leukopenia, neutropenia, or thrombocytopenia; a creatinine level of 1.5 mg/dL or higher; or grade 3 or worse diarrhea, stomatitis, or rash, the dose of S-1 was reduced by 20 mg/d.

Sample Size Determination: Statistical Methods

In the initial plan, the total target number of patients was set at 600, given a statistical power of 80%, an enrollment period of 3 years, and a follow-up period of 2 years. However, because patient enrollment was faster than expected, the target number of patients was revised to 750 to provide the study with a statistical power of 90%. Consequently, the final analysis was performed after the occurrence of 680 events had been confirmed. An interim analysis was not performed. Although the actual median OS in the gemcitabine group was better than initially expected, because an adequate number of patients had been enrolled, a power of $\geq$ 90% was maintained on recalculation of the power on the basis of the actual results.

Quality of Life

To assess the quality of life, the health status of patients on the EQ-5D questionnaire was converted into a single simple utility index ranging from 0 for death to 1 for complete health. Quality-adjusted life-years (QALYs) for individual patients were estimated as the product of the utility index during follow-up and survival time and were compared between the groups, using the generalized Wilcoxon test.

As a result, median QALYs were 0.401 in the gemcitabine group, 0.420 in the S-1 group, and 0.525 in the GS group. The QALY value in the S-1 group was similar to that in the gemcitabine group, and there was no statistically significant difference between the two groups ($P = .56$). The QALY value in the GS group was significantly better than that in the gemcitabine group ($P < .001$). The details of quality-of-life assessments will be reported elsewhere.

International Journal of
Radiation Oncology
biology • physics

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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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Received Feb 8, 2012, and in revised form Mar 24, 2012. Accepted for publication Mar 27, 2012

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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This work was presented in abstract form on June 4-6, 2010. at the 46th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL.

This study was supported in part by grants-in-aid for cancer research from the Ministry of Health, Labor, and Welfare of Japan.

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 85, No. 1, pp. 163–169, 2013
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2012.03.059

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

was delivered in 28 fractions over 5.5 weeks. Primary tumor and metastatic lymph nodes >1 cm identified on CT were contoured as gross tumor volumes (GTV). The clinical target volume (CTV) included the primary tumor with a 0.5-cm margin and metastatic lymph nodes. Regional lymph nodes were not treated electively. The definition of planning target volume (PTV) include the CTV with a 1-cm margin laterally and a 1- to 2-cm margin in the craniocaudal direction to take into account respiratory organ motion and daily set-up errors. The reference point for the radiation dose was set at the center of the PTV. The spinal cord dose was maintained at <45 Gy. The volume of liver to receive 30 Gy was required to be <40%, and the volume to receive 20 Gy was required to be <67%. At least 75% of both kidneys was required to receive less than 18 Gy.

S-1 was administered orally at a dose of 40 mg/m^2 twice daily after breakfast and dinner on the day of irradiation (Monday through Friday) during radiation therapy. The 3 initial doses were determined according to the body surface area (BSA) as follows: patients with a BSA of <1.25 m^2 received 40 mg/dose; those with BSA of 1.25 m^2-<1.5 m^2 received 50 mg/dose; and those with BSA of ≥1.5 m^2 received 60 mg/dose. The dose of S-1, which is the standard dose when S-1 is used as a single agent for systemic therapy (15, 16), had been previously determined in our phase I trial (19).

The occurrence of grade 4 hematological toxicity, grade 3 non hematological toxicity excluding nausea, anorexia, fatigue, constipation, and hyperglycemia, or a serum AST or ALT >200 IU/l resulted in the suspension of radiation therapy and S-1 administration. When the toxicities improved by at least 1 grade compared to the suspension criteria, treatment was resumed. When suspension criteria were met, dose modification was allowed as follows: patients with a BSA of <1.25 m^2 received 25 mg/dose; those with a BSA of 1.25 m^2-<1.5 m^2 received 40 mg/dose; and those with a BSA ≥1.5 m^2 received a 50 mg/dose. Chemoradiation therapy was discontinued when the patient developed grade 4 non-hematological toxicities or other unacceptable toxicities, including gastrointestinal ulcer or bleeding, interruptions in treatment of >15 days, or unequivocal tumor progression. After treatment discontinuation, patients could receive other anticancer treatments excluding S-1 with concurrent radiation therapy at their physician's discretion.

