycled every 14 days). (2): FOLFIRI (Irinotecan 180 mg/m^2, day 1; Leucovorin 200 mg/m^2 over 2 hrs, day 1; 5-FU 400 mg/m^2 bolus, day 1, followed by 2400 mg/m^2 over 46 hrs, cycled every 14 days). (3): Cisplatin-5-FU (Cisplatin 75 mg/m^2, day 1, 5-FU 750 mg/m^2 IV continuous infusion over 24 hrs daily on days 1 and 5, cycled every 21 days). And (4): Gemcitabine (1250 mg/m^2 IV weekly for 3 weeks followed by one week rest in all subsequent cycles or 1250 mg/m^2 IV weekly for 2 weeks followed by one week rest in all subsequent cycles).

Toxicity evaluation

Toxicity and treatment side effects were obtained from the patient records and registered before each chemotherapy cycle. Toxicity was classified according to World Health Organization criteria.

Response to treatment

Response to treatment was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST). Partial response (PR) was defined as radiological tumor decrease by 30%. No tumor change was defined

as stable disease (SD). Tumor increase by 20% or appearance of new lesion(s) was defined as progressive disease (PD). Disappearance of all target lesions was defined as complete response (CR).

PFS and OS were defined as the duration between the first chemotherapy administration and the date of disease progression or death, and the duration between the first chemotherapy administration and death or loss to follow-up or current date, respectively.

Statistics

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, USA). Descriptive analyses were presented using means and standard deviations for normally distributed variables. The significance of the differenc-

Table 1. Patient and disease characteristics

Characteristics	*All patients*	*According to chemotherapy regimens and BSC*					
		FOLFOX	*FOLFIRI*	*Cisplatin-5FU*	*Gemcitabine*	*BSC*	*p value*
	N=71 *N (%)*	*N=18* *N (%)*	*N=11* *N (%)*	*N=17* *N (%)*	*N=10* *N (%)*	*N=15* *N (%)*	
Age (years)							0.19
Median	56	57	55	54	56	61	
<60	46 (65)	12 (67)	8 (73)	10 (59)	9 (90)	7 (47)	
≥ 60	25 (35)	6 (33)	3 (27)	7 (41)	1 (10)	8 (53)	
Gender							0.26
Female	29 (41)	10 (56)	6 (55)	5 (29)	2 (20)	6 (40)	
Male	42 (59)	8 (44)	5 (45)	12 (71)	8 (80)	9 (60)	
Grade							0.24
1	20 (28)	2 (11)	4 (36)	6 (35)	3 (30)	5 (33)	
2	37 (52)	12 (67)	7 (64)	5 (60)	6 (60)	7 (47)	
3	14 (20)	4 (22)	0 (0)	6 (35)	1 (10)	3 (20)	
Localization							0.13
Duodenum	55 (77)	11 (61)	6 (55)	16 (94)	8 (80)	14 (93)	
Jejunum	7 (10)	3 (17)	3 (27)	0 (0)	1 (10)	0 (0)	
Ileum	9 (13)	4 (22)	2 (18)	1 (6)	1 (10)	1 (7)	
De novo metastatic disease							0,22
Yes	48 (68)	12 (67)	7 (64)	12 (71)	7 (70)	10 (67)	
No	23 (34)	6 (33)	4 (36)	5 (29)	3 (30)	5 (33)	
ECOG PS							0.001
0-1	57 (80)	16 (90)	11 (100)	16 (94)	9 (90)	5 (33)	
2-4	14 (20)	2 (11)	0 (0)	1 (6)	1 (10)	10 (67)	
Localization of metastasis							0.38
Liver	39 (55)	9 (50)	8 (73)	8 (48)	4 (40)	10 (66)	
Lung	4 (6)	1 (6)	0 (0)	3 (17)	0 (0)	0 (0.0)	
Peritoneum	18 (25)	5 (28)	3 (27)	3 (17)	3 (30)	4 (27)	
Local relapse	10 (14)	3 (17)	0 (0)	3 (17)	3 (30)	1 (7)	
Second-line chemoterapy							0.32
Yes	25 (35)	8 (44)	5 (45)	7 (41)	5 (50)	0 (0)	
No	46 (65)	10 (56)	6 (55)	10 (59)	5 (50)	15 (100)	

