A prospective feasibility study of one-year administration of adjuvant S-1 therapy for resected biliary tract cancer in a multi-institutional trial (Tokyo Study Group for Biliary Cancer: TOSBIC01)

Osamu Itano (laplivertiger@gmail.com)
Yusuke Takemura
Keio Gijuku Daigaku https://orcid.org/0000-0003-3791-9902
Norihiro Kishida
Japanese Red Cross Ashikaga hospital
Eiji Tamagawa
Machida Keisen Hospital
Hiroharu Shinozaki
Saiseikai Utsunomiya Byoin
Ken Ikeda
Sano Kousei General Hospital
Hidejiro Urakami
National Hospital Organization Tokyo Medical Center
Shigenori Ei
Kitasato Daigaku Igakubu
Shigeo Hayatsu
National Hospital Organization Saitama National Hospital
Keiichi Suzuki
National Hospital Organization Tochigi Medical Center
Tadayuki Sakuragawa
Tama Kyuryo Hospital
Masatsugu Ishii
Fussa Hospital
Masaya Shito
Kawasaki Shiritsu Kawasaki Byoin
Koichi Aiura
Kawasaki Shiritsu Kawasaki Byoin
Hiroto Fujisaki
Hiratsuka City Hospital
Kiminori Takano

Hiratsuka City Hospital
Junichi Matsui
Tokyo Shika Daigaku Ichikawa Sogo Byoin
Takuya Minagawa
Saitama City Hospital
Masahiro Shinoda
Keio Gijuku Daigaku Igakubu
Minoru Kitago
Keio Gijuku Daigaku Igakubu
Yuta Abe
Keio Gijuku Daigaku Igakubu
Hiroshi Yagi
Keio Gijuku Daigaku Igakubu
Go Oshima
Keio Gijuku Daigaku Igakubu
Shutaro Hori
Keio Gijuku Daigaku Igakubu
Yuko Kitagawa
Keio Gijuku Daigaku Igakubu

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Abstract

Background: Although surgery is the definitive curative treatment for biliary tract cancer (BTC), outcomes after surgery alone have not been satisfactory. Adjuvant therapy with S-1 may improve survival in patients with BTC. This study examined the safety and efficacy of 1 year adjuvant S-1 therapy for BTC in a multi-institutional trial.

Methods: The inclusion criteria were as follows: histologically proven BTC, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, R0 or R1 surgery performed, cancer classified as Stage IB to III. Within 10 weeks post-surgery, a 42-day cycle of treatment with S-1 (80 mg/m^2/day orally twice daily on days 1–28 of each cycle) was initiated and continued up to 1 year post surgery. The primary endpoint was adjuvant therapy completion rate. The secondary endpoints were toxicities, disease-free survival (DFS), and overall survival (OS).

Results: Forty-six patients met the inclusion criteria of whom 19 had extrahepatic cholangiocarcinoma, 10 had gallbladder carcinoma, 9 had ampullary carcinoma, and 8 had intrahepatic cholangiocarcinoma. Overall, 25 patients completed adjuvant chemotherapy, with a 54.3% completion rate while the completion rate without recurrence during the 1 year administration was 62.5%. Seven patients (15%) experienced adverse events (grade 3/4). The median number of courses administered was 7.5. Thirteen patients needed dose reduction or temporary therapy withdrawal. OS and DFS rates at 1/2 years were 91.2/80.0% and 84.3/77.2%, respectively. Among patients who were administered more than 3 courses of S-1, only one patient discontinued because of adverse events.

Conclusions: One-year administration of adjuvant S-1 therapy for resected BTC was feasible and may be a promising treatment for those with resected BTC. Now, a randomized trial to determine the optimal duration of S-1 is ongoing.