Maintenance S-1 chemotherapy

From 2-8 weeks after completion of S-1 with concurrent radiation therapy, maintenance S-1 chemotherapy was initiated at a dose of 40 mg/m^2 twice daily orally, after breakfast and dinner, for 28 consecutive days, followed by a 14-day rest period per course. Treatment cycles were repeated until the appearance of disease progression, unacceptable toxicities, or the patient's refusal to continue treatment. If a grade 3 or higher hematological toxicity or a grade 2 or higher non hematological toxicity was observed, temporary interruption or dose reduction of S-1 administration was allowed as follows: patients with a BSA of <1.25 m^2 received 25 mg/dose; those with a BSA of ≤1.25 m^2-<1.5 m^2 received a 40 mg/dose; and those with a BSA of ≥1.5 m^2 received a 50 mg/dose. When grade 4 non hematological toxicities, unacceptable toxicities, a rest period >28 days, or an unequivocal tumor progression was observed during maintenance S-1 chemotherapy, treatment was discontinued. After treatment discontinuation, patients could be given other anticancer treatment, excluding S-1 monotherapy, at their physician's discretion.

Response and toxicity assessment

Evaluations of tumor response during chemoradiation therapy and maintenance therapy were performed at the completion of chemoradiation therapy and every 6 weeks thereafter until tumor progression or 24 weeks from the start of S-1 and radiation therapy, using the Response Evaluation Criteria in Solid Tumors version 1.0 questionnaire. Responses were evaluated centrally by 3 independent reviewers. Serum carbohydrate antigen 19-9 (CA19-9) levels were measured at least every 6 weeks. In patients with a pretreatment CA19-9 level ≥100 U/ml, the CA19-9 response was assessed; a positive response was defined as a reduction of >50% from the pretreatment level (13). Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up. Progression-free survival was defined as the time from the date of initial treatment to the first documentation of progression or death. Basic laboratory tests that included a complete blood count with differentials, serum chemistry, and urinalysis were administered at least weekly during S-1 therapy and radiation therapy and then at least once every 2 weeks during S-1 maintenance therapy. Common Terminology Criteria for Adverse Events, version 3.0, were used for the assessment of treatment-related toxicities.

Radiation therapy quality assurance

All radiation therapy treatment plans for the enrolled patients were reviewed centrally by an independent radiation committee consisting of 9 radiation oncologists. To assess radiation therapy protocol compliance, the following parameters were reviewed: fraction size, prescribed dose to the reference point, energy, relationships between GTV, CTV, PTV and radiation field, overall treatment time, isodose distributions at the transverse section of the reference points, and doses to organs at risk. The quality assurance assessment was given as per protocol (PP), deviation acceptable (DA), and violation unacceptable (VU). After parameter compliance was assessed, overall radiation therapy compliance was classified as: PPoverall, no DA or VU in any parameter; VUoverall, at least 1 VU in any parameter; or DAoverall, neither PP nor VU.

Statistical considerations

Primary endpoints of this trial were overall survival for the efficacy evaluation and frequency of adverse events for the safety evaluation; secondary endpoints were progression-free survival, response rate, and serum CA19-9 level response.

The enrollment goal was set at 60 eligible patients. The number of enrolled patients was determined using a statistical power analysis. Under the assumptions of a median survival time of 10 months for patients receiving conventional chemoradiation therapy (1-4), a 2-year registration period followed by a 2-year follow-up period and a one-sided alpha level of 5%, the statistical power of the hazard ratio test was over 70% or 90% with the expected median survival time of 14 or 16 months, respectively. Therefore, the number of planned enrolled patients, the registration period, the follow-up period, and the total research period were set at 60, 2 years, 2 years, and 4 years, respectively. The full analysis set (FAS) was defined as any patient who received at least 1 course of study medication. Overall and progression-free survival curves were calculated using the Kaplan-Meier method. This open-label, multi-institutional, single arm

phase II study was approved by the review board of each institution and was conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research (Ministry of Health, Labour, and Welfare, Japan). The trial was registered at University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR) (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000486).

Patient registration and data collection were managed by the Makimoto-han datacenter. The quality of the data was ensured by a careful review performed by the data center staff and the coordinating investigator of this study (MI). All data were fixed on November 13, 2009, and all analyses in this study were performed by statisticians (NY and TS).

