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H. 知的財産権の出願・登録状況（予定を含む。）

1. 特許取得
   なし。

2. 実用新案登録
   なし。

3. その他
   特記すべきことなし。

Ⅱ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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和田 慶太、佐野 圭二、他	重粒子照射後局所再発に対してサルベージ手術を施行した局所進行膵癌の 1 例	膵臓	27	498	2012
清水京子 白鳥敬子	家族歴, 既往歴を中心とした膵癌の危険因子の検討	消化器内科	56	70-73	2012

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The Hepatobiliary and Pancreatic Oncology (HBPO) Group of the Japan Clinical Oncology Group (JCOG): History and Future Direction

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The Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology Group (JCOG) was constituted in April 2008 to develop new standard treatments for hepatobiliary and pancreatic cancer. In pancreatic cancer, the Hepatobiliary and Pancreatic Oncology Group focuses on establishing standard chemotherapy or chemoradiotherapy for unresectable locally advanced disease. The JCOG 0506 study was a Phase II study of gemcitabine alone to examine its efficacy and safety in patients with locally advanced disease. The results in survival significantly exceeded expectations, and gemcitabine monotherapy has come to be regarded as the provisional standard therapy by our group. Following JCOG 0506, the JCOG 1106 study, which is currently under investigation, is a randomized Phase II study to evaluate the efficacy of induction chemotherapy with gemcitabine in combination with S-1 chemoradiotherapy and select a candidate therapeutic agent in a Phase III study comparing with gemcitabine alone. The JCOG 0805 study was a randomized Phase II study comparing S-1 monotherapy with gemcitabine plus S-1 combination therapy for unresectable biliary tract cancer. As a result, gemcitabine plus S-1 combination therapy was considered the more promising candidate in comparison with the gemcitabine plus cisplatin combination therapy in a subsequent Phase III trial. The Hepatobiliary and Pancreatic Oncology Group is planning a Phase III study to compare gemcitabine plus S-1 combination therapy with gemcitabine plus cisplatin combination therapy (JCOG PC1113 study). No standard postoperative adjuvant treatment has been established. We plan to conduct a Phase III study to compare S-1 as adjuvant therapy after surgery with surgery alone in patients with biliary tract cancer (JCOG PC1202).

Key words: GI-Hepatobiliary-Med – GI-Pancreas-Med – clinical trials

INTRODUCTION

Hepatobiliary and pancreatic cancers have a high incidence and are associated with high mortality rates, not only in Japan, but also around the world. Despite the poor prognosis, no standard chemotherapeutic regimens were established for these cancers for a long time.

In Japan, based on the results of single-arm Phase I and II studies (1–4), gemcitabine was approved for the treatment of pancreatic cancer in 2001, and for the treatment of biliary tract cancer in 2006. S-1, a mixture of tegafur, gimeracil and oteracil potassium, was also approved for the treatment of pancreatic cancer in 2006, and for the treatment of biliary

tract cancer in 2007. Furthermore, in a Phase III study conducted mainly in Europe, sorafenib showed survival benefit in patients with unresectable hepatocellular carcinoma (HCC) (5), and in 2009, this drug was approved for the treatment of HCC in Japan. Thus, some agents have shown beneficial effects and have come to be established as standard or available treatments for these cancers. Nonetheless, treatment remains unsatisfactory, and in order to improve the survival in patients with these cancers, not only more effective treatments for unresectable disease, but also more effective postoperative adjuvant therapy regimens for patients who undergo surgical resection need to be developed.

The Hepatobiliary and Pancreatic Oncology Group (HBPO group) of the Japan Clinical Oncology Group (JCOG) was constituted in April 2008 to develop new standard treatments for hepatobiliary and pancreatic cancer. The HBPO group started with a membership of 16 institutes initially, and at present, 26 institutes are registered as active members. Furthermore, >30 institutes participate in regular meetings of the JCOG.

HEPATOCELLULAR CARCINOMA

Various treatment modalities, including resection, local ablation, transcatheter arterial chemoembolization and liver transplantation have been employed as local therapeutic strategies for the treatment of HCC. Intra-arterial infusion chemotherapy and systemic chemotherapy have also been used for the treatment of advanced HCC. Thus, the treatments for HCC are diverse, and appropriate strategies are selected for each patient according to the tumor stage and the grade of liver dysfunction. Although hepatic arterial infusion chemotherapy, which is applied for patients with advanced-stage HCC such as those with portal vein tumor thrombosis and/or huge tumors, has provided high response rates, the survival benefit of this treatment modality in HCC patients has never been confirmed. No standard systemic chemotherapy had ever been established until sorafenib was approved.

