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ORIGINAL ARTICLE

S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: a multicenter phase II study

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Abstract A pilot phase II study showed S-1 monotherapy to be safe and active against biliary tract cancer (BTC). We, therefore, conducted a multicenter phase II study to evaluate the antitumor effect and safety of S-1 in previously untreated patients with advanced BTC. Eligible patients had pathologically proven, unresectable adenocarcinoma with no prior chemotherapy or radiotherapy. Patients received S-1 orally at 80 mg/m^2 total daily dose divided b.i.d. for 28 days followed by 14 days of rest. Of the 41 enrolled patients, 40 were assessable. The primary tumor sites were as follows: gallbladder (n = 20), extrahepatic bile duct (n = 15), and the ampulla of Vater (n = 5). One patient (2.5%) achieved a complete response, 13 patients (32.5%) had partial responses, 17 patients (42.5%) had no change, 7 patients (17.5%) had progressive disease, and 2 patients (5.0%) were not evaluable. The overall objective response rate was 35.0%. The median overall survival (median OS) was 9.4 months, and the median time to progression was 3.7 months. Grade 3 or 4 toxicities included fatigue (7.5%), anorexia (7.5%) and T-Bil elevation (7.5%). Significant antitumor activity combined with a mild toxicity profile was observed. This monotherapy warrants further evaluation in a randomized study.

Keywords Biliary tract cancer · Chemotherapy · Phase II study · S-1

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Introduction

Biliary tract cancer (BTC) is a common cause of death from cancer in Japan, with an estimated 16,000 deaths annually [21]. While surgery currently remains the only potentially curative treatment, the curative resection rates for gallbladder cancer range from 10 to 30% [8, 16]. Most patients are diagnosed at an unresectable advanced stage of disease because of the lack of characteristic early symptoms. Although systemic chemotherapy is indicated for patients with unresectable disease, no standard chemotherapy regimens have been established and prognosis remains extremely poor.

A previous report showed improved survival in patients with BTC who were treated with 5-fluorouracil (5-FU)-based chemotherapy, compared to best supportive care [7]. Efforts have been made to develop promising regimens for

the treatment of BTC using clinical trials examining systemic chemotherapy [9]. Among various reports on chemotherapy for BTC, fluoropyrimidines have been regarded to form the basis of chemotherapeutic strategies [3, 9, 25].

S-1 is an oral anticancer drug that consists of tegafur (FT) as a prodrug of 5-FU, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo). The drug contains two biochemical modulators, CDHP and Oxo, that improve the tumor-selective toxicity of 5-FU [28]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD) that is involved in the degradation of 5-FU; it enables efficacious concentrations of 5-FU to be maintained in the plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase (OPRT), inhibits the phosphorylation of 5-FU in the gastrointestinal tract, and reduces the serious gastrointestinal toxicity of 5-FU. S-1 has already been demonstrated to have potent antitumor activity against various solid tumors in clinical studies [4, 11, 22, 26, 27]. For example, the response rates for advanced gastric and pancreatic cancer in the phase II studies conducted in Japan were 49 and 38%, respectively [4, 27].

Regarding BTC, a pilot phase II study of S-1 showed promising results, with a 21% response rate (at least one measurable lesion) and a manageable toxicity profile in 19 patients with unresectable disease [31]. Therefore, we conducted a multicenter phase II study of S-1 monotherapy for the treatment of unresectable BTC to confirm the results of the pilot phase II study. The objectives of this study were to evaluate the response rate, toxicity, time-to-progression, and overall survival.

Materials and methods

Patient selection

The eligibility criteria for enrollment in the study were as follows: (1) histologically or cytologically confirmed adenocarcinoma of the biliary tract (extrahepatic bile duct, gallbladder, or ampulla of Vater); (2) capable of oral intake; (3) measurable disease on computed tomography (CT), magnetic resonance imaging (MRI) or X-ray film; (4) unresectable disease; (5) no history of prior anticancer treatment except resection; (6) age of 20–74 years; (7) a Karnofsky performance status (KPS) of 80–100 points; (8) adequate organ function–bone marrow function (hemoglobin $\geq$ 10.0 g/dL, leukocyte count 4,000–12,000/mm^3, neutrophil count $\geq$ 2,000/mm^3, platelet count $\geq$ 100,000/mm^3), renal function (serum creatinine concentration $\leq$ upper limit of normal), and hepatic function (serum bilirubin level $\leq$ 3 times upper limit of normal, serum aspartate transaminase (AST) and alanine transaminase (ALT) levels $\leq$2.5 times upper limit of normal); (9) a life expectancy $\geq$ 2 months; and (10) written informed consent from the patient. Patients were excluded if they had severe complications. The study was approved by the local institutional review boards at all participating centers.

