学位論文

「Phase I trial of combination chemotherapy with gemcitabine, cisplatin, and S-1 in patients with advanced biliary tract cancer.
（進行胆道癌に対する、ゲムシタビン、シスプラチン、S-1 併用化学療法の第 I 相試験）」

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

要旨

【背景・目的】

胆道癌は初回診断時に既に切除不能な進行した状態であることが多く、化学療法が行われる症例が多い。たとえ外科的切除が行われても再発する症例も少なくなく、切除例の5年生存率も30～50%と決して高くない。進行胆道癌に対する標準的なレジメンはゲムシタビンとシスプラチンの2剤併用化学療法であるが、生存期間の中央値は11.7か月であり、さらなる治療効果の向上が望まれている。

本研究は進行胆道癌を対象とし、標準的なレジメンに含まれる2剤に加えて、胆道癌に対して有効性が認められているS-1を上乗せする3剤併用化学療法の適切な用量を決定するための臨床第I相試験である。3例コホート法を用いて、dose limiting toxicity(DLT)を評価し、最大耐用量(maximum-tolerated dose: MTD)の推定と第II相試験に向けた推奨用量(recommended dose: RD)の決定を目的とした。

【方法】

病理学的にて診断された進行もしくは再発胆道癌の症例を対象とした。計画した投与量はゲムシタビン(mg/m^2)、シスプラチン(mg/m^2)、S-1(mg/m^2/日)それぞれ以下の通り：level -1, 800/20/60; level 0, 800/25/60; level 1, 1000/25/60; and level 2, 1000/25/80。ゲムシタビンとシスプラチンをday1と15に静注し、S-1はday1-7とday15-21に内服するサイクルを4週ごとに行った。

【結果】

12例が登録され、開始用量のlevel0では3例すべてでDLTは観察されなかった。level1には6例が登録され、1例でDLT(Grade4の発熱性好中球減少症・白血球減少・好中球減少、Grade3の血小板減少症)が観察された。level2では3例すべてでDLTは観察されなかった。以上より、MTDは未定、RDはlevel2の用量と決定した。

【結語】

RDはゲムシタビン1000mg/m^2(days 1, 15)、シスプラチン25mg/m^2(days 1, 15)、S-1 80mg/日(days 1-7, 15-21)と決定した。今後、本治療法の有効性と安全性を評価する第II相試験が期待される。

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INTRODUCTION

Biliary tract cancer is more common in East Asia and Latin America than in other continents[1]. Despite recent remarkable progress in diagnostic procedures, most cases are advanced at initial diagnosis and are thus treated by chemotherapy. Moreover, even if surgery, the only potentially curative treatment, can be performed, relapse often occurs, and 5-year survival rates are not high (ampullary cancer, 52.8%; gallbladder cancer, 41.6%; bile duct cancer, 33.1%)[2].

Gemcitabine, cisplatin, and fluorouracil (including their pro-drugs) are widely used to treat biliary tract cancer. Gemcitabine is used throughout the world as a key drug for the management of biliary tract cancer because clinical trials have confirmed its effectiveness, with a response rate (RR) of 17.5% and a mean survival time (MST) of 7.6 mo[3]. In addition, the ABC-02 study, a phase III randomized controlled trial comparing gemcitabine alone with gemcitabine plus cisplatin (GC), reported that MST was significantly longer for the combination regimen (gemcitabine, 8.1 mo vs GC, 11.7 mo, $P < 0.001$)[4]. These results established GC combination therapy as a standard treatment for advanced biliary tract cancer.

S-1 is an oral fluoropyrimidine pro-drug that has been confirmed to be effective against various types of solid tumors, both alone and in combination with other cytotoxic drugs[5-12]. S-1 has also been confirmed to be effective against biliary tract cancer. Two phase 2 clinical trials reported RRs of 21.1% and 35.0% with MSTs of 252 d and 287 d, respectively[13,14]. However, these results remain unsatisfactory.