Sorafenib is a small-molecule multi-kinase inhibitor that inhibits several kinases such as Raf kinase, vascular endothelial growth factor receptor and platelet-derived growth factor receptor-β tyrosine kinases. A large randomized controlled trial of sorafenib versus placebo (the SHARP trial) in patients with advanced HCC and good liver function (Child-Pugh class A) demonstrated that sorafenib prolonged the survival in patients with advanced HCC (5). As a result, sorafenib has been applied as standard chemotherapy for the treatment of advanced HCC in many countries, including Japan.

New compounds have been investigated for HCC in clinical trials, including Phase III trials, conducted by pharmaceutical companies in various study settings, such as first-line therapy in comparison with sorafenib, second-line therapy (placebo-controlled trial) and in combination with local treatments. To date, however, no compound has yielded satisfactory results. Although sorafenib is the only antitumor drug that has shown survival benefit, the direct antitumor effect of the drug is not remarkable; the response rate has been reported to be only around 2–4%. Thus, there remains much room for improvement of the treatment efficacy and we think it is necessary to develop more effective treatment regimens containing sorafenib. The HBPO group is considering clinical trials using sorafenib to develop more effective treatments, e.g. combination of hepatic arterial infusion chemotherapy with sorafenib.

BILIARY TRACT CANCER

Bile duct cancer is subdivided according to the anatomic location of origin into intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer or ampulla of Vater cancer. Each of these types of cancer has characteristic features and the treatment strategies and prognoses differ. Furthermore, most patients present with obstructive jaundice at diagnosis, and biliary drainage is generally needed before any of the aforementioned treatments. These characteristics of biliary tract cancer have made it difficult to evaluate the efficacy of chemotherapy for biliary tract cancer, resulting in a paucity of high-quality clinical trials.

In Japan, gemcitabine and S-1 were approved for the treatment of biliary tract cancer in 2006 and 2007, respectively, based on the results of single-arm Phase II studies of the two drugs. Recently, a randomized Phase III study (ABC-02) comparing gemcitabine alone with gemcitabine plus cisplatin (GC) was conducted in the UK (6), which demonstrated a statistically significant improvement in the overall survival in the GC group when compared with that in the gemcitabine-alone group. The BT22 study was conducted to confirm the efficacy and safety of GC therapy as a company-initiated trial in Japan, and similar results to those of the ABC-02 study were demonstrated in Japanese patients with biliary tract cancer (7). Thus, GC therapy has come to be recognized as the standard chemotherapy for unresectable biliary tract cancer. Based on these results, treatment with cisplatin in combination with gemcitabine was approved for the treatment of biliary tract cancer in Japan in February 2012.

On the other hand, S-1 or gemcitabine plus S-1 (GS therapy) was demonstrated to provide high response rates and good survival rates in Phase II studies (4,8), and S-1 or GS therapy was expected to yield a superior benefit to GC therapy. Therefore, the HBPO group conducted a randomized Phase II study comparing S-1 monotherapy with GS therapy (JCOG 0805 study) to examine the efficacy and safety of the two regimens and to select the more promising one for a subsequent Phase III trial of treatment for unresectable biliary tract cancer in (Fig. 1) (9,10). The main eligibility criteria of the JCOG 0805 study were the following: (i) clinically diagnosed with biliary tract cancer, which includes intrahepatic cholangiocarcinoma, extrahepatic