Results

Patient characteristics

Sixty-one patients were enrolled in this trial between July 2006 and November 2007 at 20 institutions in Japan (see the Appendix in Supplementary Material). However, 1 patient was excluded before the start of protocol treatment because distant lymph node metastases were detected during a CT examination for radiation field planning; this patient received systemic chemotherapy with gemcitabine alone. Table 1 shows the characteristics of the 60 FAS patients.

Table 1 Patient characteristics (n=60)

Characteristics	No. of patients	Value(s)	% of patients
Age (y)			
Median		64	
Range		31-80	
Sex			
Male	35		58
Female	25		42
Eastern Cooperative Oncology Group performance status			
0	34		57
1	26		43
Biliary drainage			
Present	16		27
Pathology			
Adenocarcinoma	59		98
Adenosquamous carcinoma	1		2
Tumor location			
Head	33		55
Body or tail	27		45
Maximum tumor size, cm			
Median		3.6	
Range		2.0-6.5	
Regional lymph node swelling			
N0	44		73
N1	16		27
CA19-9 (U/ml)			
Median		304	
Range		0-4400	
Planning target volume (cm^3)			
Median		240	
Range		102-442	

Abbreviation: CA19-9 = carbohydrate antigen 19-9.

Fifty-three patients (88%) completed S-1 therapy and radiation therapy but the remaining 7 patients (12%) discontinued S-1 and radiation therapy. Reasons for treatment discontinuation were disease progression (2 patients), duodenal and bile duct perforation (1 patient), acute myocardial infarction (1 patient), treatment interruption for >15 days because of cholangitis (1 patient), severe confusion (1 patient), and patient refusal to continue treatment because of grade 3 nausea and vomiting (1 patient). The treatment delay during chemoradiation therapy was observed in 20 patients (33%), and the median delay was 3 days (range, 1-17 days). Compliance with S-1 therapy was high, with a rate of 99% (1170 of 1176 doses). Of the 53 patients who completed chemoradiation therapy 47 (89%) patients received maintenance S-1 chemotherapy, but 6 patients did not for the following reasons: disease progression (3 patients); sudden death because of septic shock of unknown origin occurring 40 days after the completion of S-1 and radiation therapy (1 patient); and patient refusal to continue treatment because of grade 2 nausea and grade 2 diarrhea (1 patient) or grade 3 appetite loss and grade 2 fatigue (1 patient). The median number of S-1 maintenance chemotherapy courses was 4 (range, 1 to ≥19). At the time of the final analysis, S-1 maintenance chemotherapy had been terminated in 46 (98%) of 47 patients because of disease progression (29 patients, 63%), adverse events (12 patients, 26%), patient refusal (2 patients, 4%), or other reasons (3 patients, 7%). Treatment delay during the first and second courses of maintenance S-1 therapy was observed in 9 patients (19%) and 7 patients (18%), respectively. The rate of compliance with S-1 chemotherapy was 91% (2503 of 2744 doses) in the first course and 98% (2149 of 2184 doses) in the second course. After the completion of protocol treatment, 53 patients (88%) received subsequent therapy including gemcitabine (47 patients), S-1 (11 patients), radiation therapy for bone metastases (2 patients), and other treatments (4 patients).

Toxicity

The toxicities of S-1 and radiation therapy observed in the 60 FAS patients are listed in Table 2. Grade 3 leukocytopenia, neutropenia, and anemia occurred in 6 (10%), 3 (5%), and 2 (3%) patients, respectively; no grade 4 hematological toxicity was seen. The most common and troublesome non-hematological toxicities for patients undergoing chemoradiation therapy were usually gastrointestinal toxicities, including anorexia, nausea, and vomiting. However, grade 3 or higher cases of these toxicities were observed only in 4 (7%), 3 (5%), and 2 (3%) patients, respectively, and the toxicities were generally mild and manageable. One treatment-related death arising from perforation of the duodenum and biliary tract occurred during chemoradiation therapy.

Toxicities occurring during S-1 maintenance chemotherapy were also mild and transient (Table 3). Grade 4 leukocytopenia was the only hematological toxicity, and it was observed in only 1 patient (2%); the incidence of grade 3 or higher gastrointestinal toxicities was <6%. In addition, no serious adverse events occurred during S-1 maintenance chemotherapy. No late toxicities that could be associated with S-1 and radiation therapy were reported.

