Gemcitabine and S-1 Combination Chemotherapy in Patients with Advanced Biliary Tract Cancer: A Retrospective Study

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Abstract

Background: The aim of this study was to investigate the efficacy and safety of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. *Patients and Methods:* A retrospective study was performed on 15 consecutive patients. Gemcitabine was administered intravenously at 1,000 mg/m^2 on days 8 and 15. Oral S-1 (60 mg/m^2 in 2 divided doses) was given daily for the first 2 weeks, followed by 1 week of rest. This 3-week course of treatment was repeated. The primary endpoint was response rate, and the secondary endpoints were overall survival, progression-free survival, and safety. *Results:* The overall response rate was 26.7%, and the disease control rate was 73.4%. The overall survival was 12.0 months (95% CI, 9.5–14.5 months), and the progression-free survival was 8.0 months (95% CI, 4.3–11.7 months). Adverse events of grade 3 or 4 occurred in 33.3%, and the major grade 3/4 toxicities were anemia (20.0%), leukopenia (13.3%), and anorexia (13.3%). *Conclusion:* Gemcitabine and S-1 combination chemotherapy is effective and safe in patients with advanced biliary tract cancer.

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Introduction

Biliary tract cancer is uncommon but has a poor prognosis in Western countries [1]. In Japan, however, it is a common cause of death, accounting for an estimated 16,000 deaths annually [2]. While surgery remains the only curative treatment, most patients are diagnosed at an unresectable advanced stage of disease.

A previous report showed a superior survival time among patients with biliary tract cancer who were treated with 5-fluorouracil-based regimens, compared with best-supportive care [3]. Recently, many phase II studies have been reported for various regimens, such as gemcitabine, S-1, capecitabine, cisplatin, and oxaliplatin [4–7]. According to a pooled analysis of 112 trials, Eckel and Schmid [8] suggested that the combination of gemcitabine and platinum compounds represents the provisional standard for chemotherapy in patients with advanced biliary tract cancer. Furthermore, a prospective multicenter phase III trial of gemcitabine and cisplatin versus gemcitabine (ABC-02 study) was reported in 2009, and a statistically significant improvement in survival was observed among patients treated with gemcitabine and cisplatin, compared with gemcitabine alone [9].

S-1 (TS-1; Taiho Pharmaceutical) is an oral fluoropyrimidine anticancer drug designed to enhance the anticancer activity and to reduce the gastrointestinal toxicity of fluorouracil. S-1 consists of tegafur and 2 biochemical modulators, 5-chloro-2,4-dihydroxypyridine and potassium oxonate (molar ratio: 1:0.4:1). Previous phase II studies of S-1 monotherapy have reported overall response rates of 17.2 to 35.0% with tolerable toxicity for patients with advanced biliary tract cancer [6, 7]. Therefore, S-1 may be a key antitumor agent for these patients. Meanwhile, gemcitabine and S-1 combination chemotherapy also showed promising results, with a 34% response rate and mild toxicity for patients with advanced biliary tract cancer [10].

Based on these results, we studied the efficacy and safety of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. The primary endpoint was the response rate. The secondary endpoints were overall survival (OS), progression-free survival (PFS), and toxicity.

Patients and Methods

Eligibility Criteria

This is a single-center, retrospective study. Eligible patients had to have (i) histologically or cytologically confirmed adenocarcinoma of the biliary tract; (ii) an Eastern Cooperative Oncology Group performance status of 2 or less; (iii) an age of 20 years or older; (iv) a measurable tumor (in patients who had unresectable or recurrent disease); (v) an expected survival of at least 3 months; (vi) no previous treatment for any cancer; (vii) adequate organ function (hemoglobin >9 g/dl, leukocyte count >3,000/μl, platelet count >100,000/μl; transaminases <2.5 times the upper limit of normal, total bilirubin <3 times the upper limit of normal; and a serum creatinine level no greater than the upper limit of normal). Written informed consent was obtained from all the patients before enrollment in the study.