Treatment plan

Patients received S-1 orally at 80 mg/m^2 total daily dose divided b.i.d. on days 1–28, followed by a 14-day recovery period. Specifically, during the treatment weeks, patients with a body-surface area of less than 1.25 m^2 received 80 mg daily (i.e. two doses of two 20 mg capsules, twice daily); those with a body-surface area of 1.25 m^2 or more but less than 1.5 m^2 received 100 mg daily (i.e. two doses of two 25 mg capsules, twice daily); and those with a body-surface area of 1.5 m^2 or more received 120 mg daily (i.e. two doses of three 20 mg capsules, twice daily). The drug was administered after the morning and evening meals. Chemotherapy was continued until evidence of progression, a request for withdrawal, or the development of unacceptable toxicity in the investigator's opinion. Compliance and drug accountability were thoroughly scrutinized: patients were asked to keep a diary tracking the intake of S-1 and other medications. S-1 was provided by Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan).

Evaluation of response and safety

All the patients who received at least one dose of the test drug were included in the response and toxicity evaluations. Tumor response was assessed by computed tomography (CT), magnetic resonance imaging (MRI) or X-ray films during each course and was evaluated according to the Japan Society for Cancer Therapy (JSCT) Criteria [15], which is basically similar to the World Health Organization Criteria. The response was secondarily assessed using the response evaluation criteria in solid tumors (RECIST) [29]. Objective responses were confirmed by a second evaluation performed at least 4 weeks later. Serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels were measured monthly using an immunoradiometric assay.

Assessments of the physical findings, blood biochemistry and urinalysis tests were conducted biweekly; vital signs were assessed as necessary. All adverse events were evaluated for severity according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The duration and causal relationship to S-1 was first judged by the attending physicians.

An independent review committee reviewed the objective responses and the adverse events.

Statistical considerations

The primary efficacy parameter in this study was the overall response rate, as defined by the outcome based on tumor measurements. The other parameters were response duration, overall survival time and time-to-progression (TTP). Response duration was calculated from the date of the first documentation of a partial response to the date of progressive disease. The TTP was determined by the interval between the initiation of treatment and the date when disease progression (according to the JSCT criteria) was first documented. Overall survival was calculated from the first day of registration until death from any cause. The median OS and the median TTP were estimated using the Kaplan–Meier method. The threshold of the response rate was defined as 5%, and the expected rate was set at 20% because the response rate in the previous study was 21.1% [31]. If the true response rate of S-1 was 20%, a sample size of 40 would ensure that there was at least an 80% power, at a one-sided significance level of 2.5%, to reject the null hypothesis that the response rate was less than 5%. If objective responses were obtained in six or more of the 40 patients, the lower limit of the 95% confidence interval (95% C.I.) of the response rate would clear the 5% threshold.

Results

Patients

A total of 41 patients were recruited from 7 institutions between January and December 2004. S-1 was not administered in 1 patient because this patient's γ-GTP level increased to grade 4 prior to the start of treatment. The 40 patients who received S-1 treatment were assessed for toxicity, response, response duration, TTP and survival. The baseline patient characteristics are listed in Table 1. Most patients (95.0%) had a good KPS of 90–100 points. Eighteen patients (45.0%) had undergone a prior resection of the primary tumor with curative intent and were offered chemotherapy after the documentation of metastatic or local recurrence. Among the 18 patients who had undergone resection, 11 patients had extrahepatic bile duct carcinoma, 4 had gallbladder cancer, and 3 had ampulla of Vater cancer.