Table 2. Tumor response

Patients with measurable disease	*According to chemotherapy regimens*				
	FOLFOX (N=18) N	*FOLFIRI (N=11) N*	*Cisplatin-5FU2 (N=17) N*	*Gemcitabine (N=10) N*	*p value*
Complete response	3	2	1	0	0.88
Partial response	7	4	5	2	0.92
Stable disease	2	2	3	3	1.01
Disease progression	6	3	8	5	0.85
Overall response rate (%)	56	55	35	20	0.75

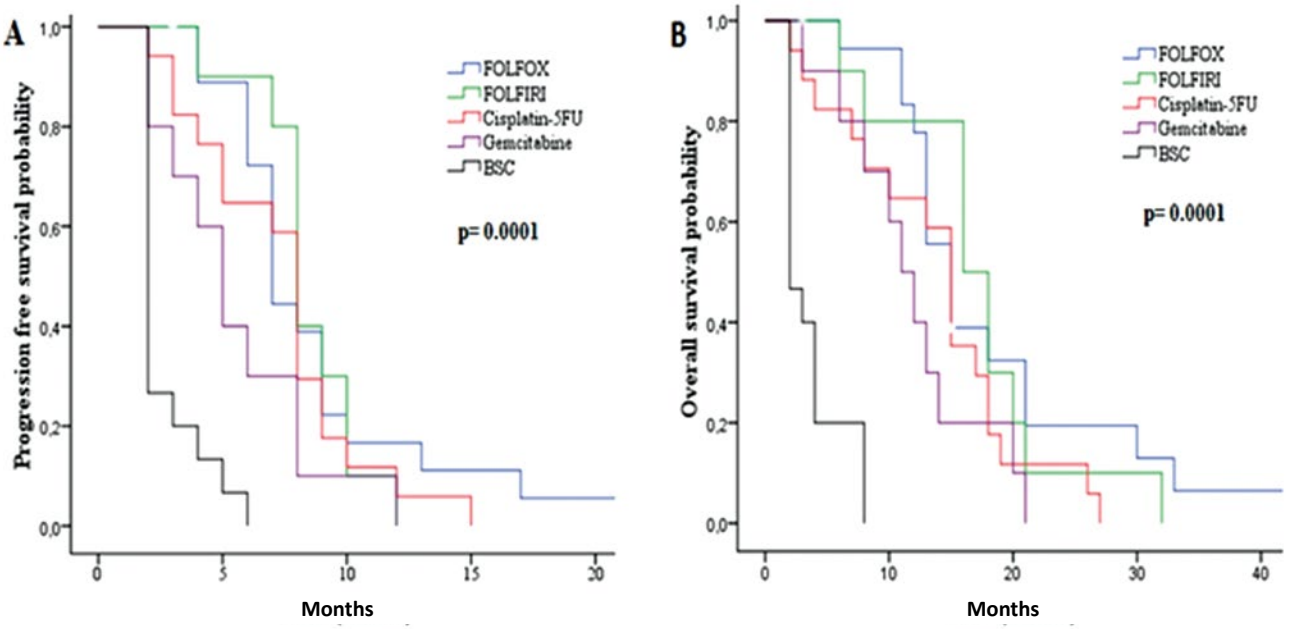

Figure 1. Progression-free survival **(A)** and overall survival **(B)** according to first-line chemotherapy subgroups and best supportive care group.

es between the mean values was determined by the Mann–Whitney U test. The difference in the distribution of ordinal variables was evaluated with the x^2 test or Fisher's exact test. Survival curves were generated by Kaplan–Meier method and were compared using the log-rank test. Univariate and multivariate analyses (Cox proportional hazards model) were used to calculate hazard ratios (HRs) with 95% confidence interval (95% CI). A two-sided p-value of <0.05 was considered to indicate statistically significant difference.

