JBUON 2019; 24(6): 2542-2548
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Clinicopathological features and treatment outcomes of metastatic or locally unresectable small bowel adenocarcinoma

Xiaoyuan Li, Hongyan Ying, Yuejuan Cheng, Lin Zhao, Sun Zhao, Chunmei Bai, Jianfeng Zhou

Department of Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing 100730, China

Summary

Purpose: *Small bowel adenocarcinoma (SBA) is an uncommon malignancy with poor prognosis and therefore difficult to study. The purpose of this study was to evaluate the characteristics, treatments and prognostic factors in patients with metastatic or locally unresectable SBA.*

Methods: *Epidemiological and treatment data from metastatic or locally unresectable SBA patients who were admitted to Peking Union Medical College Hospital for first-line chemotherapy between December 2003 and November 2016 were retrospectively analyzed.*

Results: *Of the 34 enrolled patients, 22 (64.7%) were male and 12 (35.3%) female, with a median age of 52 years. Tumors originated in the duodenum in 24 (70.6%) patients. All patients received one of the following regimens as first-line therapy: FOLFOX or XELOX (n=27), FOLFIRI or CAPIRI (n=5), GEMOX (n=1), and TP (n=1). The response rate and disease control rate were 11.8 and 61.8%, respectively. The median progression-free survival (PFS) and overall survival (OS) were 4.5 and 13.8 months, respectively. Multivariate analysis revealed that liver metastasis was independently associated with poor PFS, and both unresected primary tumor and males were significantly associated with poor OS. The survival of three metastatic patients was 52-96 months after combination treatment of chemotherapy, resection of primary tumor and metastasis.*

Conclusions: *The prognosis of metastatic or locally unresectable SBA was poor, and unresected primary tumor and males were significantly associated with poor OS. Combined modality therapy of systemic chemotherapy combined with local treatment of the primary tumor and oligometastasis might improve prognosis in selected patients.*

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

Introduction

Although the small intestine is 5 to 7 m long and occupies more than two-thirds of the length of the digestive tract, small intestinal neoplasms are rare and account for less than 3% of all malignant gastrointestinal tumors [1]. Histologically, adenocarcinoma is the second most common malignant tumor of the small bowel after carcinoid tumor [2]. Owing to the rarity of small bowel adenocarcinoma (SBA), the nonspecific clinical symptoms, and the lack of effective tools for exploring the small bowel, SBA is usually diagnosed at an advanced stage [3-5].

The prognosis of metastatic SBA is poor, with a median overall survival of less than 6 months without chemotherapy [3,5]. Systemic treatment is considered the main option for controlling metastatic or locally unresectable SBA. Although randomized

Corresponding author: Jianfeng Zhou, MD. Department of Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Shuai Fu Yuan no. 1, Dongcheng district, Beijing 100730, China.
Tel: +86 010 69158764, Email: ZhouJF@pumch.cn
Received: 27/04/2019; Accepted: 22/05/2019

trials have not been undertaken, a few retrospective series suggest that chemotherapy helps patients with advanced SBA live longer [3,6-9]. However, data from investigating treatments and prognosis in advanced SBA are still limited due to its low incidence, and there is still no established standard treatment strategy for patients with metastatic and locally advanced SBA.

The aim of this retrospective study was to evaluate the clinicopathologic features, treatment outcomes and prognostic factors in patients with metastatic or locally advanced SBA. The results would contribute to the literature on this uncommon entity.

Methods

Patient selection

We searched the Peking Union Medical College Hospital (PUMCH) database to identify all patients who were admitted to receive systemic chemotherapy for advanced SBA between December 2003 and November 2016. Patients were included if they were ≥ 18 years of age and had histologically confirmed SBA with documentation of non-curative resection of locally advanced or metastatic disease. Patients with cancer of the ampulla of Vater or periampullary cancer were excluded. Patients' medical records were reviewed to extract demographic data, tumor characteristics, type of treatment, response to treatment, and survival information. 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.