Available evidence suggests that a three-drug combination regimen of gemcitabine, cisplatin, and S-1 might further enhance response and improve outcomes. However, the effectiveness of combination therapy with gemcitabine, cisplatin, and S-1 has not been evaluated previously in advanced biliary tract cancer. We designed this phase I study to evaluate the safety and determine the maximum-tolerated dose (MTD) and recommended dose (RD) of this triplet combination in patients with advanced biliary tract cancer.

MATERIALS AND METHODS

Patient eligibility

Patients with histologically or cytologically confirmed biliary tract cancer were eligible for enrollment if they met the following criteria: unresectable or recurrent disease; no prior therapy (radiation or chemotherapy) other than surgery; 20-79 years of age; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate bone marrow function (white blood cell count 3500-12000/mm3, neutrophil

count ≥ 2000/mm3, platelet count ≥ 100000/mm3, and hemoglobin ≥ 10 g/dL), adequate liver function (aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤ three times the upper limit of normal (ULN) (in patients with obstructive jaundice, ≤ five times the ULN after biliary drainage), and total bilirubin ≤ 2 mg/dL (in patients with obstructive jaundice, ≤ 3 mg/dL after biliary drainage), adequate renal function (creatinine clearance ≥ 60 mL/min; 24-h urine collection was recommended, or the Cockcroft-Gault formula could be used if 24-h collection was not possible), and adequate heart function (practically normal); and adequate oral intake. All patients provided written informed consent. The exclusion criteria were as follows: the presence of another cancer; severe complications (for example, congestive heart disease, coronary artery disease, active arrhythmias, a history of cerebral infarction or hemorrhage, active gastrointestinal bleeding or ulcer, uncontrollable diabetes mellitus, renal failure, active hepatitis, liver cirrhosis, or liver failure); the presence of a fever with suspected infection; paresis, peripheral neuropathy, or edema unrelated to biliary tract cancer; severe pleural or pericardial effusion; moderate or severe ascites; pregnancy or nursing infants, women of childbearing age; pulmonary fibrosis or interstitial pneumonia; severe mental disorders; a history of severe allergy or allergies to the drugs used in this study; treatment with another fluoropyrimidine cytotoxic agent; and treatment with flucytosine. All procedures were performed in accordance with the 1964 Declaration of Helsinki.

Study design

This dose-escalating, single-center phase I study was performed at Kitasato University East Hospital in Japan. The protocol was approved by the institutional review board of the hospital. Patient registration and data management were conducted at the Department of Gastroenterology, Kitasato University School of Medicine. All laboratory tests required to assess eligibility were completed within 14 d before starting the protocol treatment. The doses and treatment schedules of each level are summarized in Table 1; these recommendations were based on previous studies evaluating gemcitabine, cisplatin, and S-1 in advanced biliary tract cancer[3,4,13-15].

Dose-limiting toxicities (DLTs) were defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, as the following events: grade 4 leucopenia, neutropenia, or anemia; grade 3 neutropenia complicated by fever (> 38 °C) persisting for more than 2 d; grade 3 thrombocytopenia; any other grade 3-4 non-hematologic toxicity, with the exception of alopecia, anorexia, fatigue, nausea, and vomiting; a delay of more than 2 wk in starting the second cycle of chemotherapy; and a

delay of more than 2 wk in the administering the cytotoxic agents scheduled to be given on day 15. At least three patients were enrolled at each dose level. If DLT occurred in one patient during the first cycle, three additional patients were enrolled at the same dose level. If only one of the six patients had DLT, the dose was escalated to the next level. There was no dose escalation in individual patients. MTD was defined as the dose that caused DLT in two or more of the first six patients or in two initially treated patients. If the MTD was defined as level 0, which was used as the starting dose, the dose was de-escalated to level -1. RD was defined as one dose lower than the MTD, given the toxicity and tolerability of treatment in this study. If no patient had DLT at level 2, level 2 was defined as the RD.