Results

Patient characteristics

Of the 71 patients, 42 (59%) were male and 29 (41%) female with a median age of 56 years (range, 23-75). The location of primary tumor was the duodenum, jejunum and ileum in 77, 10 and 13% of the patients, respectively. Clinical presentation was with locally advanced disease in 14% of the patients and with metastatic disease in 86%, most of whom had de novo metastatic disease (68%). There were 23 (32%) patients who failed previous curative resection and progressed to advanced stage. Of the patients who underwent curative resection (N=23), 15 were administered adjuvant chemotherapy. Liver metastasis was present in more than half of the patients (55%). Fifty-six patients received one of the four different chemotherapy regimens and 15 patients were treated with BSC. Median patient follow-up time was 12 months (range, 2-44) in the chemotherapy groups and they received a median of 6 chemotherapy cycles (range, 1-10). While statistically significant difference was not found between chemotherapy regimen subgroups in terms of patient characteristics with advanced SBA, the number of patients with ECOG PS between 2 and 4 was higher in the BSC group as compared to chemotherapy groups (p=0.0001) The distribution

Table 3. Univariate analysis for progression free survival and overall survival

Characteristics	*All patients* *N (%)*	*Median PFS, months (95% CI))*	*p value*	*Median OS, months (95% CI)*	*p value*
Age, years			0.467		0.37
< 60	46 (64.8)	9 (7-11)		14 (11-16)	
≥ 60	25 (35.2)	6 (1-11)		8 (6-9)	
Gender			0.824		0.32
Female	29 (40.8)	9 (7-11)		14 (8-19)	
Male	42 (59.2)	6 (3-9)		11 (8-13)	
Grade			0.27		0.41
1	20 (28.2)	6 (0-11)		10 (5-14)	
2	37 (52.1)	8 (7-9)		12 (9-14)	
3	14 (19.7)	9 (6-11)		14 (11-16)	
Localization			0.27		0.27
Duodenum	55 (77.5)	7 (4-10)		11 (7-14)	
Jejunum	7 (9.9)	8 (4-11)		14 (11-16)	
Ileum	9 (12.7)	11 (7-15)		17 (0-34)	
De novo metastatic disease			0.03		0.017
Yes	48 (67.6)	9 (8-10)		11 (4-17)	
No	23 (32.4)	4 (2-6)		13 (10-15)	
ECOG PS			0.008		0.001
0-1	57 (80.3)	9 (7-10)		14 (12-15)	
2-4	14 (19.7)	3 (0-5)		4 (2-5)	
Localization of metastasis			0.25		0.34
Liver	39 (54.9)	8 (7-9)		11 (7-14)	
Lung	4 (5.6)	13 (10-16)		15 (8-21)	
Peritoneum	18 (25.4)	9 (6-11)		16 (8-23)	
Local relapse	10 (14.1)	6 (3-9)		12 (8-15)	
Systemic treatment			0.04		0.004
Yes	55 (77.5)	9 (7-10)		14 (12-15)	
No	16 (22.5)	2 (0-5)		2	
Type of treatment			0.001		0.001
FOLFOX	18 (25.4)	9 (7-10)		13 (10-15)	
FOLFIRI	11 (15.5)	10 (7-13)		16 (9-22)	
Cisplatin-5FU	17 (23.9)	8 (5-11)		15 (13-16)	
Gemcitabine	10 (14.1)	6 (3-9)		11 (0-14)	
BSC	15 (21.1)	2 (0-5)		2	
Response to treatment			0.001		0.001
CR	6 (10.7)	11 (10-12)		30 (4-55)	
PR	18 (32.1)	11 (9-13)		17 (15-19)	
SD	10 (17.9)	9 (7-10)		13 (11-14)	
PD	22 (39.3)	6 (4-7)		11 (7-14)	

For abbreviations see text

of patient characteristics in relation with regimen subgroups and BSC group is shown in Table 1.

Therapeutic response

Response to treatment was evaluated in all patients receiving chemotherapy (N=56). In chemotherapy groups, overall response rate (ORR) (complete response+partial response), was 45% and complete response, partial response and stable disease were observed in 6, 19 and 12 patients,

respectively. There was no significant difference between the four chemotherapy regimen groups in terms of ORR (p=0.75) (Table 2).