Systemic treatment regimens

All the patients received one of the following regimens as first-line therapy. These regimens involved: (1) FOLFOX (oxaliplatin 85 mg/m^2 on day 1; leucovorin 200 mg/m^2 over 2 hours on day 1; fluorouracil 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 over 46 h, cycled every 14 days). (2) XELOX (oxaliplatin 130 mg/m^2 on day 1; oral capecitabine 1000 mg/m^2 twice daily on days 1 through 14, cycled every 21 days). (3) GEMOX (oxaliplatin 130 mg/m^2 on day 1; gemcitabine 1000 mg/m^2 on days 1 and 8, cycled every 21 days). (4) FOLFIRI (irinotecan 180 mg/m^2 on day 1; leucovorin 200 mg/m^2 over 2 hours on day 1; fluorouracil 400 mg/m^2 bolus on day 1, followed by 2400 mg/m^2 over 46 h, cycled every 14 days). (5) CAPIRI: (irinotecan 100 mg/m^2 on days 1 and 8; oral capecitabine 1000 mg/m^2 twice daily on days 1 through 14, cycled every 21 days). (6) TP (cisplatin 25 mg/m^2 on days 1, 2, and 3; paclitaxel 175mg/m^2 on day 1, cycled every 21 days). One patient with RAS wild-type received cetuximab (250 mg/m^2/week, with a loading dose of 400 mg/m^2 for the first week) combined with FOLFIRI, and another patient received bevacizumab (7.5 mg/kg, on day 1, cycled in every 21 days) combined with TP. All the other patients received chemotherapy alone.

Table 1. Patient characteristics

Characteristics	*No. of patients (n=34) n (%)*
Age, years	
<60	25 (73.5)
≥60	9 (26.5)
Gender	
Male	22 (64.7)
Female	12 (35.3)
Primary site	
Duodenum	24 (70.6)
Jejunum	7 (20.6)
Ileum	3 (8.8)
Histology	
Moderately differentiated	15 (44.1)
Poorly differentiated	12 (35.3)
Signet ring cell carcinoma	1(2.9)
Not further determined	6 (17.6)
Initial tumor stage	
I	1 (2.9)
II	2 (5.8)
III	5 (14.7)
IV	26 (76.5)
Primary tumor resected	
Yes	24 (70.6)
No	10 (29.4)
Adjuvant chemotherapy	
Yes	5 (14.7)
No	29 (85.3)
Disease status	
Metastatic	32 (94.1)
Locally unresectable	2 (5.9)
No. of metastatic sites	
0 or 1	10 (29.4)
≥2	24 (70.5)
Liver metastasis	
Yes	15 (44.1)
No	19 (55.9)
Peritoneal metastasis	
Yes	10 (29.4)
No	24 (70.6)
Elevation of CEA	
Yes	12 (35.3)
No	22 (64.7)
Elevation of CA19-9	
Yes	17 (50.0)
No	16 (47.1)
Not available	1 (2.9)

CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

Response to treatment

Response to treatment was evaluated as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST version 1.1 [10]. Progression-free survival (PFS) and overall survival (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 data, respectively.

Statistics

Descriptive statistics were used to assess the clinicopathologic variables. The difference in the distribution of ordinal variables was evaluated with the x^2 test or the Fisher exact test. Estimates of survival function for PFS and OS were obtained using the Kaplan-Meier method. The comparison of survival for different patients was made using the log-rank test. Factors with a p value less than 0.1 in the univariate analysis were included in the Cox proportional hazards model to determine the independent predictors of survival. The statistical analyses were performed using SPSS Statistics version 19 (IBM Corp). A two-tailed p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Thirty-four patients met the inclusion criteria to enter this retrospective analysis. The median age of the 34 patients was 52.0 years (range, 22.0-73.0), and 76.5% of them were with synchronous metastasis. The detailed baseline characteristics are illustrated in Table 1.

First-line treatments and responses

First-line treatment was administered to 27 patients who received FOLFOX or XELOX regimen, to 4 patients who received FOLFIRI or CAPIRI, 1 patient who received GEMOX, 1 patient who received FOLFIRI combined with cetuximab, and 1 patient who received TP combined with bevacizumab. The response of each regimen is shown in Table 2. The overall response rate (ORR) of the whole population was 11.8%, with 1 CR and 3 PR. Stable disease was observed in 18 patients. The disease control rate (DCR) was 61.8%.