Trial registration: UMIN-CTR, UMIN000009029. Registered 5 October 2012-Retrospectively registered, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000009347)

Background

Biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, gallbladder carcinoma, and ampulla of Vater carcinoma. BTC is well-known as one of the most dismal prognostic malignant diseases and its incidence has been increasing. (1-3) Although surgical resection may provide curative treatment, the risk of recurrence is quite high and the reported prognosis of patients with resected advanced BTC is relatively low. (4, 5) Therefore, development of effective perioperative adjuvant therapy is currently being investigated. A meta-analysis series has shown the potential benefit of adjuvant chemotherapy, especially for patients with node-positive resected biliary tract cancer. (6) Despite the potential benefits, no prior randomized control trial (RCT) proved the positive effect of postoperative adjuvant chemotherapy in patients with BTC. (7, 8) Recently, a RCT assessing a 6-month administration of capecitabine for adjuvant therapy for BTC demonstrated improvements in

survival (9); however, the optimal adjuvant chemotherapy regimen for resected BTC has not yet been standardized.

S-1 is well-known as an oral anticancer drug consisting of tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate. S-1 has already been established as a standardized adjuvant therapy for patients with gastric and pancreatic cancer. (10, 11) Regarding BTC, a phase Ⅱ trial evaluating unresectable and recurrent cholangiocarcinoma indicated that S-1 had a 35% response rate, and adverse events were also relatively controlled.(12) One prospective phase Ⅱ trial comparing the efficacy of 6-month administration of S-1 and gemcitabine for adjuvant therapy after curative resection of BTC also showed better prognosis in the S-1 group. (13) Moreover, in Japan, the efficacy of 6-month administration of S-1 for postoperative BTC is currently being investigated in the large-scale phase Ⅲ ASCOT trial. (14) Thus, S-1 is expected to become a standard treatment in adjuvant therapy for resected BTC.

However, the duration of administration was not verified. One non-inferiority study comparing 1-year administration of S-1 with 6-month administration of S-1 for adjuvant therapy of resected gastric cancer was performed; eventually the study was censored because the 1-year administration group had significantly better prognosis in the interim analysis. (15) 1-year administration is still the standard for the treatment of gastric cancer. Therefore, we hypothesized that 1-year administration of S-1 would improve the prognosis, more than 6-month administration for resected BTC. Although the pilot ASCOT trial showed a high completion rate (75.8%) with 6-month administration of S-1 for BTC adjuvant therapy(16), there has been no conclusive evidence on the feasibility of 1-year administration of S-1. Thus, we planned a phase 2 study to investigate the feasibility of 1-year administration of S-1.

Methods

Eligibility criteria

Patients who underwent radical surgery for BTC and who were diagnosed pathologically were eligible if they met the following inclusion criteria: those with BTCs classified into either intrahepatic, hilar/perihilar, or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary of Vater carcinomas according to the WHO classification 2010;(17) Moreover, patients were included, if the eligible pathological stage ranged from Stage IB to Stage III according to the 6th edition of the UICC/AJCC staging system (18) without macroscopic residual tumors; if no distant metastases and no peritoneal dissemination was observed; if no prior chemotherapy or radiation for BTC was administered; patients who were able to start chemotherapy within 10 weeks after surgery; age ≥20 years; Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0 or 1; adequate oral intake; adequate bone marrow function (white blood cells ≥3500/mm^3, neutrophils ≥2000/mm^3, platelet ≥100000/mm^3, hemoglobin ≥9.0 g/dL), adequate liver function [aspartate aminotransferase (AST) ≤100 IU/L (or 150 IU/L under biliary drainage), alanine aminotransferase (ALT) ≤100 IU/L (or 150 IU/L under biliary drainage)] serum total bilirubin ≤2.0 mg/dL (or ≤3.0 mg/dL under biliary drainage), adequate renal function [serum creatinine ≤1.2 mg/dL and creatinine clearance or estimated glomerular filtration rate (GFR) by Cockcroft-Gault formula ≥60

mL/min], and serum albumin ≥3.0 g/dL; normal EKG findings within 28 days before registration; and written informed consent.