Table 1 Patient characteristics

	No. of patients (%)
Total	40
Sex	
Male	22 (55.0)
Female	18 (45.0)
Age (years)	
Median age (range)	59.5 (33–74)
Karnofsky performance status	
100	25 (62.5)
90	13 (32.5)
80	2 (5.0)
Location of primary tumor	
Extrahepatic bile duct	15 (37.5)
Gallbladder	20 (50.0)
Ampulla of Vater	5 (12.5)
Extent of disease	
Locally advanced	10 (25.0)
Metastatic	30 (75.0)
Metastatic sites	
Liver	26 (65.0)
Lymph node	24 (60.0)
Lung	2 (5.0)
Peritoneum	5 (12.5)
Ovary	1 (2.5)
Prior resection	
(+)	18 (45.0)
(−)	22 (55.0)
CA19-9 before treatment (U/mL)	
≤37	8 (20.0)
>37	32 (80.0)
CEA before treatment (ng/mL)	
≤5.0	22 (55.0)
>5.0	18 (45.0)

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

Treatment

The initial dose of S-1 was 80 mg/day in 1 patient (2.5%), 100 mg/day in 18 (45.0%), and 120 mg/day in 21 (52.5%). A total of 160 cycles of S-1 chemotherapy were delivered, with a median of three cycles per patient (range, 1–24 cycles). Across all the cycles, patients received 91.4% of the initially prescribed chemotherapy. As of writing, 1 patient is continuing to receive the protocol therapy. Of the 39 patients who discontinued this treatment, 31 (79.5%) experienced disease progression, 6 (15.4%) refused further treatment because of adverse events such as an increase in serum bilirubin, anemia, rash, thrombocytopenia, edema and anorexia, one withdrew consent before the completion of the first course, and one discontinued the treatment based on the attending physician's advice after the patient had experienced a complete response for more than 2 years. After abandoning the S-1 treatment, 13 patients received second-line treatment: 10 patients had systemic chemotherapy with gemcitabine in 3 patients, cisplatin plus irinotecan

in 3, uracil/tegafur in 2, uracil/tegafur plus doxorubicin in 1, an investigational compound in 1; 2 patients had radiotherapy; and 1 patient had hepatic arterial chemoembolization. The other 25 patients received only the best supportive care, and the other patient was observed without anti-cancer treatment after CR.

Response and Survival

One patient achieved a complete response (CR), and 13 patients achieved partial responses (PRs), producing an overall objective response rate of 35.0% (95% C.I., 20.6–51.7%) according to the JSCT criteria. No change (NC) was noted in 17 patients (42.5%) and progressive disease (PD) was noted in 7 patients (17.5%). The remaining 2 patients were not evaluated because the radiographic assessment was not determined; one was treatment-related death and the other refused the further treatment. One patient evaluated as having a PR according to investigator assessments was assessed as having NC according to the independent review committee assessments, thus the response rate was 37.5% assessed by investigators, and the 35.0% according to the independent review committee, which corresponded reasonably well. The median response duration was 4.5 months. The response rate in patients with gallbladder cancer was higher than that of patients with other BTCs, but no significant difference in response rate was observed when the patients were grouped according to the location of their primary sites (Table 2). According to the RECIST criteria, there were 1 CR, 12 PRs, 18 stable disease (SD), 7 progression disease (PD) and 2 NE. Thus, the overall response rate was 32.5% (95%C.I., 18.6–49.1%). The criteria of JSCT describe the assessment of both the investigators and the independent review committee, while RECIST only concerns the latter.

The serum CA 19-9 level decreased by more than 50% in 13 (40.6%) of the 32 patients who had pretreatment levels of over the upper normal limit, and the serum CEA level decreased by more than 50% in 5 (27.8%) of the 18 patients who had pretreatment levels of over the upper normal limit. Among the 14 patients who experienced a reduction in their CA 19-9 level, CEA level or both, 9 patients (64.3%) had objective responses.

The median TTP was 3.7 months (95% C.I., 3.2–5.8 months; Fig. 1). The median OS was 9.4 months (95% C.I., 6.0–11.0 months), and the 1-year survival rate was 32.5% (Fig. 2). The median OS for patients with extrahepatic bile duct cancer was 9.3 months, while that for patients with gallbladder cancer was 8.1 months; while for patients with cancer in the ampulla of Vater, the median OS has not yet been reached (Fig. 3).