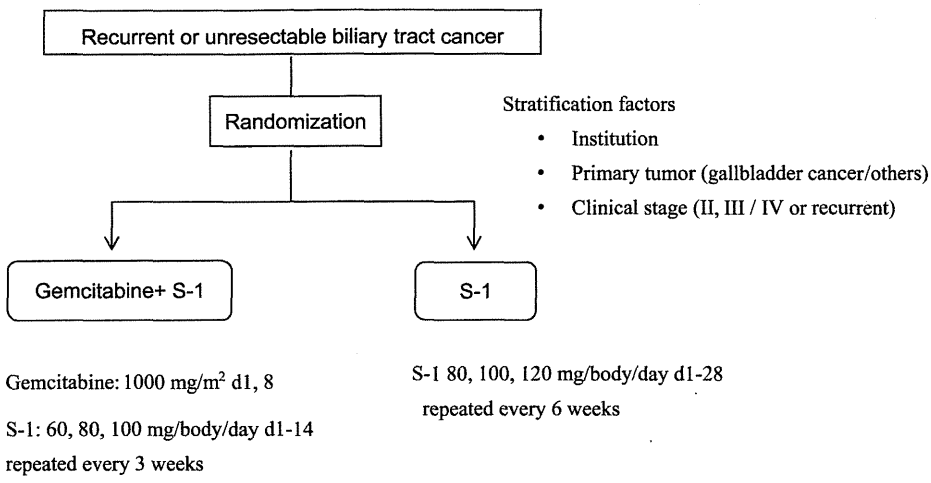


Figure 1. Study design of the JCOG 0805 study.

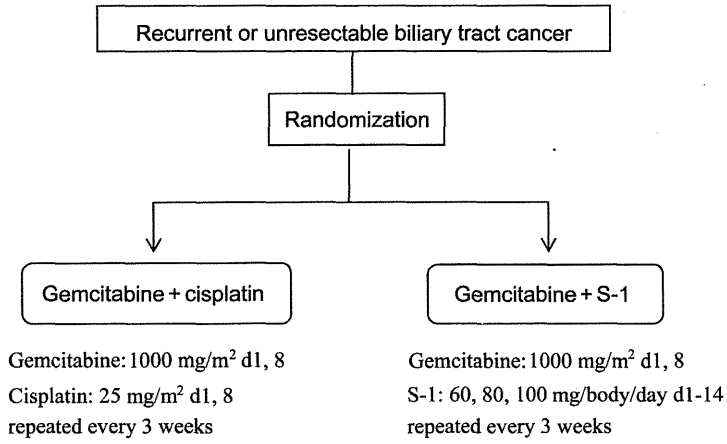


Figure 2. Study design of the JCOG PC1113 study.

cholangiocarcinoma, gallbladder cancer and ampulla of Vater cancer and histologically proven adenocarcinoma or adenosquamous carcinoma; (ii) recurrent or unresectable biliary tract cancer; (iii) no previous therapy against biliary tract cancer except surgery; (iv) no previous chemotherapy or radiotherapy for any other malignancies; (v) ECOG performance status of 0 or 1 and (vi) adequate organ function. The regimen that shows the higher point estimate in terms of the proportion of 1-year survival will be considered to be more promising. We assumed that the 1-year survival rate of one regimen is 30% and that of the other regimen is >40%. In this situation, the sample size ensuring at least 85% probability of correct selection of the more effective regimen is 98 patients, with 49 patients in each of the two arms. Considering the likelihood of some ineligible patients being enrolled, the total number of patients was set at 100 (9).

In the JCOG 0805 study, 101 patients were enrolled between February 2009 and April 2010, with 51 allocated to the GS arm and 50 to the S-1 arm. The 1-year survival rates were 52.9 and 40.0%, the median overall survival rates were 12.5 and 9.0 months [hazard ratio 0.86; 95% confidence interval (CI): 0.54–1.36; $P = 0.52$)] and the median progression-free survival rates were 7.1 and 4.2 months (hazard ratio 0.44; 95% CI: 0.29–0.67; $P < 0.0001$), respectively, in the GS arm and S-1 arm. The most common toxicities were hematological toxicities, fatigue and rash. Grade 3 or 4 toxicities were generally more frequent in the GS arm than that in the S-1 arm, although both treatments were quite well tolerated. As a result, GS therapy was considered as the more promising candidate in comparison with the GC regimen in a subsequent Phase III trial (10). The HBOP is planning a Phase III study to compare GS therapy with GC therapy (JCOG PC1113 study), with the aim of determining whether GS therapy could be established as a new standard therapy for unresectable biliary tract cancer (Fig. 2).