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Treatment

Gemcitabine was administered intravenously at a dose of 1,000 mg/m^2 as a 30-min infusion on days 8 and 15. Oral S-1 (60 mg/m^2 in 2 divided doses) was given daily for the first 2 weeks, followed by 1 week of rest. In the case of grade 3/4 hematological toxicity or grade 2 or higher non-hematological toxicity, treatment was delayed until recovery to a grade 1 toxicity level. The dose of gemcitabine was not reduced during the next course. If further toxicity was observed, the gemcitabine dose was reduced to 800 mg/m^2. This 3-week course of treatment was repeated until the appearance of unacceptable toxicity, withdrawal of consent by the patient, or the detection of progressive disease.

Statistical Analysis

The primary endpoint was overall response rate. Hematologic tests were performed, and clinical symptoms were assessed biweekly. Tumors were evaluated every 2 months using imaging studies (computed tomography, magnetic resonance imaging, chest radiography, ultrasonography). The Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess all the images. Secondary endpoints were OS, PFS and toxicity. OS was defined as the period between the date of the start of the first cycle of chemotherapy and the date of death. Deaths from other diseases were considered events, and data on patients without an event were censored as of the date of the final evaluation. PFS was defined as the period between the date of the start of treatment and the date on which the first evidence of disease progression was obtained. OS and PFS were calculated using the Kaplan-Meier method. Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0 [11].

Results

Patient Characteristics

From January 2008 to June 2010, 15 patients (median age 70 years; range 53–79 years) with locally advanced or metastatic biliary tract cancer were enrolled. The patient characteristics are summarized in **table 1**. There were 10 men (66.7%) and 5 women (33.3%). All patients had a performance status of 0 or 1. The primary tumor site was the gallbladder in 8 patients (53.3%), the extrahepatic biliary tract in 4 patients (26.7%), the intrahepatic biliary tract in 2 patients (13.3%), and the ampulla of Vater in 1 patient (6.7%). Twelve patients (80.0%) had undergone a resection of the primary tumor with curative intent.

Response and Survival

The responses of all 15 patients are summarized in **table 2**. None of the patients achieved a complete response. Four patients (26.7%) achieved partial response. The overall response rate was 26.7%. An additional 7 patients (46.7%) had stable disease; consequently, the disease control rate was 73.4%. Progressive disease was noted in 4 patients (26.6%); all of these patients died within 7 months. According to the tumor site, the overall response rate and the disease control rate were 25.0 and 62.5% for the patients with gallbladder cancer and 28.6 and 71.4% for the patients with non-gallbladder cancer, respectively.

The median OS was 12.0 months (95% CI, 9.5–14.5 months) (**fig. 1**), and the median PFS was 8.0 months (95% CI, 4.3–11.7 months) (**fig. 2**). The OS and PFS for the patients

with gallbladder cancer were 9.0 and 5.0 months, respectively, while the OS and PFS for non-gallbladder cancer had not yet been reached.

Toxicity

A total of 109 cycles of gemcitabine and S-1 combination chemotherapy were administered. The median number of cycles administered per patient was 7 (range 3–15 cycles). There were no treatment-related deaths. The most common hematologic toxicities were leukopenia (10/15, 66.7%) and anemia (9/15, 60.0%). The most common non-hematological toxicities were fatigue (5/15, 33.3%) and anorexia (5/15, 33.3%). Grade 3 or 4 toxicities were observed in 5 of the 15 patients (33.3%), and the major grade 3/4 toxicities were anemia (3/15, 20.0%), leukopenia (2/15, 13.3%), anorexia (2/15, 13.3%), nausea (1/15, 6.7%), and dehydration (1/15, 6.7%). The dose intensities of gemcitabine and S-1 were 90.6 and 97.3%, respectively.