Treatment

All patients received the first course of chemotherapy in an inpatient clinic to closely monitor toxicity. Chemotherapy was started on day 1 in eligible patients. Treatment was repeated on day 15 or subsequently, provided that all of the following criteria were met: white-cell count > 3000/mm3; neutrophil count > 1500/mm3; platelet count > 75000/mm3; no fever (> 38 °C) due to infection; hemoglobin > 9 mg/dL; AST/ALT < five times the ULN (patients without biliary drainage) or < three times the ULN (patients with biliary drainage); total bilirubin < 3 mg/dL (patients without biliary drainage) or < 2 mg/dL (patients with biliary drainage); creatinine clearance > 60 mL/min; no diarrhea/fatigue/mucositis or oral/peripheral neuropathy of grade 2 or higher; no non-hematologic toxicities of grade 3 or higher (except for abnormal blood test results not relevant to the study drugs). If the patient did not meet the above criteria, chemotherapy was postponed by several days to 3 wk until recovery. If chemotherapy was delayed by more than 3 wk, the protocol therapy was discontinued. S-1 was discontinued if the patient met any of the following criteria during the treatment course: white-cell count < 2000/mm3; neutrophil count < 1000/mm3; platelet count < 75000/mm3; fever (> 38 °C) due to infection; hemoglobin < 9 mg/dL; AST/ALT > five times the ULN (patients without biliary drainage) or >three times the ULN (patients with biliary drainage); total bilirubin > 3 mg/dL (patients without biliary drainage) or > 2 mg/dL (patients with biliary drainage); creatinine clearance < 60 mL/min; diarrhea/fatigue/oral mucositis of grade 2 or higher; or non-hematologic toxicities of grade 3 or higher (excluding abnormal blood test results not relevant to the study drugs). Because this was a dose-escalation study a reduction in dosage was not allowed. If dose reduction was required, the protocol therapy was discontinued.

Pretreatment and follow-up evaluations

Pretreatment evaluations included a complete medical history, physical examinations, blood tests, imaging studies by contrast-enhanced computed tomography, electrocardiography, and chest radiography. Creatinine clearance was evaluated using 24-h urine specimens (by the Cockcroft-Gault formula if impossible). During protocol treatment, physical examinations and blood tests were scheduled every week. Carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) were measured at the time of enrollment in the study and every month thereafter. Toxicity was evaluated according to the CTCAE, version 4.0. In patients with measurable target lesions, the objective RR was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and imaging tests were planned after the first cycle. Additional imaging tests were performed if clinically indicated or at the discretion of the treating physician.

RESULTS

Characteristics

Twelve patients were enrolled between June 2011 and January 2014 (Table 2). The median age was 69 years (range, 44-77 years), and no patient had recurrent disease. Seven patients had gallbladder cancer (58%), three (25%) had extrahepatic bile duct cancer, and two (17%) had intrahepatic bile duct cancer. Six patients (50%) required biliary drainage before starting treatment.

DLTs

DLTs are summarized according to dose level in Table 3. Level 0 was chosen as the starting dose. Three patients were assigned to level 0, and no patient had DLT. Therefore, the dose was escalated to level 1. At level 1, DLT occurred in one of the first three patients, and three additional patients were assigned to this level. In total, one of the six assessable patients had DLTs (grade 4 febrile neutropenia, leucopenia and neutropenia; grade 3 thrombocytopenia), and the dose was further escalated to level 2. At level 2, DLT did not occur in the first three assessable patients. Therefore, level 2 was designated as the RD.

Toxicity

Common hematologic and non-hematologic adverse events occurring during the first cycle of chemotherapy are summarized in Tables 4 and 5. Grade 3-4 neutropenia, leucopenia, thrombocytopenia, and anemia occurred in 2, 1, 1, and 0 patients (17%, 8%,

8%, and 0%), respectively. Febrile neutropenia occurred in one patient at level 1. Common non-hematologic adverse events were anorexia (5 cases, 42%), nausea (2 cases, 17%), vomiting (1 case, 8%), fatigue (2 cases, 17%), constipation (2 cases, 17%), and elevation of AST (5 cases, 42%) or ALT (4 cases, 33%). In addition, hyperbilirubinemia (4 cases, 33%) was common; however, this adverse event was attributed primarily to obstruction of the biliary tract caused by the primary disease. Among these adverse events, the incidences of grade 3-4 events were generally low (Table 5). On the basis of the incidences of DLTs and adverse events, we selected level 2 as the RD for a phase II study designed to evaluate the effectiveness of a combination of gemcitabine, cisplatin, and S-1.