Although surgery currently remains the only potentially curative treatment, most patients develop recurrence. An effective adjuvant therapy is required after surgery to increase the curability of the surgery and to prolong the survival in patients with biliary tract cancer who undergo surgery. To

date, since no large randomized controlled trials of adjuvant therapy have been conducted, no standard postoperative adjuvant treatment has been established. We consider S-1 as a potential candidate for adjuvant therapy, because a high response rate of 35% was demonstrated to S-1 in a Phase II study for unresectable biliary tract cancer (4). S-1 has also been already established as a standard adjuvant therapeutic agent for the treatment of gastric cancer. Surgical methods for the treatment of biliary tract cancer are highly diverse, including pancreaticoduodenectomy, hepatectomy, etc., when compared with those for gastric cancer. Therefore, a feasibility study of S-1 chemotherapy after surgery was conducted by a study group comprising some member institutes of the HBPO group. A treatment completion rate of 82% was achieved. The most common grade-3 toxicity was neutropenia (18%), and the rates of other grade 3 adverse events were under 5% (11). Therefore, S-1 is considered to be suitable as a postoperative adjuvant therapeutic agent for the treatment of patients with resected biliary tract cancer. Based on these results, we plan to conduct a Phase III study to compare S-1 as adjuvant therapy after surgery with surgery alone in patients with biliary tract cancer (JCOG PC1202).

PANCREATIC CANCER

Pancreatic carcinoma is a disease with one of the worst prognoses; the 5-year survival rate of patients diagnosed as having pancreatic cancer remains at 5–10%. Since it is difficult to diagnose pancreatic cancer at an early stage, 70–80% patients with pancreatic cancer have unresectable disease, including locally advanced or distant metastatic disease, at diagnosis. Since gemcitabine demonstrated a better survival benefit when compared with 5-fluorouracil (5-FU) in a Phase III study (12), it has been widely used as the standard chemotherapy for unresectable pancreatic cancer for >10 years. Despite a number of new compounds, including molecular-targeted agents, having been examined in combination with gemcitabine, no regimen, except for gemcitabine plus erlotinib, has been demonstrated to provide statistically significant improvement in the overall survival over gemcitabine alone (13,14). Thus, the prognosis of these patients with this cancer remains poor, and the development of more effective treatments for pancreatic cancer is urgently needed.

Under these situations, it is important to continue the development of new compounds in industry-initiated clinical trials and also participate in global registration trials. On the other hand, the HBPO group also considers itself as having the important role of establishing standard chemotherapy or chemoradiotherapy for unresectable locally advanced disease or postoperative adjuvant therapy.

With regard to treatments for unresectable locally advanced disease, we first conducted a Phase II study of gemcitabine alone to examine its efficacy and safety in patients with locally advanced disease of the JCOG 0506 study (15). This study was conducted to be foreseeing a Phase III trial comparing gemcitabine monotherapy with conventional chemoradiotherapy using 5-FU, which, at that time, was used as a standard therapy for locally advanced disease. The main eligibility criteria of the JCOG 0506 study were the following: (i) patients with histologically or cytologically proven pancreatic adenocarcinoma or adenosquamous carcinoma; (ii) International Union Against Cancer clinical stage III (T4N0-1 and M0); (iii) no previous chemotherapy or radiotherapy for any other malignancies; (iv) ECOG performance status of 0, 1 or 2 and (v) adequate organ function. The primary endpoint of this study was the 1-year survival rate. A sample size of 50 was required for a one-sided α of 0.20 and β of 0.10, with an expected 1-year survival rate of 40% and a threshold 1-year survival rate of 25%. Fifty patients were enrolled from January 2006 to February 2007 in this study. The results revealed a median overall survival of 15.0 months with a 1-year survival rate of 64.0% (Table 1), which significantly exceeded expectations. The toxicities were generally mild and the drug was well tolerated. Furthermore, a randomized controlled trial of gemcitabine vs. conventional chemoradiotherapy using 5-FU and cisplatin failed to show any survival benefit of chemoradiotherapy (16). Based on these results, gemcitabine monotherapy has come to be regarded as the provisional standard therapy by our group (Table 2).