The exclusion criteria were as follows: previous history of S-1 administration; uncontrollable diarrhea; history of flucytosine, phenytoin, or warfarin potassium treatments; accumulated pleural effusion or ascites; presence of active infection without viral hepatitis; presence of other cancer except carcinoma in situ within 3 years; severe organ dysfunction (such as heart failure, renal failure, liver failure, intestinal paralysis, uncontrollable diabetes mellitus); presence of pulmonary fibrosis or interstitial pneumonitis; presence of severe mental disorder; presence of severe drug allergy; transfusion within 14 days before registration; women who were pregnant or nursing; women who may have been pregnant or were willing/trying to get pregnant; and unsuitable candidates for this study as judged by the physician.

Study design (Single-arm, non-randomized, open, historical control)

This study was designed by the Keio Surgery Research Network (KSRN) and was conducted at the Keio University Hospital. This study was registered with University Hospital Medical Information Network (UMIN) center (unique trial number: UMIN000009029). Patient registration and data management were conducted at an independent center at Keio University School of Medicine. All laboratory tests required to assess eligibility were completed within 28 days before the start of protocol treatment.

Treatment schedule

S-1 (tegafur, gimeracil, oteracil potassium; Taiho Pharmaceutical, Tokyo, Japan) was administered within 10 weeks after the surgery. An oral dose of 80 mg/m^2 S-1 was given every day on days 1 to 28 of a 6-week cycle for a year. The total dose was based on the patient's body surface area as follows: <1.25 m^2, 80 mg; 1.25–1.5 m^2, 100 mg; >1.5 m^2, 120 mg. After a-year of chemotherapy, additional chemotherapy was not given unless the patient was diagnosed with recurrence.

The protocol permitted dose modifications and cycle interruptions were as follows: white blood cells < 2000/mm^3, neutrophils < 1000/mm^3, platelet < 75000/mm^3, hemoglobin < 8.0 g/dL, adequate liver function (AST >150 IU/L, ALT >150 IU/L), serum total bilirubin > 3.0 mg/dL, serum creatinine > 1.5 mg/dL, and adverse events associated with gastrointestinal symptom ≥ Grade 3. In cases for which the S-1 dose was reduced, the dose was decreased by 20 mg/body weight while maintaining a minimum dose of 60 mg/body weight, and it was not subsequently increased for any reason. When dose interruptions were prolonged for longer than 4 weeks or if dose reductions below 60 mg/m^2 were required, the patient was considered for medication discontinuation. Patients had the option to withdraw from the trial or during follow-up at any stage. Furthermore, criteria for treatment discontinuation included factors such as the physician's decision, recurrence, and development of other cancers.

Follow up after surgery

Postoperative follow-up CT scanning were performed at 3, 6, 12 months for the first year and every 6 months following that. Tumor marker tests were conducted every 3 months for 2 years.

Evaluation of toxicity

Toxicity was categorized according to the Common Terminology Criteria for Adverse Events, version 4.0. Toxicity was recorded during treatment continuously.

Outcomes

The primary outcome was completion rate at 1 year after first administration of S-1. Secondary outcomes included relative dose intensity (RDI), toxicity, overall survival rate, and disease-free survival rate at two years, which was defined as the time from registration until the event. RDI was defined as the proportion of actual dose intensity received to the planned dose intensity.

The expected treatment completion rate was set at 50% based on the data of the ACTS-GC trial, of which completion rate was 65.8%. (10) The sample size was calculated as 43 patients with a 95% confidence interval for the completion rate of treatment within 30%. Therefore, the target number of patients was set to be 50 for possible ineligible patients.

Results

Patient characteristics

Between June 2011 and December 2014, 50 patients were enrolled in this study. A total of 46 patients were eligible; patient characteristics are summarized in Table 1. The median age was 68.5 years (range, 39–84 years). Nineteen (41%) patients had extrahepatic cholangiocarcinoma, 8 (17%) patients had intrahepatic cholangiocarcinoma, 10 (22%) had gallbladder carcinoma and 9 (20%) had ampulla of Vater carcinoma. Surgical procedures consisted of 25 (54%) pancreatoduodenectomies, 6 (13%) hepatectomies without bile duct resection, 6 (13%) hepatectomies with bile duct resection, and 9 (20%) extended cholecystectomies. Forty-three (94%) patients achieved R0 resection and 20 (46%) had regional lymph node metastases.