Survival analysis

The median duration of follow-up was 12.1 months (range, 1.7-96.0), and 29 patients (85.3%) died of disease. The median PFS and OS were 4.5 months (95% CI: 2.8-6.2) and 13.8 months (95% CI: 8.7-18.8; Figure 1), respectively. The survival evaluation showed that although prognosis of most patients was poor, a small number of patients achieved long-term survival. The following 3 cases survived long with no evidence of disease after combined modality therapy of systemic chemotherapy and local treatment of the primary tumor and oligometastasis: one patient diagnosed with isolated liver metastasis immediately after resection of duodenal adenocarcinoma underwent resection of liver metastasis after her disease was controlled by 6 cycles of XELOX chemotherapy, and her current survival has been 96 months; one patient with ileal adenocarcinoma underwent cytore-

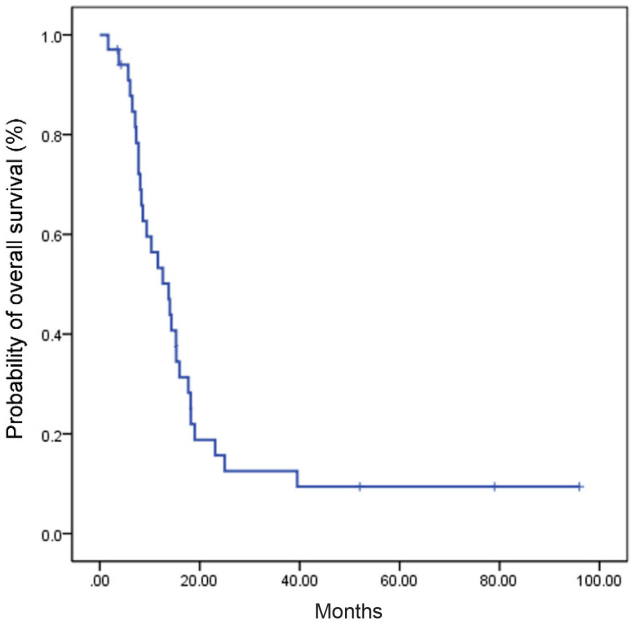

Figure 1. Overall survival of all patients.

Table 2. Response to first-line treatment

	Response			
According to regimens	*Complete response*	*Partial response*	*Stable disease*	*Disease progression*
mFOLFOX6 or XELOX (n=27)	1	2	13	11
FOLFIRI or CAPIRI (n=4)	0	1	2	1
GEMOX (n=1)	0	0	0	1
FOLFIRI-Cetuximab (n=1)	0	0	1	0
TP-Bevacizumab (n=1)	0	0	1	0

ductive surgery of the primary tumor and omental metastasis, followed by 12 cycles of FOLFOX and one year of capecitabine maintenance therapy, and her survival has been 52 months; and one patient with jejunal adenocarcinoma and multiple, non-regional lymph node metastases achieved CR after 8 cycles of XELOX chemotherapy and resection of the primary tumor, followed by nearly 5 years of capecitabine maintenance therapy, and her survival has been 79 months.

In univariate analysis, liver metastasis and elevation of CA19-9 were significantly associated