Table 1. Recent randomized controlled trials using gemcitabine, cisplatin and/or S-1 for unresectable biliary tract cancer

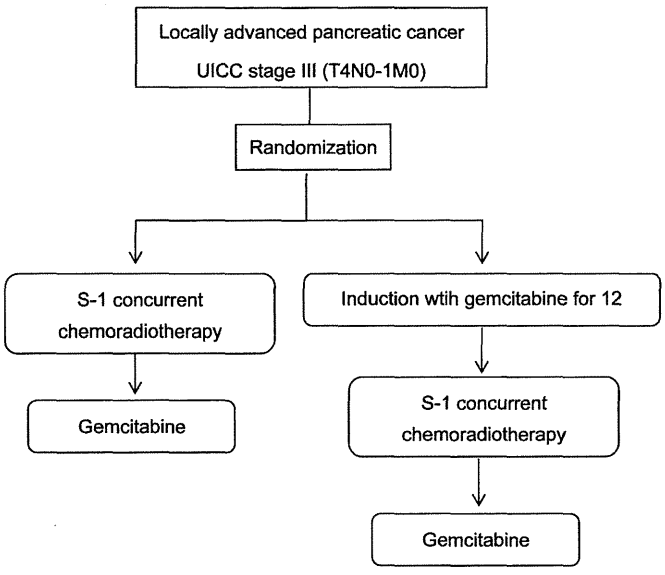
Study	Chemotherapy	*n*	Response rate (%)	Median PFS (months)	Median OS (months)	Study
ABC-02 study	Gemcitabine	206	15.5	5.0	8.1	Valle *et al.* (6)
	Gemcitabine + cisplatin	204	26.1	8.0	11.7	
BT-22 study	Gemcitabine	42	11.9	3.7	7.7	Okusaka *et al.* (7)
	Gemcitabine + cisplatin	41	19.5	5.8	11.2	
JCOG 0805 study	S-1	50	17.4	4.2	9.0	Ueno *et al.* (8)
	Gemcitabine + S-1	51	36.4	7.1	12.5	

PFS, progression-free survival; OS, overall survival.

Table 2. Recent clinical trials of chemotherapy or chemoradiotherapy for locally advanced pancreatic cancer

Study	Radiotherapy (Gy)	Chemotherapy	*n*	Median OS (month)	%1-year survival	Study
JCOG 0506 study	–	Gemcitabine	50	15.0	64	Ishii *et al.* (15)
S-1 radiation Phase II study	50.4	S-1	61	16.2	72	Ikeda *et al.* (18)
2000-01 FFCD/SFRO study	60	5-fluorouracil + cisplatin	59	8.6	32	Chauffert *et al.* (16)
	–	Gemcitabine	60	13.0	53	
ECOG 4201 study	50.4	Gemcitabine	34	11.1	50	Loehrer *et al.* (17)
	–	Gemcitabine	37	9.2	32	

%1-year survival, one-year survival rate.



Gemcitabine: 1000 mg/m^2 d1, 8, 15, repeated every 4 weeks
S-1: 80 mg/m^2/day on the day of irradiation

Figure 3. Study design of the JCOG 1106 study.

A clinical trial conducted in the USA comparing gemcitabine plus radiotherapy vs. gemcitabine alone reported that the overall survival rate was superior in the combined treatment group when compared with that in the gemcitabine-alone group in patients with locally advanced pancreatic cancer (17). Furthermore, chemoradiotherapy using S-1 demonstrated promising efficacy in a Phase II study, which was conducted as an in-house trial of some member institutes of the HBPO group; the median overall survival was 16.2 months (18). There is a possibility that new methods of chemoradiotherapy might improve the survival, especially prolonged survival of >2 years. Thus, in order to develop more promising new chemoradiotherapies, we conducted a randomized Phase II study of two chemoradiotherapeutic methods, one consisting of S-1 chemoradiotherapy and maintenance therapy with gemcitabine, and the other consisting of induction gemcitabine chemotherapy for 3 months followed by S-1 chemoradiotherapy and maintenance therapy with gemcitabine (JCOG 1106 study).

The JCOG 1106 study is a multi-institutional open-label randomized Phase II study to evaluate the efficacy of induction chemotherapy of gemcitabine in combination with S-1 chemoradiotherapy and select a candidate in a Phase III study comparing with gemcitabine alone (Fig. 3). The main eligibility criteria of the JCOG 1106 study were as follows: (i) clinically diagnosed with pancreatic cancer without distant metastasis, and histologically proven adenocarcinoma; (ii) no previous chemotherapy or radiotherapy for any other malignancies; (iii) ECOG performance status of 0 or 1 and (iv) adequate organ function. The primary endpoint is the overall survival, and we shall select the treatment method providing the better survival benefit between the two for use in a subsequent Phase III study. The 1-year survival rate of the two treatments would be expected to be >60% at least, because that of patients administered gemcitabine monotherapy was 64% in the JCOG 0506 study. The sample size is 100 patients and this study is under investigation in September 2012.