Table 2 Tumor response

	$n = 40$
Complete response	1 (2.5%)
Partial response	13 (32.5%)
Overall response	14 (35.0%) 95% CI, 20.6–51.7%
Extrahepatic bile duct	4/15 (26.7%)
Gallbladder	9/20 (45.0%)
Ampulla of Vater	1/5 (20.0%)
No change	17 (42.5%)
Progressive disease	7 (17.5%)
Not evaluable[a]	2 (5.0%)

[a] Radiographic assessment was not determined

Toxicity

Table 3 shows treatment-related adverse events. The most common hematological toxicities were anemia and

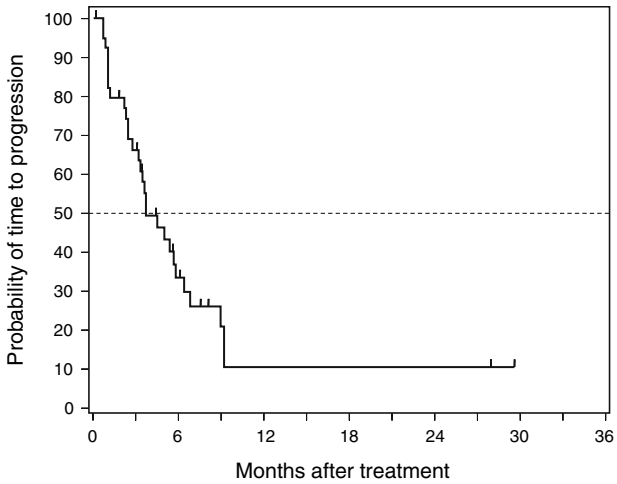

Fig. 1 Time to progression in 40 patients treated with S-1. The median time to progression was 3.7 months

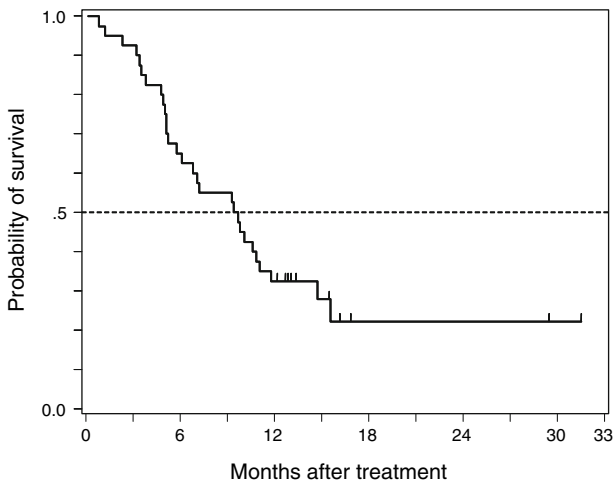

Fig. 2 Overall survival in 40 patients treated with S-1. The median overall survival period was 9.4 months, and the 1-year survival rate was 32.5%

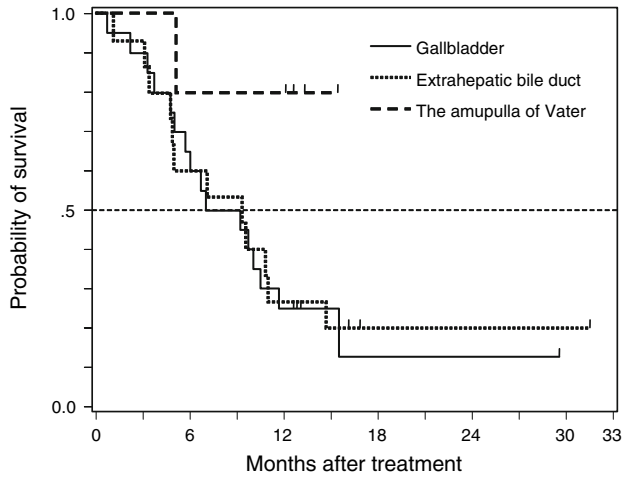

Fig. 3 Survival curves of patients with extrahepatic bile duct carcinoma ($n = 15$), gallbladder carcinoma ($n = 20$), or ampulla of Vater cancer ($n = 5$)