Feasibility analysis (Tables 2, 3)

Table 2 shows the main results. The completion rate for all patients was 54.3% while the completion rate without recurrence during the 1 year administration was 62.5%. The median relative dose intensity was 62.9%. Of 25 patients with completion, 13 needed dose reduction or temporary therapy withdrawal, 13 patients withdrew from S-1 administration owing to adverse events and 8 of these discontinued cases were due to gastrointestinal adverse events. The reason for discontinuation is summarized in Table 3. Nine cases discontinued because of adverse events at the first course and 3 cases discontinued at the second course. Only one case withdrew after receiving 2 courses due to adverse events.

Completion rate by primary disease and surgical procedures (Tables 4)

Completion rate for all patients and those without recurrence based on their primary disease and surgical procedures are shown in Table 4. The completion rate excluding recurrent cases ranged from 60.0% to 66.7% by the type of surgical procedures.

Adverse Events (Table 5)

Adverse events are shown in Table 5. In total, 41 (89%) patients suffered adverse events (any grade). Hematological events were most common in all grade adverse events. Overall, 7 (15%) patients suffered severe adverse events at grade 3 or more. Gastrointestinal events such as anorexia or diarrhea were more frequent than hematologic events or other events.

Long-term outcome (Figure 1)

The median follow-up time for all patients in this study was 38.4 months (range, 7.5–56.8 months). The 2-year OS and DFS were 80.0 % [95% confidence interval (CI), 68.2–91.8 %] and 77.2 % (95% CI, 64.7–89.7 %) and, respectively (Figure 2). Eight (60%) of 14 patients who had recurrence in this study period developed recurrence in the liver. The other recurrence sites were as follows: lymph nodes, 5; lung, 3; local recurrence, 2; peritoneal dissemination, 2 and bone, 2.

Discussion

In this study, we evaluated the feasibility of adjuvant chemotherapy by assessing the outcomes of 1-year administration of 80 mg/m^2 S-1 for resected BTC. Our prospective phase II study demonstrated that a completion rate without recurrence during the 1-year administration of S-1 was over 60% and the rate was 50% or more regardless of the surgical procedures or primary disease. The most frequent reason for withdrawal was gastrointestinal adverse events occurring early in the treatment course.

The completion rate in this study was 54.3% (when recurrence cases were excluded, the rate was 62.5%). Previous reports regarding adjuvant chemotherapy for resected gastric cancer showed that 1-year administration of S-1 was tolerable in 48.6 - 65.8% of patients (in those without recurrence, 60.7 - 69.1%). (10, 19) Several studies have evaluated the 6-month administration of S-1 in BTC. One reported the completion rate was 51.4% (the rate for those without recurrence was not available) for BTC after major hepatectomy (13) and the other reported a complete rate of 75.8% (the rate for those without recurrence, 86.0%). (16) Regarding other types of cancer, a 6-month administration of S-1 was completed in 76.5% of cases (rate for non-recurrence, not available) in colon cancer (20) and 72.2% (rate for those without recurrence, 75.8%) in pancreatic cancer.(11) Compared to other regimens for BTC, the BILCAP trial that evaluated a 6-month administration of capecitabine and the BCAT trial that evaluated a 6-month administration of gemcitabine showed the complete rates were 54.7% and 52.1%, respectively. (9, 21) In the current study, 65.2% (those without recurrence, 70.0%) completed a four-course administration (data were not shown) which seems to be almost comparable with other cancers or other regimens.