FUTURE DIRECTION

In hepatobiliary tract and pancreatic cancers, major advances have been made in relation to the establishment of standard treatments in recent years. However, the survival of patients with these cancers still remains dismal. The HBPO group considers it essential to actively conduct clinical trials to establish more effective standard treatments, including a combination of chemotherapy with local treatments including surgery or radiotherapy.

In HCC, many clinical trials using new agents are conducted as an Asian study including Japan or a global study. However, it is difficult to conduct investigator-initiated trials in HCC, because there are various differences in the etiology and treatment strategy among Asian countries, Japan and Western countries. However, it is also important for the HBPO group to discuss Asian studies on HCC and biliary tract cancer in the future, because these diseases are very common in Asia, compared with Western countries.

Establishment of standard therapies for relatively rare tumors is urgently needed. We are planning to conduct a

phase III study for the treatment of gastrointestinal neuroendocrine tumors in cooperation with other groups of the JCOG.

Although our HBPO group is growing in size, only 26 institutes are active members of the group. On the other hand, >30 institutes participate in our regular meetings as observers. It is therefore also important to increase the number of institutes as active members so as to make it possible to conduct larger clinical trials of higher quality in the future.

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Conflict of interest statement

None declared.

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Clinical Investigation: Pancreatic Cancer

A Multicenter Phase II Trial of S-1 With Concurrent Radiation Therapy for Locally Advanced Pancreatic Cancer

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Summary

S-1 is the first single anti-cancer agent to be judged non-inferior to gemcitabine in a large-scale, randomized, phase III trial for advanced pancreatic cancer, and it can also act as a radiosensitizer. S-1 with concurrent radiation therapy showed very favorable activity, with mild toxicity in patients with

Purpose: The aim of this trial was to evaluate the efficacy and toxicity of S-1 and concurrent radiation therapy for locally advanced pancreatic cancer (PC).

Methods and Materials: Locally advanced PC patients with histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma, who had no previous therapy were enrolled. Radiation therapy was delivered through 3 or more fields at a total dose of 50.4 Gy in 28 fractions over 5.5 weeks. S-1 was administered orally at a dose of 80 mg/m^2 twice daily on the day of irradiation during radiation therapy. After a 2- to 8-week break, patients received a maintenance dose of S-1 (80 mg/m^2/day for 28 consecutive days, followed by a 14-day rest period) was then administered until the appearance of disease progression or unacceptable toxicity. The primary efficacy endpoint was survival, and the secondary efficacy endpoints were progression-free survival, response rate, and serum carbohydrate antigen 19-9 (CA19-9) response; the safety endpoint was toxicity.

Results: Of the 60 evaluable patients, 16 patients achieved a partial response (27%; 95% confidence interval [CI], 16%-40%). The median progression-free survival period, overall survival period, and 1-year survival rate of the evaluable patients were 9.7 months (95% CI, 6.9-11.6 months),

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Conflict of interest: none.

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locally advanced pancreatic cancer.

16.2 months (95% CI, 13.5-21.3 months), and 72% (95%CI, 59%-82%), respectively. Of the 42 patients with a pretreatment serum CA19-9 level of ≥100 U/ml, 34 (81%) patients showed a decrease of greater than 50%. Leukopenia (6 patients, 10%) and anorexia (4 patients, 7%) were the major grade 3-4 toxicities with chemoradiation therapy.

Conclusions: The effect of S-1 with concurrent radiation therapy in patients with locally advanced PC was found to be very favorable, with only mild toxicity. © 2013 Elsevier Inc.

Introduction

Pancreatic cancer (PC), one of the most lethal human cancers, has become the fifth most common cause of death due to cancer in Japan; it has been estimated that PC was responsible for 26,791 deaths in 2009, representing approximately 3% of all deaths. PC patients have a dismal prognosis, as their 5-year survival after diagnosis is less than 5%. Of all treatment modalities available for PC, only resection offers an opportunity for a cure. However, approximately half of patients already have metastases at the time of diagnosis, and approximately one-third of patients are diagnosed as having locally advanced disease, whereas only a small proportion of patients are eligible for surgery, as a result of the lack of effective screening. Concurrent chemoradiation therapy with external beam radiation therapy and chemotherapy using 5-fluorouracil (5-FU) is often used in patients who have unresectable PC due to vascular involvement that includes the celiac artery or supra-mesenteric artery, with no distant metastases on radiological examination, because it is generally accepted as a standard therapy for locally advanced PC (1-4). A variety of anticancer agents, including gemcitabine (5) and capecitabine (6), and various radiation schedules (7-8) have been examined in clinical trials, but survival has not been significantly improved.