Efficacy

The response evaluation included all 60 FAS patients, but tumor response was not evaluable in 1 patient in whom contrast-enhanced CT examination could not be performed due to deterioration of her general condition following duodenal perforation.

Table 2 Toxicity during S-1 and concurrent radiation therapy (n=60)

Toxicity	No. of patients (%)*			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukocytes	15 (25)	28 (47)	6 (10)	0 (0)
Neutrophils	9 (15)	15 (25)	3 (5)	0 (0)
Hemoglobin	16 (27)	13 (22)	2 (3)	0 (0)
Platelets	24 (40)	3 (5)	0 (0)	0 (0)
Non hematological				
Rash	2 (3)	0 (0)	0 (0)	0 (0)
Pigmentation	6 (10)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	1 (2)	0 (0)	0 (0)	0 (0)
Gastric ulcer/gastritis	0 (0)	1 (2)	1 (2)	0 (0)
Abdominal pain	0 (0)	0 (0)	1 (2)	0 (0)
Bilirubin	4 (7)	1 (2)	1 (2)	0 (0)
Aspartate aminotransferase	11 (18)	3 (5)	0 (0)	0 (0)
Alanine aminotransferase	10 (17)	5 (8)	0 (0)	0 (0)
Alkaline phosphatase	4 (7)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	15 (25)	7 (12)	0 (0)	-
Amylase	0 (0)	1 (2)	0 (0)	-
Creatinine	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycemia	2 (3)	4 (7)	0 (0)	0 (0)
Cholangitis	0 (0)	1 (2)	0 (0)	0 (0)

* Grading followed Common Terminology Criteria for Adverse Events version 3.0.

Table 3 Toxicity during S-1 maintenance therapy (n=47)

Toxicity	No. of patients (%)*			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Leukocytes	4 (9)	27 (57)	4 (9)	1 (2)
Neutrophils	5 (11)	19 (40)	6 (13)	0 (0)
Hemoglobin	8 (17)	18 (38)	3 (6)	0 (0)
Platelets	8 (17)	2 (4)	1 (2)	0 (0)
Non hematological				
Malaise	13 (27)	8 (17)	2 (4)	0 (0)
Anorexia	15 (32)	11 (23)	3 (6)	0 (0)
Nausea	7 (15)	4 (9)	1 (2)	0 (0)
Vomiting	4 (9)	1 (2)	0 (0)	0 (0)
Diarrhea	3 (6)	3 (6)	0 (0)	0 (0)
Stomatitis	4 (9)	0 (0)	0 (0)	0 (0)
Alopecia	1 (2)	0 (0)	-	-
Rash	2 (4)	1 (2)	0 (0)	0 (0)
Pigmentation	11 (23)	1 (2)	0 (0)	0 (0)
Hand-foot syndrome	1 (2)	0 (0)	0 (0)	0 (0)
Duodenal ulcer	0 (0)	1 (2)	0 (0)	0 (0)
Taste alteration	1 (2)	2 (4)	-	-
Bilirubin	7 (15)	5 (11)	0 (0)	0 (0)
Aspartate aminotransferase	8 (17)	3 (6)	1 (2)	0 (0)
Alanine aminotransferase	5 (11)	2 (4)	0 (0)	0 (0)
Alkaline phosphatase	1 (2)	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	10 (21)	5 (11)	0 (0)	-
Amylase	0 (0)	1 (2)	0 (0)	-
Creatinine	3 (6)	0 (0)	0 (0)	0 (0)
Hyperglycemia	2 (4)	4 (9)	0 (0)	0 (0)

* Grading followed Common Terminology Criteria for Adverse Events version 3.0.