This study showed a higher incidence of gastrointestinal adverse events compared to that of the phase II trials for unresectable or recurrent BTC (12) and a high incidence of discontinuation due to gastrointestinal adverse events in the first course. Specifically, there were several patients who had their medication discontinued due to refusal following grade 1 or 2 gastrointestinal adverse reactions. The abovementioned findings could be attributed to the influence of surgery. Most of the curative surgeries performed for BTC were extremely invasive with extensive lymph node dissections and upper-gastrointestinal reconstructions such as pancreatoduodenectomy or major hepatectomy with extra bile duct resection. Similar data was reported in gastric cancer. (19) One recent prospective study demonstrated that the completion rate of adjuvant therapy increased with combining Kampo for appetite increase.(22) Therefore, control or prevention of gastrointestinal symptoms is important in patients who have undergone upper abdominal surgery. However, it should be noted only one patient discontinued treatment due to a gastrointestinal adverse event after the second course. These results suggest 1-year administration may be tolerable for patients who can receive administration for 6 months.

The ASCOT trial is evaluating the efficacy of 6-month administration of S-1 postoperatively for patients with bile duct cancer. (14) . However, the duration was decided according to the adjuvant therapy regimen for pancreatic cancer. (11) There was no evidence regarding the duration of administration. Rather, in a non-inferiority study comparing the 1-year administration of S-1 with a 6-month administration for gastric cancer, the 1-year administration group had better prognosis in the interim analysis. Thus, 1-year administration is still the standard for gastric cancer treatment. (15) Based on the results of this feasibility study and other recent reports described above, we started a prospective randomized controlled trial in 2018 to evaluate the efficacy of 1-year administration of S-1 as adjuvant chemotherapy by comparing that of 6-months administration of S-1 (TOSBIC-03 trial UMIN: 000029421) for adjuvant therapy of BTC. We are expecting that this study will show a significant survival benefit for 1-year administration with high completion rate and that the 1-year administration of S-1 could be one of the standard treatments after curative surgery for BTC.

Conclusion

The 1-year administration of adjuvant S-1 therapy for resected BTC was feasible. This regimen has a potential to become a promising treatment for resected BTC.

List Of Abbreviations

BTC, biliary tract cancer

DFS, disease-free survival

OS, overall survival

RCT, randomized control trial

ECOG-PS, Eastern Cooperative Oncology Group Performance Status

AST, aspartate aminotransferase

ALT, alanine aminotransferase

GFR, glomerular filtration rate

RDI, relative dose intensity

CI, confidence interval

CEA, carcinoembryonic antigen

CA19-9, carbohydrate antigen 19-9

Declarations

Ethics approval and consent to participate

The protocol was approved by the institutional review board of Keio University School of Medicine (#20110027), and also approved by the other institutional review board in Tachikawa hospital, Kawasaki Municipal Ida Hospital, Eiju General Hospital, Japanese Red Cross Ashikaga Hospital, Saiseikai Utsunomiya Hospital, National Hospital Organization Tokyo Medical Center, Sano Kousei General Hospital, National Hospital Organization Saitama National hospital, Tama Kyuryo Hospital, Kawasaki Municipal Kawasaki Hospital, Kitasato University Kitasato Institute Hospital, Tokyo Dental College and Isehara Kyodo Hospital. The research met the standards of the Declaration of Helsinki. The forms of informed consent were written by all participants.

Consent for publication

Not applicable

Availability of data and materials

The protocol and the datasets are available from the corresponding author on reasonable request.

Competing interests

Y. Kitagawa and M. Shinoda received designated donation for research funding from Taiho Pharmaceutical. Y. Kitagawa and O. Itano has an endowed chair of Taiho Pharmaceutical. Other authors have no conflict of interest.

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We have no funding to declare

Authors' contributions

OI conceived the study. OI, TM, MS, MK, YA, HY, GO and SH designed the study. YT, NK, ET, HS, KI, HU, SE, SH, KS, TS, MI, MS, KA, HF, KT and JM managed this study and collected data in each institute. KY oversaw the study, OI and YT carried out data analyses, interpreted data and drafted the manuscript; all authors reviewed and approved the final version of the manuscript.