S-1 is a new oral fluoropyrimidine derivative in which tegafur is combined with 2 5-chloro-2,4-dihydroxypyridine modulators and oteracil potassium, a potentiator of 5-FU's antitumor activity that also decreases gastrointestinal toxicity. A multi-institutional, late-phase II trial of S-1 involving metastatic PC patients reported a good tumor response rate (38%) and improved survival (median, 9.2 months) (9). A phase III trial compared therapy with S-1, with gemcitabine alone, and with gemcitabine plus S-1 in patients with unresectable PC in Japan and Taiwan, and S-1 therapy was found to provide efficacy and toxicity similar to gemcitabine when it was used as a first-line treatment for advanced PC (median survival: S-1, 9.7 months; gemcitabine, 8.8 months [hazard ratio, 0.96; non-inferiority P value <.001]); thus, S-1 was judged to be non-inferior to gemcitabine (10). S-1 also acts as a radiosensitizer, and preclinical and clinical studies have demonstrated the radiosensitizing potency of S-1 (11). Not only is S-1 a potent radiosensitizer that has been shown to have promising antitumor activity against advanced PC, but also, since it is active orally, it is also much more convenient for patients than intravenous 5-FU infusion. Thus, concurrent raditation therapy and oral S-1 instead of 5-FU infusion may be a more efficient treatment that also improves patients' quality of life. In a phase I trial conducted in one of our hospitals, the recommended S-1 dose with concurrent radiation therapy was found to be 80 mg/m^2/day on the day of irradiation; at this dose, S-1 was found to have excellent antitumor activity with mild toxicity (12). Consequently, a multi-institutional phase II study was conducted to clarify the efficacy and safety of concomitant radiation therapy with S-1 in patients with locally advanced PC.

Methods and Materials

Patients and eligibility

Patients eligible for study entry had locally advanced nonresectable clinical stage III (T4N0-1 and M0) PC, according to International Union Against Cancer criteria. Eligibility criteria were adenocarcinoma or adenosquamous carcinoma confirmed on cytology or histology; no previous chemotherapy for PC; a square (10 cm × 10 cm) radiation field could encompass all pancreatic lesions and lymph node metastases; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate oral intake; satisfactory hematological functions (hemoglobin concentration, ≥9.0 g/dl; leukocyte count, ≥3500/mm^3; platelet count, ≥100,000/mm^3); adequate hepatic function (serum total bilirubin ≤2.0 times the upper normal limit [UNL] or ≤3.0 mg/dl with biliary drainage); aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤2.5 times UNL or ≤5 times UNL with biliary drainage; serum albumin ≥3.0 g/dl; and normal renal function (serum creatinine ≤UNL). Written informed consent was obtained from all patients.

Exclusion criteria were active infection; active gastroduodenal ulcer; watery diarrhea; phenytoin, warfarin potassium, or flucytosine treatment; pleural effusion or ascites; severe complications such as cardiac or renal disease; psychiatric disorder; history of drug hypersensitivity; and active concomitant malignancy. In addition, pregnant and lactating women and women of childbearing age who were not using effective contraception were also excluded.

Pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast medium-enhanced computed tomography (CT) or magnetic resonance imaging of the abdomen and X-ray or CT of the chest was performed for pretreatment staging to assess the local extension of the tumor and to exclude the presence of distant metastases. The criteria for local extension surrounding the pancreas included tumor invasion to the celiac trunk or superior mesenteric artery, or both, which corresponded to clinical stage III according to the International Union Against Cancer (6th edition). All patients with obstructive jaundice underwent percutaneous transhepatic or endoscopic retrograde biliary drainage before treatment. Laparoscopy and laparotomy to rule out occult peritoneal dissemination prior to study entry were not necessary.

Treatment schedule

The regimen consisted of S-1 with concurrent radiation therapy and maintenance S-1 chemotherapy.

S-1 with concurrent radiation therapy

Radiation therapy was delivered with >6-MV photons, using a multiple (three or more) field technique. A total dose of 50.4 Gy