Discussion

Until the ABC-02 study was reported in 2009 [9], no standard chemotherapy for advanced biliary tract cancer existed. The median OS of the gemcitabine and cisplatin-treated group was longer than that of the gemcitabine-treated group (11.7 vs. 8.3 months, p = 0.002). The PFS of the gemcitabine and cisplatin-treated group was also longer than that of the gemcitabine-treated group (8.5 vs. 6.5 months, p = 0.003). After this study was reported, gemcitabine and cisplatin began to become the new worldwide standard of care for advanced biliary tract cancer.

In our study, gemcitabine and S-1 combination chemotherapy achieved a disease control rate (partial response: 26.7%, stable disease: 46.7%) of 73.4%, an OS of 12.0 months, and a PFS of 8.0 months. Sasaki et al. [10] reported that the OS and PFS of gemcitabine and S-1 chemotherapy were 11.6 months and 5.9 months, respectively. Furuse et al. [6] and Sasaki et al. [7] evaluated the effectiveness of S-1 monotherapy, and reported an OS and PFS of 9.4 and 3.7 months (Furuse et al.) and 8.7 and 4.2 months (Sasaki et al.), respectively. Based on these results, the addition of gemcitabine to S-1 monotherapy may be more promising as a superior regimen, compared with S-1 monotherapy.

Regarding the primary tumor site, no difference in tumor response was observed in this trial, although the OS and PFS of patients with gallbladder cancer tended to be shorter than those of patients with non-gallbladder cancer. Several clinical trials have shown a statistically significant difference in the OS and PFS of patients with gallbladder cancer and those with non-gallbladder cancer [6, 12–14]. The reason for this is not clear, but the heterogeneous nature of gallbladder cancer and non-gallbladder cancer may be one explanation. Different expressions in cell cycle-regulatory proteins have been observed in biliary tract adenocarcinomas according to tumor location and morphology. Jarnagin et al. [15] suggested that the different OS according to tumor site was at least partly related to a significant difference in p27 expression. Gallardo et al. therefore suggested the necessity of individual trials, since gallbladder cancer has a more aggressive progression than non-gallbladder cancer [16]. However, the relationship between the response to chemotherapy and tumor location remains unclear.

Most adverse events were grade 1 or 2. The incidence of grade 3 or 4 hematologic toxicities were less than 20%, which was equivalent or inferior to that of previous phase II or III studies of gemcitabine-based combination chemotherapy [4, 5, 9, 10]. According to the incidence of non-hematological toxicities, the grade 3 or 4 toxicities were less than 13.3%; moreover, peripheral sensory neuropathy and hand-foot syndrome were especially uncommon, while these toxicities were commonly observed during treatment with oxaliplatin and capecitabine. Therefore, this combination chemotherapy was relatively well tolerated.

In conclusion, our study indicates that gemcitabine and S-1 combination chemotherapy for the treatment of advanced biliary tract cancer was effective and was well tolerated as a first-line chemotherapy. However, further phase III studies to investigate first-line regimens should be encouraged, and the relationship between survival and the tumor location of biliary tract cancer should be clarified.

Table 1. Characteristics of patients

Characteristic	Patients (n = 15)
Sex	
Male	10 (66.7)
Female	5 (33.3)
Age, years; median (range)	70 (53–79)
ECOG performance status	
0	12 (80.0)
1	3 (20.0)
2	0
Location of primary tumor	
Gallbladder	8 (53.3)
Intrahepatic bile duct	2 (13.3)
Extrahepatic bile duct	4 (26.7)
Ampulla of Vater	1 (6.7)
Disease status	
Locally advanced	3 (20.0)
Metastatic	7 (46.7)
Reccurent	5 (33.3)
Prior resection	
Yes	12 (80.0)
No	3 (20.0)

Values are n (%) unless indicated otherwise.