Response

Although tumor response was not the primary endpoint of this study, imaging studies to evaluate tumor response were planned after the first cycle. Eleven of the 12 patients were assessable for response according to RECIST; four patients had a partial response (one at dose level 0, two at dose level 1, and one at dose level 2), four patients had stable disease (one at dose level 0, two at dose level 1, and one at dose level 2), and three patients had disease progression (one at each dose level), resulting in an overall RR of 33.3%.

DISCUSSION

This phase 1 dose-escalation study was designed to define the MTD and RD of combination chemotherapy with gemcitabine, cisplatin, and S-1 in patients with advanced biliary tract cancer. Dose level 2 (gemcitabine 1000 mg/m2, cisplatin 25 mg/m2, S-1 80 mg/m2 per day) was designated as RD; however, the MTD could not be estimated.

We expected that our triple-drug regimen for chemotherapy would enhance effectiveness as compared with previously studied singlet or doublet regimens, because previous clinical trials obtained low RRs and short MSTs. In a phase 2 study of gemcitabine alone, Okusaka et al[3] obtained an RR of 17.5% and an MST of 7.6 mo. The ABC-02 study was reported that MST of patients who received GC (11.7 mo) was significantly longer than that of patients who received gemcitabine alone (8.1 mo, $P < 0.001$)[4]. Two phase 2 clinical trials showed that S-1 monotherapy has clinically significant antitumor activity with mild toxicity[13,14]. Kanai et al[15] conducted a phase 2 study of gemcitabine plus S-1 (GS) in patients with advanced biliary tract cancer and reported this regimen provided a promising survival benefit with acceptable

toxicity.

The efficacy and tolerability of triplet chemotherapy regimens for other solid cancers were reported recently. Vermorken et al[16] conducted a clinical trial comparing a combination of docetaxel, cisplatin, and fluorouracil (DCF) with cisplatin plus fluorouracil in patients with head and neck cancer. DCF significantly improved median progression-free survival as compared with cisplatin plus fluorouracil (DCF, 11.0 mo vs cisplatin plus fluorouracil, 8.2 mo, P = 0.007) and had tolerable toxicities. Furthermore, Conroy et al[17] compared FOLFILINOX (a combination of fluorouracil, oxaliplatin, and irinotecan) with gemcitabine alone. Although triplet therapy was significantly more effective (MST: FOLFILINOX 11.1 mo vs gemcitabine 6.8 mo, P < 0.001), FOLFILINOX had increased toxicity[17]. Koizumi et al[18] conducted a phase 2 study of combination therapy with docetaxel, cisplatin and S-1 in advanced gastric cancer and reported that this regimen was highly active and well tolerated. These triplet regimens with high RRs have been suggested to be useful for neoadjuvant chemotherapy[19,20]. The findings of these previous studies support our concept of combination therapy with gemcitabine, cisplatin, and S-1.

However, multiple-drug regimens for chemotherapy probably increase the risk of severe adverse events. We based the treatment schedule of our regimen on the results of previous pivotal clinical trials. First, in the ABC-02 trial, the GC group received gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on days 1 and 8 every 3 wk. Adverse events of grade 3 or higher were neutropenia (25.3%), thrombocytopenia (8.6%), and anemia (7.6%). Second, as for GS, we referred to the results of a study of GS performed by Ookawa et al[21] in patients with pancreatic cancer, because fewer studies of GS have been reported for biliary tract cancer than for pancreatic cancer. In that study, gemcitabine 1000 mg/m2 was given on day 1, and S-1 80 or 100 mg/m2 was given orally on days 1 to 7, every 2 wk. Adverse events or grade 3 or higher were only leucopenia (25%) and neutropenia (20%); moreover, there were no grade 4 events. On the basis of these findings, we decided to administer gemcitabine and cisplatin on days 1 and 15 and S-1 on days 1 to 8 and 15 to 21 every 4 wk because the triple-drug combination of gemcitabine, cisplatin, and S-1 was based on the GC and GS regimens and was expected to have a higher risk of adverse events.