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

Factors	*Patients, n*	*Median PFS, months (95% CI)*	*p value*	*Median OS, months (95% CI)*	*p value*
Age, years			0.437		0.234
<60	25	5.5 (3.1-8.0)		14.3 (12.0-16.6)	
≥60	9	3.0 (1.5-4.5)		7.30 (6.7-7.9)	
Gender			0.128		0.001
Male	22	4.5 (2.2-6.8)		9.4 (4.5-14.3)	
Female	12	5.5 (0.4-10.6)		19.0 (8.5-29.5)	
Primary site			0.080		0.316
Duodenum	24	4.0 (2.2-5.8)		14.0 (7.2-20.8)	
Jejunum + ileum	10	6.0 (1.4-10.7)		12.6 (7.3-17.9)	
Histology			0.536		0.297
Poorly differentiated and signet ring carcinoma	13	4.5 (2.7-6.3)		12.6 (5.9-19.3)	
Others	21	5.0 (1.3-8.7)		13.8 (7.2-20.3)	
Resection of primary tumor			0.444		0.046
Yes	24	5.0 (3.6-6.4)		14.3 (8.7-18.8)	
No	10	3.0 (1.5-4.5)		7.7 (4.6-10.9)	
Adjuvant chemotherapy			0.771		0.778
Yes	5	7.1 (1.5-12.7)		14.0 (13.5-14.5)	
No	29	4.5 (2.7-6.3)		11.6 (6.2-17.1)	
Metastatic disease			0.441		0.971
Synchronous	26	4.5 (2.1-7.0)		10.3 (5.4-15.2)	
Metachronous	8	7.1 (1.1-13.1)		15.3 (12.0-18.5)	
No. of metastatic sites			0.506		0.109
1	10	4.5 (3.0-6.1)		15.3 (8.8-21.8)	
≥ 2	24	4.5 (1.6-7.4)		10.3 (5.2-15.5)	
Liver metastasis			0.040		0.763
Yes	15	4.5 (1.7-7.3)		12.6 (6.4-18.8)	
No	19	7.1 (2.8-11.4)		13.8 (6.2-21.3)	
Peritoneal metastasis			0.775		0.374
Yes	10	5.0 (2.8-6.2)		8.1 (6.7-9.5)	
No	24	4.5 (2.7-6.3)		14.3 (11.2-17.4)	
Elevation of CEA			0.680		0.764
Yes	12	5.0 (2.5-7.6)		10.3 (0.3-20.3)	
No	22	4.5 (2.2-6.8)		13.8 (10.4-17.2)	
Elevation of CA19-9[a]			0.037		0.183
Yes	17	4.5 (2.5-6.5)		12.6 (3.5-21.7)	
No	16	5.5 (0-12.4)		13.8 (6.7-20.8)	
Regimen of first-line chemotherapy[b]			0.806		0.731
Oxaliplatin-based	28	4.5 (2.6-6.5)		12.6 (6. -18.7)	
Irinotecan-based	5	7.1 (1.5-12.7)		14.0 (13.5-14.5)	
Second-line chemotherapy			-		0.368
Yes	18	-		12.6 (6.4-18.8)	
No	16	-		13.8 (5.0-22.5)	

CEA: carcinoembryonic antigen, CA19-9:carbohydrate antigen 19-9. [a]Baseline CA19-9 was not available in one patient. [b]One patient received paclitaxel plus cisplatin combined with bevacizumab as first-line therapy

with poor PFS outcome (Table 3). The three factors with a p value less than 0.1 in the PFS univariate analysis in Table 3 were included in the subsequent multivariate analysis, and only liver metastasis was independent factor associated with poor PFS (HR 2.345, 95% CI: 1.078-5.100, p=0.032). With regard to OS, univariate analysis revealed that males and unresected primary tumors were factors significantly associated with poor OS (Table 3). In addition, the best efficacy of first-line treatment was also a significant prognostic factor of OS (PD vs Non-PD: 7.3 vs 15.3 months, p=0.005). Upon subsequent multivariate analysis, males and unresected primary tumors were independently associated with poor OS, with hazard ratio (HR) 11.210 (95% CI:3.402-36.938, p=0.000) and 5.742 (95% CI:2.211-14.916, p=0.000), respectively.

Discussion

In the present study, we retrospectively analyzed the clinicopathologic features, treatment, and outcomes of metastatic or locally unresectable SBA patients who were admitted to receive systemic treatment in our institution. Our data showed that advanced SBA was slightly more prevalent in males, the onset age was usually less than 60 years, and the majority was of duodenal origin. These baseline features are very similar to those previously reported in advanced SBA [3,4,11-14]. Another characteristic of this series is that most of the patients had synchronous metastasis, and the proportion of patients with metastatic sites ≥2 was relatively high, which meant that this group of patients was in a more advanced condition.

Although randomized trials have not been undertaken, some retrospective studies suggested that patients with advanced SBA who got chemotherapy lived longer than did those without chemotherapy [3,6-9,15]. However, both data in previous studies and the results of our study suggest that the prognosis of advanced SBA is poor even after chemotherapy. Previous studies have shown that independent prognostic factors for the OS of advanced SBA included performance status, tumor marker levels, chemotherapy regimen, primary site, response to treatment, resection of the primary tumor, liver metastasis, etc. [6,8,13,16-18]. The independent factors are not completely consistent in different studies, and patient selection bias likely accounts for at least some of the discrepancies. Our multivariate analysis revealed that gender and resection of the primary tumor were independent prognostic factors of OS in patients with advanced SBA. Tumor resection had previously been identified as good prognostic factor in other studies [6,19]. The tumor burden in patients experiencing recurrence after primary tumor resection or metastasis with palliative resection has been thought to be lower than the burden in patients who did not undergo surgical resection, which might partly explain why those patients have a good prognosis. Another reason might be that the risk of obstruction, perforation and hemorrhage in the follow-up treatment is reduced after removal of the primary foci. However, gender had not been reported to be a prognostic factor in earlier studies.