Table 2. Tumor response

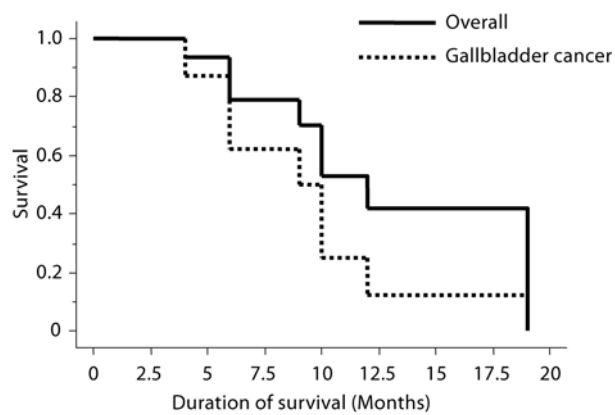| Site of lesion	Response rate	Disease control rate
Overall	26.7	73.4
Gallbladder	25.0	62.5
Intrahepatic bile duct	0	100
Extrahepatic bile duct	50.0	100
Ampulla of Vater	0	100

n = 15. Values are percentages.

Fig. 1. OS curves of patients with advanced biliary tract cancer and gallbladder cancer; the OS curve for patients with non-gallbladder cancer has not yet been reached.
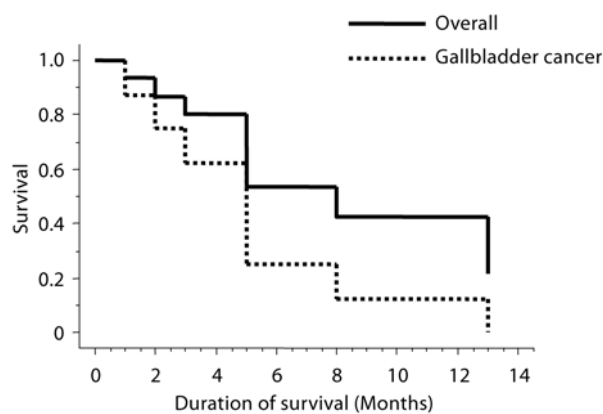

Fig. 2. PFS curves of patients with advanced biliary tract cancer and gallbladder cancer; the PFS curve for patients with non-gallbladder cancer has not yet been reached.

References

1 Patel T: Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2002;2:10.

2 Nomura K (ed): Cancer Statistics in Japan 2005. Foundation for Promotion of Cancer Reseach (FPCR), Tokyo, 2005.

3 Glimelius B, Hoffman K, Sjoden PO, et al: Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996;7:593–600.

4 André T, Reyes-Vidal JM, Fartoux L, et al: Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. Br J Cancer 2008;99:862–867.

5 Valle JW, Wasan H, Johnson P, et al: Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – the UK ABC-01 Study. Br J Cancer 2009;101:621–627.

6 Furuse J, Okusaka T, Boku N, et al: S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: a multicenter phase II study. Cancer Chemother Pharmacol 2008;62:849–855.

7 Sasaki T, Isayama H, Yashima Y, et al: S-1 monotherapy in patients with advanced biliary tract cancer. Oncology 2009;77:71–74.

8 Eckel F, Schmid RM: Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902.

9 Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281.

10 Sasaki T, Isayama H, Nakai Y, et al: Multicenter, phase II study of gemcitabine and S-1 combination chemotherapy in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 2010;65:1101–1107.

11 Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.

12 Penz M, Kornek GV, Raderer M, et al: Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 2001;12:183–186.

13 Knox JJ, Hedley D, Oza A, et al: Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332–2338.

14 André T, Tournigand C, Rosmorduc O, et al: Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 2004;15:1339–1343.

15 Jarnagin WR, Klimstra DS, Hezel M, et al: Differential cell cycle-regulatory protein expression in biliary tract adenocarcinoma: correlation with anatomic site, pathologic variables, and clinical outcome. J Clin Oncol 2006;24:1152–1160.

16 Gallardo JO, Rubio B, Fodor M, et al: A phase II study of gemcitabine in gallbladder carcinoma. Ann Oncol 2001;12:1403–1406.

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