Tumor response was evaluated based on the best response as of 24 weeks after S-1 and radiation therapy were started. Overall, a partial response was seen in 16 patients for an overall response rate of 27% (95% confidence interval [CI], 16%-40%). The median survival in patients with partial response was 19.4 months (range, 9.8-32.6 months; 95% CI, 13.9-25.1 months), with a median duration of response of 7.3 months (range, 5.5-10.1 months). Forty patients (67%) showed stable disease, and 3 patients (5%) had progressive disease. Additionally, tumor response was evaluated for all periods because tumor shrinkage was obtained in some patients after 24 weeks. Of the 40 patients who were judged to have stable disease on the response evaluation at 24 weeks, an additional 6 patients were judged to have a partial response by the central independent reviewers. The median time to partial response was 4.7 months (range, 1.4-16.8 months) after chemoradiation therapy commenced. Therefore, the response rate for all periods was 37% (95% CI, 25%-50%). Of the 42 patients with a pretreatment serum CA19-9 level $\geq$100 U/ml, 34 (81%) patients had a >50% decrease compared to the pretreatment level. During this protocol treatment, 2 patients underwent surgical resection because tumor shrinkage occurred and their tumors became resectable.

Fifty-four of the 60 patients had disease progression at the time of the analysis. The median progression-free survival time and the 6-month and 1-year progression-free survival proportions for all patients were 9.7 months (95% CI, 6.9-11.6 months), 68%, and 32%, respectively (Fig.). The pattern of disease progression was distant metastases in 26 patients (46%), locoregional recurrence in 16 patients (27%), distant metastases and locoregional recurrence in 3 patients (5%), and deterioration of general condition in 9 patients (15%). At the time of analysis, 49 patients had died, and the median follow-up period was 16.3 months (range, 3.0-34.0 months). The median survival time and the 1-year and 2-year survival proportions for the 60 patients were 16.2 months (95% CI, 13.5-21.3 months), 72% (95% CI, 59%-82%), and 26%, respectively (Fig.).

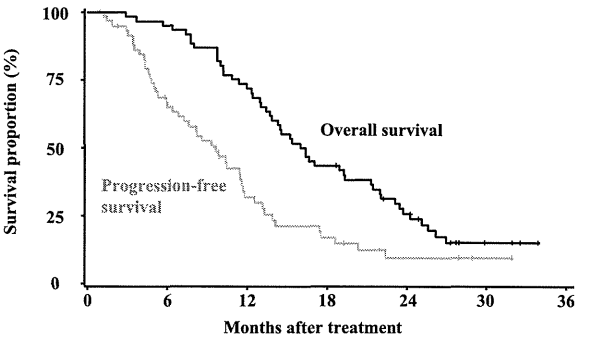

Fig. Overall survival and progression-free survival curves of the 60 locally advanced PC patients treated with S-1 with concurrent radiation therapy. Censored cases are shown by tick marks.

Radiation therapy quality assurance

Radiation therapy quality assurance was reviewed centrally by an independent radiation committee for all 60 FAS patients. DA was observed for 2 parameters in 4 patients (relationship between GTV and radiation field, 2 patients; isodose distribution, 2 patients), but no instances of VU were seen in this study. Therefore, PPoverall, DAoverall, and VUoverall were assessed in 56 (93%) patients, 4 (7%) patients, and 0 (0%) patients, respectively.

Discussion

The combination of radiation therapy and 5-FU chemotherapy has been acknowledged as a standard therapy for locally advanced PC (1-4). However, optimal chemotherapeutic regimens continue to be pursued, as the survival benefit remains modest. S-1 is the first single anticancer agent to be judged non-inferior to gemcitabine in a large-scale randomized phase III trial for advanced PC (10), and it is expected to become a first-line treatment for patients with advanced PC, at least in Asian countries. In addition, it has been shown that combined S-1 and radiation therapy has a synergistic effect against 5-FU-resistant cancer xenografts; thus, S-1 may also have a radiosensitizing effect (11). With S-1 and standard-dose radiation therapy (50.4 Gy/28 fractions), the full dose (80 mg/m^2) of S-1 can be given on the day of irradiation (12) with a reduced risk of distant metastases. Therefore, S-1 may act not only against systemic tumor spread but also a as a potent radiosensitizer to enhance local control. Furthermore, the fact that S-1 can be given orally is an additional benefit over 5-FU infusion.