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Tables

Due to technical limitations the Tables are available as a download in the Supplementary Files.

Figures

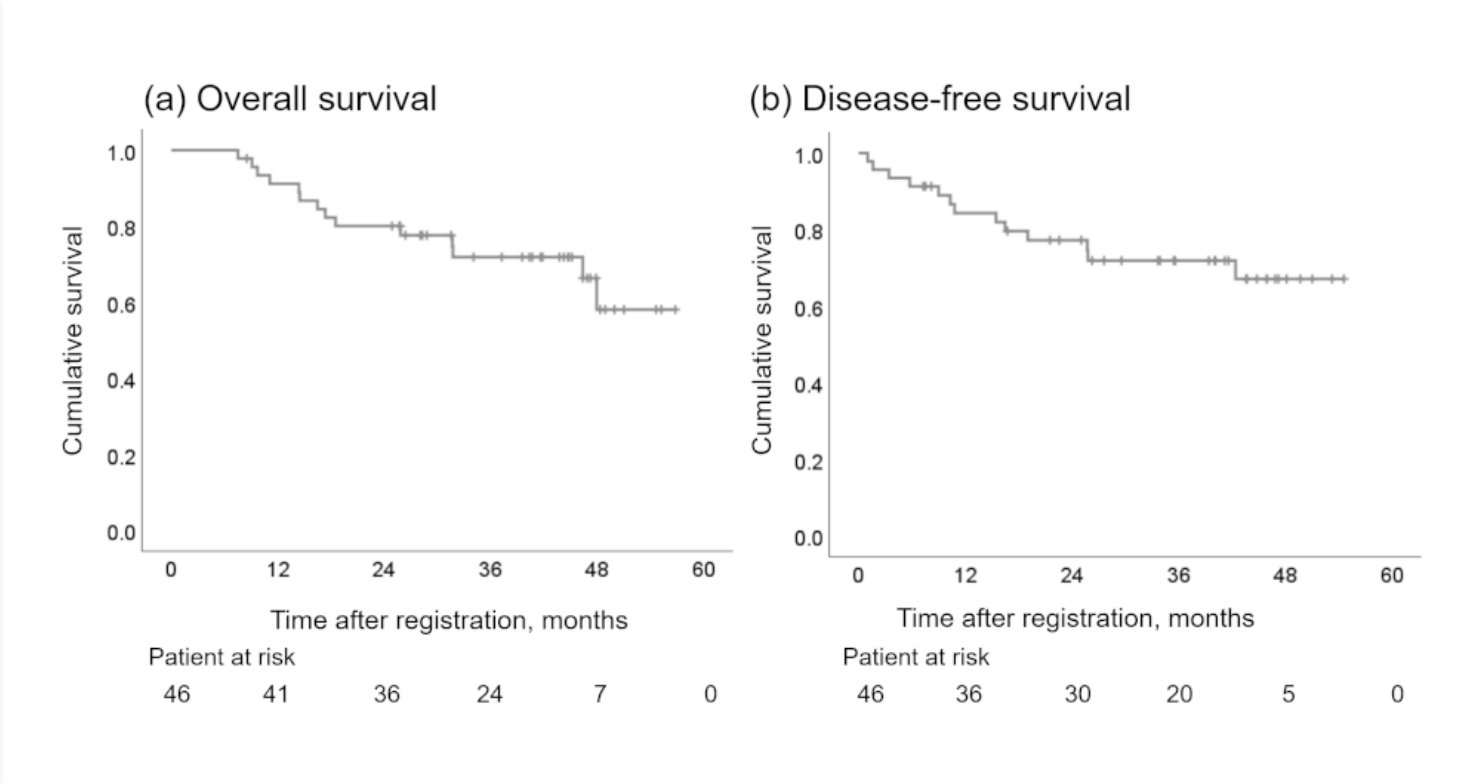

Figure 1

Survival analysis. Kaplan-Meyer curves for overall survival (a) and disease-free survival (b) are shown.

Supplementary Files

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