leukopenia (each over 50%), while the most common non-hematological toxicities were fatigue, an elevated serum bilirubin level, a reduced serum albumin level, a reduced serum total protein level, anorexia and an elevated AST level (each over 40%). Other major symptoms included nausea, stomatitis, and rash. Grade 3 or 4 toxicities were observed in 16 of the 40 patients (40%). The major Grade 3 or 4 toxicities were lymphopenia (17.5%), anemia (10.0%), fatigue (7.5%), anorexia (7.5%), and serum bilirubin elevation (7.5%). Five patients required S-1 dose reduction because of adverse events. One treatment-related death occurred prior to the completion of the first cycle. The patient had been treated for gallbladder cancer and abdominal lymph node metastases, including metastases of the paraaortic lymph nodes. Although the patient had a history of obstructive jaundice, the condition was resolved using percutaneous biliary drainage before enrollment in this study. Grade 3 anorexia and fatigue in addition to dehydration developed, and S-1 was discontinued on day 16 after the start of administration. Grade 4 leukopenia was observed on day 17, and renal dysfunction developed on the same day; the serum creatinine level was 1.7 mg/dL, and the serum urea nitrogen level was 106 mg/dL. Thereafter, septic shock and disseminated intravascular coagulation (DIC) occurred, and the patient died 20 days after the start of treatment.

Discussion

This multicenter phase II study was initiated to confirm the efficacy and safety of S-1 monotherapy in advanced BTC. The expected response rate was set at 20%, but a 35.0% response rate was achieved, according to the JSCT criteria.

Table 3 Treatment-related adverse events ($n = 40$): worst grade reported during the treatment period

Toxicity	Grade				Grades 1–4	Grades 3–4
	1	2	3	4		
Total	2	20	14	2	95.0%	40.0%
Hematological						
Leukopenia	17	3	1	1[a]	55.0%	5.0%
Neutropenia	12	4	2	0	45.0%	5.0%
Anemia	9	11	3	1	60.0%	10.0%
Lymphopenia	0	11	7	0	45.0%	17.5%
Thrombocytopenia	7	5	1	0	32.5%	2.5%
Non-hematological						
Nausea	8	4	1	0	32.5%	2.5%
Vomiting	6	2	2	0	25.0%	5.0%
Fatigue	13	5	3	0	52.5%	7.5%
Anorexia	8	6	3	0	42.5%	7.5%
Diarrhea	4	4	0	0	20.0%	0%
Stomatitis	9	3	0	0	30.0%	0%
Rash	6	7	0	0	32.5%	0%
T-Bil elevation	3	12	3	0	45.0%	7.5%
AST elevation	9	6	1	0	40.0%	2.5%
ALT elevation	4	5	1	0	25.0%	2.5%
ALB reduction	7	10	0	0	42.5%	0%
T-protein reduction	14	3	0	0	42.5%	0%
Sepsis	0	0	0	1[a]	2.5%	2.5%
DIC	0	0	0	1[a]	2.5%	2.5%

T-Bil serum total bilirubin; *AST* serum aspartate aminotransferase; *ALT* serum alanine aminotransferase; *ALB* serum albumin; *DIC* disseminated intravascular coagulation

[a] Death related to adverse events

The lower limit of the 95% C.I. was over 20% of the expected response rate. Additionally, this multicenter phase II study was designed so that the response could also be evaluated according to the RECIST criteria. Accordingly, 1 patient achieved a CR, and 12 patients achieved a PR, for a response rate of 32.5% (95% C.I., 18.6–49.1%). Although 1 patient who was evaluated as having a PR according to the JSCT criteria was assessed as having SD according to the RECIST, the 35.0% response rate according to the JSCT criteria and the 32.5% response rate according to the RECIST criteria corresponded reasonably well.

The use of other oral fluoropyrimidines, like uracil/tegafur and capecitabine, against BTC has also been investigated. Uracil/tegafur alone or uracil/tegafur plus leucovorin were reported to have objective responses of 5 and 0%, respectively, and more than 60% of the patients were evaluated as having progressive disease after treatment with these regimens [10, 19]. The responses to capecitabine, a new prodrug of fluorouracil, and a combination of capecitabine and cisplatin were 19 and 21%, respectively [12, 24].

Thus, S-1 monotherapy may have a stronger activity against BTC than other fluoropyrimidine-based regimens, with regard to tumor response.