In the present multicenter trial, the 24-week tumor response rate was 27%, although the overall tumor response rate for the complete period was 37%; in fact, tumor resection was possible in 2 patients after treatment. Thus, excellent tumor shrinkage appears to be an additional benefit of this treatment. Furthermore, other outcomes, including the serum CA19-9 level response (81%), progression-free survival (median, 9.7 months), and overall survival (median, 16.2 months), showed excellent results. As the subsequent therapy, most patients (78%) received gemcitabine, as it might lead to favorable overall survival. However, the outcome of S-1 and concurrent radiation therapy has been reported by other groups (14-16), which were single institutional studies with small numbers of enrolled patients and had slight differences in S-1 administration (Table 4). Similar results were obtained, although such nonrandomized data must be interpreted with caution. Given the recent reports of chemoradiation therapy (4-8, 17, 18), S-1 with concurrent radiation therapy appears to have a favorable treatment efficacy for locally advanced PC, and its survival time will approach that of resected PC patients.

During chemoradiation therapy the major troublesome adverse events were gastrointestinal toxicities (anorexia, nausea, and vomiting), which required intravenous fluid infusion and, sometimes, the termination of chemoradiation therapy (4). One approach to reducing these toxicities that has recently come to be used in chemoradiation therapy using conventional photons for the treatment of PC (4, 6), is a limited radiation field, with a PTV including gross tumor volume alone, without prophylactic nodal irradiation; this minimizes the irradiation of normal tissue and was adopted in the present study. Grade 3 or higher of the above-mentioned toxicities were observed in less than 7% of the patients, and the gastrointestinal toxicities were very mild and easily managed. Other grade 3 or higher non hematological and hematological toxicities of S-1 and concurrent radiation therapy were observed in only 10% or less of the patients and were mild, although there was one treatment-related death due to a perforated duodenum. The toxicities associated with maintenance S-1 therapy were also mild, and this regimen was considered to be well tolerated.

Regarding the results of the radiation therapy quality assurance evaluations performed in this study, 93% of the treatments were assessed as PPoverall; this result is excellent compared with that of a previous trial (5). This result was achieved thanks to the efforts made by the radiation oncologists. The radiation technique that was used in this study was thoroughly explained to all of the radiation oncologists at each institution before patient registration, and the radiation therapy records of the enrolled patients were reviewed by the radiation committee. Results of the review were returned to the radiation oncologists at each institution if any problem with the radiation technique was noted. Therefore, a high quality of radiation therapy was maintained in this study.

There continues to be debate about the role of chemoradiation therapy for patients with locally advanced PC. Prior to the 1990s, it was shown that concurrent external-beam radiation therapy and 5-FU chemotherapy offers a survival benefit over radiation therapy (1, 2) or chemotherapy alone (3). Since the introduction of gemcitabine, which is acknowledged as the first-line therapy for advanced PC, 2 randomized controlled trials comparing chemoradiation therapy with gemcitabine alone have been reported:

Table 4 Results of phase II trials of S-1 and radiation therapy for locally advanced pancreatic cancer

Study (ref.)	Y	Chemotherapy	Radiation therapy	No. of patients	Response rate	Median survival time (mo)	1-y survival rate (%)	Median progression-free survival time (mo)	Maintenance chemotherapy
Kim et al (20)	2008	S-1, 80 mg/m^2, days 1-14 and 22-35	50.4 Gy/28 fractions	25	24%	12.9	43%	6.5	Gemcitabine-based regimen
Sudo et al (15)	2011	S-1, 80 mg/m^2, days 1-14 and 22-35	50.4 Gy/28 fractions	34	41%	16.8	70.6%	8.7	S-1
Shinchi et al (16)	2011	S-1, 80 mg/m^2, days 1-21	50 Gy/40 fractions	50	30%	14.3	62%	6.7	S-1
Current study		S-1, 80 mg/m^2, on the day of irradiation	50.4 Gy/28 fractions	60	27%	16.2	72%	9.7	S-1

a French group reported an inferior outcome with radiation therapy plus 5-FU and cisplatin to chemotherapy with gemcitabine alone (17); and the ECOG study demonstrated that radiation therapy plus gemcitabine had a superior survival outcome compared with gemcitabine alone (18). Thus, these 2 recent randomized controlled trials comparing chemoradiation therapy with gemcitabine alone demonstrated opposite survival results, although both trials were terminated halfway through because of poor patient accrual. In addition, gemcitabine monotherapy for locally advanced PC has been reported to have a favorable efficacy (median survival, 15 months) according to our Japanese group (19), although the time to treatment failure (median, 6.0 months) was not optimal. Thus, in patients with locally advanced PC, it is not clear whether chemoradiation therapy or chemotherapy alone has a better outcome, and there is a need for a prospective, randomized, controlled study comparing chemoradiation therapy with chemotherapy in such patients. Recently, induction chemotherapy followed by chemoradiation therapy has been reported (20). The role of induction chemotherapy is to prevent distant metastases and to define a subset of patients who are likely to benefit from chemoradiation therapy excluding patients with chemoresistant and rapidly progressive disease. Further clinical trials are needed to elucidate the usefulness of this therapeutic strategy.