With regard to systemic treatment, in the absence of randomized trials comparing different regimens, there is no standard chemotherapy approach for patients with advanced SBA. In general, chemotherapy for advanced SBA has been based on those established for metastatic colorectal cancer [20]. The modern chemotherapy regimens, such as FOLFOX, XELOX, or FOLFIRI showed an ORR of 30-50%, a DCR of 60-80%, and an OS of only a little more than one year as first-line treatment in most previous studies [7,11,12,17,21-24]. In refractory SBA, the newer drug nab-paclitaxel had shown some promise [25]. Although most cases in our series used fluoropyrimidine in combination with oxaliplatin or irinotecan as first-line treatment, the ORR was lower than most of the previous reported analyses. However, the DCR and survival data were comparable to the literature. The difference in efficacy between different reports might be due to difference in the condition of patients treated in each trial. Patients in the real world are generally more complicated than those in prospective trials. As to the benefit of targeted therapies in advanced SBA, only limited data is available. In a multicenter retrospective study, use of bevacizumab together with chemotherapy suggested a trend toward a survival benefit compared with chemotherapy alone [12]. A report of 4 patients with advanced SBA who received cetuximab in conjunction with irinotecan showed 3 objective responses [26]. On the other hand, no benefit for single-agent panitumumab could be proven in a small prospective study of 8 patients with RAS wild-type SBA [27]. In the present study, it was difficult to prove the benefits of targeted drugs due to the small number of cases treated with targeted agents.

In addition, it is worth noting that 3 cases in this series achieved long-term survival. All three patients achieved disease response or control after first-line chemotherapy. The primary tumors were all resected, and oligometastatic lesions were removed in 2 patients. Similar cases had been reported by other authors [19,28,29]. The median survival of 10 patients receiving combined modality therapy of primary resection, chemotherapy, and

local treatment of metastasis was 36.9 months in a retrospective Japanese study [29]. A study in the Netherlands showed median survival of 32.0 months in highly selected patients with probably limited peritoneal tumor spread after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy [19]. These data suggest that although most advanced SBAs have poor prognosis, selected patients with good biological condition and relatively limited metastatic disease should be considered for chemotherapy combined with local treatment of the primary tumor and metastasis to prolong survival and even to achieve Disease-Free Survival (DFS). However, how to improve the efficacy of systemic chemotherapy and distinguish patients with different biological behaviors needs further large-scale clinical studies.

The present study has several limitations. It is a retrospective analysis, and patients were from a single institution, which could have selection biases. Furthermore, chemotherapy regimens were not homogeneous even though the majority consisted of fluoropyrimidines combined with oxaliplatin or irinotecan. Nonetheless, our retrospective analysis of treatment outcomes in metastatic or unresectable SBA represents a further contribution to the literature on this rare tumor.

Our data suggests that although chemotherapy prolonged the survival of advanced SBA, its prognosis was still poor. Unresected primary tumor and males were significantly associated with poor OS. Combined modality therapy of systemic chemotherapy combined with local treatment of the primary tumor and oligometastatic disease might improve prognosis in selected patients. Multi-centered prospective studies containing adequate numbers of patients are required to suggest a standardized treatment strategy for advanced SBAs. We hope that the present study will contribute to the designs of further prospective studies.

Compliance with Ethical Standards

All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Acknowledgement

This study was funded by grants from the CAMS Innovation Fund for Medical Sciences (No.2016-I2M-1-001) and CSCO-Simcere Research Fund for Targeted Therapy of Anti-tumor Angiogenesis (Y-S 2016-027).