S-1 has been reported to be generally well tolerated in clinical trials, including a phase II study for patients with BTC [4, 11, 22, 26, 27]. In the current study, the most common toxicities were anemia, leukopenia, fatigue and elevated serum bilirubin and AST levels. Grade 3 or 4 toxicities were observed in 40% patients; thus, S-1 is considered to be tolerable, with toxicity levels comparable to those seen in patients with other solid tumors who underwent S-1 therapy [11, 22, 26, 27]. However, one treatment-related death occurred in this series; this patient developed severe leukopenia, septic shock and DIC prior to the completion of the first cycle of S-1 therapy. DPD deficiencies have been observed in some patients, and a close correlation has been reported between DPD activity and severe toxicity profiles in patients treated with fluorouracil [32]. In the above patient, severe toxicities occurred soon after the start of treatment, and a DPD deficiency was suspected. The DPD activity was investigated in the case of treatment-related death, but the activity was within the normal range. Based on the above-mentioned investigations, we speculated that dehydration as a result of biliary drainage and anorexia deteriorated the patient's renal function, in turn causing the excretion of 5-FU to decrease and resulting in the development of severe toxicities.

The gastrointestinal toxicity of fluorouracil is caused by the phosphorylation of fluorouracil by OPRT. Oxo, which is included in S-1, inhibits OPRT in the gastrointestinal tract, thereby reducing gastrointestinal toxicity. Among the grade 3 or 4 toxicities that occurred in the present study, the incidences of nausea (2.5%), anorexia (7.5%), vomiting (5.0%), and diarrhea (0%) were relatively low. Patients with biliary cancer often have obstructive jaundice before treatment. In these patients, treatment of cancer is initiated after jaundice has been treated. In the present study, 9 patients had abnormal T-Bil at the time of enrollment. In only 3 of the 9 patients, a treatment-emergent increase was considered to be an adverse drug reaction. However, it should be kept in mind that the incidence of T-Bil elevation was 45.0%. Although S-1 should be carefully administered to patients with external biliary drainage, it can be used in an outpatient setting with only minor toxicities, because of its safety, and this enhances its convenience.

In the current study, the median OS was 9.4 months, which was similar to the median OS of 8.3 months reported in the pilot phase II study on S-1. Recently, gemcitabine has shown promise as a new agent for the treatment of BTCs. In phase II trials, gemcitabine as a single agent achieved good responses of between 13 and 36% [6, 17, 23]. Moreover, gemcitabine-based combination regimens are reported to have response rates of more than 30% [1, 2, 13, 14]. In particular, a combination of gemcitabine and capecitabine achieved a 31% response rate and a median OS of 14.0 months. Combination regimens consisting of gemcitabine and S-1 have also been reported as promising in patients with advanced pancreatic cancer [30]. Based on these results, the combination of gemcitabine and S-1 should also be investigated for the treatment of BTC.

Various regimens, including combination chemotherapy regimens incorporating gemcitabine and the S-1 monotherapy reported in this study, have achieved encoureging response rates of 30% or more, but the median OS have varied from 4.6 to 15.4 months [1, 2, 13, 14]. Thus, there is variation in the survival period, despite of the high response rate. All of these trials, including the current study, consisted of a small number of patients (less than 50); thus the limited size of these series may account for the above variety. Survival can be affected by various factors, such as performance status and the site of the disease. Regarding the site of the disease, the median OS of patients with gallbladder cancer has been reported to be significantly shorter than that of patients with intrahepatic or extrahepatic bile duct carcinoma [5, 13]. A phase II study of gemcitabine plus cisplatin, reported by Doval et al., showed that the median OS was very short (20 weeks), although the response rate was relatively high at 36.6% [2]. The patients in Doval's study were limited to those with gallbladder cancer. The present study excluded patients with intarahepatic bile duct carcinoma because it is classified as a primary liver cancer, not a BTC, in the Japanese liver cancer and BTC guidelines [20, 18]. In the current study, no difference in survival was observed between patients with gallbladder cancer and those with extrahepatic bile duct carcinoma, but the median OS for the patient subgroup with ampulla of Vater cancer has not yet been reached. Although many clinical trials of chemotherapy for BTC have been conducted, no standard chemotherapy that can clearly prolong survival has been identified. The survival benefit of chemotherapy should be evaluated in large randomized prospective comparative studies that take the site of the biliary tumor and the performance status into consideration in the stratification strategy.

In conclusion, S-1 monotherapy was generally well tolerated and showed promising activity against advanced BTC. Further investigation in randomized studies is warranted to confirm the efficacy of S-1 in patients with BTC, including those with intrahepatic bile duct carcinoma. A multicenter randomized phase II study between S-1 alone and the combination of gemcitabine and S-1 is currently being planned by the Japan Clinical Oncology Group (JCOG).

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