Survival analysis

Median follow-up duration was 14.3 months (range 3.7-44.1). PFS rates at first and second years were 14 and 1.4%, respectively; the OS rates were 53 and 9% at first and second years, respectively (Figure 1). The median PFS and OS were 7 months (SE: 0.7; 95%CI: 5.6-8.3) and 13 months (SE: 1; 95%CI: 10.96-15.03) for all of the patients. In the FOLFOX, FOLFIRI, Cisplatin-5-FU and Gemcitabine groups, the median PFS and OS were 7, 8, 8 and 5 months, and 15, 16, 15 and 11 months, respectively, whereas the median PFS and OS were 2 months in the BSC group. There were no significant difference between chemotherapy groups in terms of PFS and OS; however, in the BSC group, PFS and OS were significantly lower than in the chemotherapy groups (p=0.001) (Figure 1). With regard to OS and PFS, univariate analysis revealed chemotherapy administration, *de novo* metastatic disease, ECOG PS 0 and 1, and ORR to therapy were significantly related to improved outcome (Table 3). On the other hand, only ORR to treatment was significantly prognostic in multivariate analysis (p= 0.001;Table 4).

Toxicity

Patients were evaluated in terms of chemotherapy-dependent toxicity. In FOLFOX, FOLFIRI, Cisplatin-5-FU and Gemcitabine subgroups, 4, 3, 5 and 2 patients experienced grade 3-4 hematological toxicity, respectively. The main toxicities recorded were haematological with grade 3-4 neutropenia (66%) representing the most frequent adverse event followed by thrombocytopenia (22%). Nephrotoxicity and sensory neuropathy were developed in 2 patients (Cisplatin subgroup), whereas neurotoxicity was seen in 1 patient (Oxaliplatin subgroup). No treatment-related fatal adverse events occurred in any of the chemotherapy regimen, and there was no significant difference between chemotherapy regimens in terms of grade 3-4 toxicity.

Second-line chemotherapy

Second-line chemotherapy was given to 25 (35%) advanced SBA patients that received first-line chemotherapy. Of the patients that received FOLFOX, FOLFIRI, Cisplatin-5-FU and Gemcitabine as first-line therapy, 8 (44%), 5 (45%), 7 (41%) and 5 (50%) received second-line chemotherapy, respectively. As second-line chemotherapy, irinotecan-based and oxaliplatin-based chemotherapy were given to patients who had received first-line platinum-based and FOLFIRI chemotherapy, respectively. Oxaliplatin- or Irinotecan-based chemotherapy was administered to patients who had received first-line gemcitabine. Overall response rates to second-line therapy were 26%, 45% of the patients showed SD and the remaining showed disease progression.

Discussion

Univariate analysis revealed that PFS and OS were significantly longer in patients who received systemic therapy, in those with *de novo* metastatic disease, ECOG PS 0 and 1, and in those who responded to therapy. However, only overall response obtained from systemic therapy was found significantly prognostic in multivariate analysis (p=0.001). In the present study, ECOG PS was not an independent prognostic factor when compared to other studies probably due to the low strength of our study [16,17].

A relationship was found between tumor localization and prognosis, and the poor prognosis of primary duodenal cancer was reported by other investigators [11-14]. In the current study, although no statistically significant difference was determined, the prognosis was better especially in primary tumors of ileum and jejunum in comparison with primary duodenal tumors. No significant difference was detected between patients with local relapse and distant metastasis in terms of OS; however, the prognosis of patients with local relapse was worse in comparison to patients with distant metastasis as a result of complications from the recurrent lesion such as obstruction, perforation and hemorrhage.