Conclusions

S-1 therapy with concurrent radiation therapy had very favorable activity, with mild toxicity in patients with locally advanced PC, and the survival time of such patients is expected to approach that of resected PC patients. This regimen appears to be a good platform for incorporation of biologic agents, and the present results should be confirmed in a prospective, randomized, controlled study to elucidate whether chemoradiation therapy or chemotherapy alone results in a better treatment outcome.

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Cancer Chemother Pharmacol (2014) 73:389–396
DOI 10.1007/s00280-013-2368-6

ORIGINAL ARTICLE

Randomized controlled study of gemcitabine plus S-1 combination chemotherapy versus gemcitabine for unresectable pancreatic cancer

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Received: 5 August 2013 / Accepted: 2 December 2013 / Published online: 10 December 2013

Abstract
Purpose The aim of this study was to evaluate efficacy and safety of gemcitabine plus S-1 (GS) combination chemotherapy in patients with unresectable pancreatic cancer.
Methods Patients were randomly assigned to receive GS (oral S-1 60 mg/m^2 daily on days 1–15 every 3 weeks and gemcitabine 1,000 mg/m^2 on days 8 and 15) or gemcitabine (1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks). The primary endpoint was progression-free survival (PFS).
Results One hundred and one patients were randomly assigned. PFS was significantly longer in the GS arm with an estimated hazard ratio (HR) of 0.65 (95 % CI 0.43–0.98; $P = 0.039$; median 5.3 vs 3.8 months). Objective response rate (ORR) was also better in the GS arm (21.6 vs 6 %, $P = 0.048$). Median survival was 8.6 months for GS and 8.6 months for GEM (HR 0.93; 95 % CI 0.61–1.41; $P = 0.714$). Grade 3–4 neutropenia (44 vs 19.6 %, $P = 0.011$) and thrombocytopenia (26 vs 8.7 %, $P = 0.051$) were more frequent in the GS arm.
Conclusions GS therapy improved PFS and ORR with acceptable toxicity profile in patients with unresectable pancreatic cancer.

Keywords Pancreatic cancer · S-1 · Gemcitabine · Randomized controlled study

Introduction

Chemotherapy with gemcitabine (GEM) has been the mainstay in the treatment for unresectable pancreatic cancer. However, the prognosis of patients with unresectable pancreatic cancer remains extremely poor with a median

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survival time of 6–7 months [1–3]. Development of more effective treatment is essential to improve patient survival.

S-1 is an oral anticancer agent that consists of a 5-FU prodrug (tegafur) and two modulators of 5-FU metabolism, gimeracil and oteracil, in a 1:0.4:1 molar concentration ratio [4]. Tegafur is gradually converted to 5-FU in the liver after oral ingestion. Gimeracil is a potent inhibitor of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in the catabolism of 5-FU. The combined use of tegafur and gimeracil leads to prolonged maintenance of 5-FU concentrations in plasma and tumor tissues [5]. Oteracil preferentially localizes in the gut and inhibits its phosphorylation of 5-FU. Thus, coadministration of oteracil theoretically reduces the gastrointestinal toxicity of 5-FU [6].

A phase II study of S-1 in patients with metastatic pancreatic cancer has shown favorable efficacy with a response rate of 37.5 % and median survival of 9.2 months [7]. Up to the present, S-1 has shown favorable efficacy in various settings in the management of pancreatic cancer, such as second-line therapy after GEM failure [8, 9], chemoradiotherapy for locally advanced disease [10] and, more recently, adjuvant treatment after surgery [11].

We conducted the first phase I and II study of combination chemotherapy with GEM and S-1 (GS) for metastatic pancreatic cancer [12, 13]. We administered GEM on days 8 and 15 with S-1 from days 1 to 15 every 3 weeks based on a theoretical rationale that pretreatment with S-1 strengthened cytotoxic effects of GEM by up-regulating human equilibrative nucleoside transporter 1 (hENT1), a key protein transporting GEM into cancer cells [14]. Our phase II study of GS therapy for metastatic pancreatic cancer showed promising results with a response rate of 48 % and median survival time of 12.5 months [13].