CONCLUSION

Our results showed that combination therapy with gemcitabine, cisplatin, and S-1 was well tolerated and feasible in patients with advanced biliary tract cancer. We are now proceeding to a phase II study to investigate the efficacy of this combination regimen in

advanced biliary tract cancer.

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Table 1 Doses and treatment schedules for each level.

	Gemcitabine	Cisplatin	S-1 (mg/d, Days 1-7, 15-21)		
	(mg/m^2, Days 1, 15)		BSA < 1.25	1.25 < BSA < 1.5	BSA > 1.5
Level -1	800	20	60	80	100
Level 0	800	25	60	80	100
Level 1	1000	25	60	80	100
Level 2	1000	25	80	100	120

BSA: Body surface area.

Table 2 Patient characteristics.

Characteristic	*n* (%)
Sex	
Male	10 (83)
Female	2 (17)
Median age	69 (range 44-77)
Primary lesion	
Intrahepatic	2 (17)
Extrahepatic	3 (25)
Gallbladder	7 (58)
Ampulla of vater	0 (0)
Disease status	
Unresectable	12 (100)
Recurrent	0 (0)
Performance status (0/1)	12/0
Biliary drainage	6 (50)
Median CEA (ng/mL)	3 (range 1.1-33.4)
Median CA19-9 (U/mL)	156.5 (range 1.0- > 10000)

CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen.

Table 3 Dose-limiting toxicities at each level.

Level	Age	Sex	Primary lesion	Biliary drainage	DLT	Response (RECIST)
0	71	M	Extrahepatic	Yes	None	PR
0	73	M	Extrahepatic	Yes	None	SD
0	63	F	Gallbladder	No	None	PD
1	77	M	Intrahepatic	Yes	Gr 4 febrile neutropenia and leucopenia, Gr 3 thrombocytopenia	PD
1	67	M	Gallbladder	Yes	None	NE
1	64	M	Gallbladder	No	None	SD
1	70	M	Extrahepatic	Yes	None	SD
1	72	M	Gallbladder	No	None	PR
1	74	M	Gallbladder	No	None	PR
2	58	M	Intrahepatic	No	None	PR
2	68	F	Gallbladder	No	None	SD
2	44	M	Gallbladder	Yes	None	PD

DLT: Dose-limiting toxicities; Gr: Grade; NE: Not evaluable; PD: Progressive disease; PR: Partial response; SD: Stable disease.

Table 4 Hematologic adverse events during the first cycle.

	Level 0	(n = 3)	Level 1	(n = 6)	Level 2	(n = 3)
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4
Neutropenia	0	0	0	1	0	1
Leucopenia	1	0	2	1	1	0
Thrombocytopenia	2	0	1	1	0	0
Anemia	2	0	1	0	0	0
Febrile neutropenia	NA	0	NA	1	NA	0

NA: Not applicable.

Table 5 Non-hematologic adverse events during the first cycle.

	Level 0	(n = 3)	Level 1	(n = 6)	Level 2	(n = 3)
	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4	Gr 1-2	Gr 3-4
Anorexia	2	0	1	0	2	0
Nausea	1	0	1	0	0	0
Vomiting	1	0	0	0	0	0
Fatigue	0	0	0	0	2	0
Constipation	1	0	1	0	0	0
Fever	1	0	2	0	0	0
Biliary tract infection	NA	3	NA	0	NA	1
Infections (others)	0	0	0	2	0	0
AST	3	0	2	0	0	0
ALT	2	0	2	0	0	0
Hyperbilirubinemia	2	0	1	0	1	0
Creatinine	0	0	3	0	0	0

NA: Not applicable; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.