Due to the lack of randomized studies comparing the different chemotherapy protocols, there is no standardized first-line chemotherapy in advanced SBA. Therefore, the chemotherapy protocols of SBA are based on the protocols of gastric and ampullary tumors, and particularly on protocols for advanced colorectal tumors in most of the oncology centers. Randomized studies with large patient population are required for the determination of a standard chemotherapy regimen. The number of prospective phase II studies is quite low due to the low incidence of disease and difficulties in diagnosis. Of these studies, a study including 31 patients who had

Table 4. Multivariate analysis for progression free survival and overall survival

Variables	*Multivariate analyses for DFS*			*Multivariate analyses for OS*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
De novo metastatic disease (YES)	0.49	0.07- 1.41	0.13	0.59	0.42-1.93	0.25
ECOG PS (0-1)	0.45	0.08-2.29	0.67	0.61	0.07-2.32	0.31
Systemic treatment	0.64	0.23-4.04	0.73	0.79	0.21-4.25	0.93
Response to treatment (ORR)	0.37	0.11-1.26	0.11	0.21	0.04-0.65	0.001

ORR: objective response rate, HR: hazard ratio, CI: confidence interval, PFS: progression-free survival, OS: overall survival

been diagnosed with advanced or inoperable small bowel or ampullary adenocarcinoma was a single-center study conducted in MD Anderson Cancer Center [18]. The authors concluded that significant results were obtained with CAPOX regimen (Capecitabine 750 mg/m^2 twice daily on days 1 through 14, and Oxaliplatin 130 mg/m^2 on day 1, every 21 days). The ORR rate and the median OS were 52% and 15.5 months, respectively in 25 patients with metastatic disease. The response rate was higher in SBA (N=18) than in ampullary adenocarcinoma (61 and 33%, respectively). In another multicenter phase II study including 24 unresectable patients who were diagnosed with metastatic SBA, the mFOLFOX6 regimen was evaluated [19]. ORR and median PFS and OS were 45%, 5.8 months and 17.3 months in patients that received mFOLFOX6. In our study, a total of 18 patients received mFOLFOX6 and of these, 3 patients achieved complete response with ORR 56%. In the present study ORR, PFS, and OS of patients who received FOLFOX is comparable to that of the two before-mentioned studies.

In addition to the low number of prospective studies, there are retrospective studies evaluating various chemotherapy regimens in advanced SBAs [16,17,20-23]. One of these studies was performed in MD Anderson Cancer Center and included 80 patients who had been diagnosed with metastatic SBA and received various chemotherapy regimens [20]. Twenty patients received 5-FU and Platinum (mostly Cisplatin), 41 received platinum-free 5-FU-based chemotherapy and 10 received non-5-FU chemotherapy. The response rates and the median PFS of Platinum plus 5-FU regimens were significantly better in comparison with other regimens (46 vs 16% and 8.7 vs 3.9 months, respectively). However, these results did not affect the median OS (14.8 vs 12 months, respectively). The results obtained by platinum plus 5-FU regimens of the above-mentioned study and Cisplatin-5-FU (N=17) group of our study (PFS 8 months, OS 15 months) showed similar outcomes.

There are also retrospective studies demonstrating the efficacy of Irinotecan and Gemcitabine excluding Platinum regimens [16,21-23]. The ORR rate was 42% with Irinotecan-based chemotherapy regimens [16]. In our study, the results of 11 patients receiving FOLFIRI are promising in terms of ORR, PFS and OS (55%, 8 months and 16 months, respectively).

Although the number of randomized studies [24,25] is inadequate, our study results suggest receiving chemotherapy in metastatic and locally advanced unresectable SBA in terms of survival advantage. In the existing literature, the number of studies [17,20] comparing the chemotherapy regimens with or without Platinum is very low in patients with advanced SBA. Among the chemotherapeutic regimens, FOLFOX is obviously better than other regimens [17,20,24,25]. In our study, it was found that FOLFIRI and Cisplatin-5-FU may also be preferred in addition to FOLFOX in terms of both efficacy and tolerability. However, although gemcitabine-based regimen is a tolerable treatment, no significant difference has been found in PFS (5 months) and OS (11 months), making it a choice behind other regimens.

SBA is a rare but aggressive disease. Most of the studies were retrospective due to low incidence and difficulties in the diagnosis of disease. The population of our study is low, as in other studies. The strength of our study is low as this is a non-randomized and retrospective study with low patient number and the homogeneity is not at the optimal level between the groups. Multi-centered prospective studies containing adequate number of patients are required to suggest a therapy method for advanced SBAs. The results of our retrospective study will contribute to the design of our planned prospective study.

Conflict of interests

The authors declare no confict of interests.

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