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Qubaiah O, Devesa SS, Platz CE, Huycke MM, Dores GM. Small intestinal cancer: a population-based study of incidence and survival patterns in the United States, 1992 to 2006. Cancer Epidemiol Biomarkers Prev 2010;19:1908-18.
3. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer 2004;101:518-26.
4. Zhang S, Yuan W, Zhang J et al. Clinicopathological features, surgical treatments, and survival outcomes of patients with small bowel adenocarcinoma. Medicine 2017;96:e7713.
5. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 2010;199:797-803.
6. Koo DH, Yun SC, Hong YS et al. Systemic chemotherapy for treatment of advanced small bowel adenocarcinoma with prognostic factor analysis: retrospective study. BMC Cancer 2011;11:205.
7. Mizushima T, Tamagawa H, Mishima H et al. The effects of chemotherapy on primary small bowel cancer: A retrospective multicenter observational study in Japan. Mol Clin Oncol 2013;1:820-4.
8. Duerr D, Ellard S, Zhai Y, Taylor M, Rao S. A Retrospective Review of Chemotherapy for Patients with Small Bowel Adenocarcinoma in British Columbia. J Cancer 2016;7:2290-5.
9. Fishman PN, Pond GR, Moore MJ et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. Am J Clin Oncol 2006;29:225-31.
10. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
11. Overman MJ, Kopetz S, Wen S et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer 2008;113:2038-45.

12. Aydin D, Sendur MA, Kefeli U et al. Evaluation of Bevacizumab in Advanced Small Bowel Adenocarcinoma. Clin Colorectal Cancer 2017;16:78-83.
13. Aydin D, Sendur MA, Kefeli U et al. Evaluation of prognostic factors and treatment in advanced small bowel adenocarcinoma: report of a multi-institutional experience of Anatolian Society of Medical Oncology (ASMO). JBUON 2016;21:1242-9.
14. Guo X, Mao Z, Su D, Jiang Z, Bai L. The clinical pathological features, diagnosis, treatment and prognosis of small intestine primary malignant tumors. Med Oncol 2014;31:913.
15. Nakanoko T, Koga T, Taketani K et al. Characteristics and Treatment Strategies for Small Bowel Adenocarcinoma in Advanced-stage Cases. Anticancer Res 2015;35:4135-8.
16. Hirao M, Komori M, Nishida T et al. Clinical use of molecular targeted agents for primary small bowel adenocarcinoma: A multicenter retrospective cohort study by the Osaka Gut Forum. Oncol Lett 2017;14: 1628-36.
17. Zaanan A, Costes L, Gauthier M et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol 2010;21:1786-93.
18. Tsushima T, Taguri M, Honma Y et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. Oncologist 2012;17:1163-70.
19. Legue LM, Simkens GA, Creemers GM, Lemmens V, de Hingh I. Synchronous peritoneal metastases of small bowel adenocarcinoma: Insights into an underexposed clinical phenomenon. Eur J Cancer 2017;87:84-91.
20. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.
21. Zhang L, Wang LY, Deng YM et al. Efficacy of the FOLFOX/CAPOX regimen for advanced small bowel adenocarcinoma: a three-center study from China. JBUON 2011;16:689-96.
22. Xiang XJ, Liu YW, Zhang L et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs 2012;23:561-6.
23. Overman MJ, Varadhachary GR, Kopetz S et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 2009;27:2598-603.
24. Horimatsu T, Nakayama N, Moriwaki T et al. A phase II study of 5-fluorouracil/L-leucovorin/oxaliplatin (mFOLFOX6) in Japanese patients with metastatic or unresectable small bowel adenocarcinoma. Int J Clin Oncol 2017;22:905-12.
25. Overman MJ, Adam L, Raghav K et al. Phase II study of nab-paclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol 2018;29:139-44.
26. Santini D, Fratto ME, Spoto C et al. Cetuximab in small bowel adenocarcinoma: a new friend? Br J Cancer 2010;103:1305; author's reply 1306.
27. Gulhati P, Raghav K, Shroff R et al. Phase II Study of Panitumumab in RAS Wild-Type Metastatic Adenocarcinoma of Small Bowel or Ampulla of Vater. Oncologist 2018;23:277-e26.
28. Lai S, Leslie W. A Patient With Metastatic Adenocarcinoma of the Jejunum Who Had a Prolonged Complete Response to FOLFOX. Gastrointest Cancer Res 2012;5:71-2.
29. Sakae H, Kanzaki H, Nasu J et al. The characteristics and outcomes of small bowel adenocarcinoma: a multicentre retrospective observational study. Br J Cancer 2017;117:1607-13.