We report this multicenter, prospective randomized controlled trial to assess the efficacy and safety of GS therapy in patients with locally advanced or metastatic pancreatic cancer.

Patients and methods

This multicenter, prospective, randomized controlled trial was conducted at 10 centers in Japan. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR) and safety. This study was performed according to the guidelines of the Declaration of Helsinki. The protocol was approved by the institutional review board of participating institutions. Written informed consent was obtained from all patients before their inclusion into the study. The study was registered in the UMIN Clinical Trial Registry (www.umin.ac.jp/ctr/) as UMIN000002244.

Randomization was done centrally via a Web-based system (Mebix, inc., Tokyo, Japan), and patients were stratified according to center, PS (0 vs 1), and extent of disease (locally advanced vs metastatic) by a minimization method.

Eligibility

Patients with metastatic or locally advanced adenocarcinoma or adenosquamous carcinoma of the pancreas were eligible for this study. Histological or cytological confirmation was required. Eligibility criteria included 20–79 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior chemotherapy or radiotherapy and adequate organ function defined by the following parameters: leukocytes $\geq$3,500/mm^3, neutrophils $\geq$2,000/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$9.0 g/dl, normal serum creatinine, creatinine clearance $\geq$50 ml/min, a serum aspartate transaminase (AST) $\leq$120 IU/l, a serum alanine transaminase (ALT) $\leq$120 IU/l and serum bilirubin $\leq$2.0 mg/dl or <3.0 mg/dl after biliary drainage if the patient had obstructive jaundice.

Exclusion criteria included severe concurrent disease, interstitial pneumonia, massive abdominal or pleural effusion, mental disorder, active concomitant malignancy, severe diarrhea, brain metastasis, severe drug hypersensitivity, pregnant or lactating females, and regular use of phenytoin, warfarin or frucitocin.

Treatment

GS therapy consisted of oral administration of S-1 at 60 mg/m^2 divided in two daily doses on days 1–15 and 30-min infusion of GEM at 1,000 mg/m^2 on days 8 and 15 every 3 weeks. In the GEM arm, GEM was administered at 1,000 mg/m^2 in a 30-min infusion on days 1, 8 and 15 every 4 weeks. Treatment was continued until disease progression or unacceptable adverse events, or withdrawal of consent. Drug doses were modified according to the predefined criteria.

Follow-up evaluation

Pretreatment evaluation included a medical history and physical examination, record of PS, complete blood count and biochemistry test, chest radiography, and contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Complete blood count and serum biochemistry test were performed at the beginning of each course and each time of GEM administration. Treatment-related toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Follow-up CT was performed every 2 months to assess objective tumor response according to the Response

Evaluation Criteria in Solid Tumors, version 1.0. Serum carbohydrate antigen 19-9 (CA19-9) levels were measured monthly.

Statistics

A total of 99 patients were needed to detect an improvement in median PFS from 3.5 months for GEM to 5.8 months for GS, with a power of 80 % and with a one-sided alpha level of 0.05. This study was initially designed to recruit 250 patients to detect an improvement in median OS from 7.5 months for GEM to 10.5 months for GS, with a power of 80 % and a one-sided alpha level of 0.05. However, the accrual was slower than expected. As an alternative to protocol termination, we changed the primary endpoint and reduced the sample size in 2010. Further accrual was continued to a total of 99 patients, which was recalculated based on the primary endpoint of PFS.

PFS and OS were calculated with the Kaplan–Meier method, and the difference between both arms was compared by the log-rank test. Hazard ratios (HR) were calculated using the Cox proportional hazards model. Final analyses were done using follow-up data on November 2012, when 12 months follow-up completed after the last randomization. Analyses were done by intention to treat. The distribution of categorical variables in both arms was compared by the χ^2 test or Fisher's exact test. The Mann–Whitney U test or Student's t test was used for comparison of quantitative variables. Differences were considered to be significant when <0.05.

Results

Patient characteristics

One hundred and one patients were randomized from November 2007 to November 2011 (Fig. 1). Fifty-one patients were assigned to GS, and 50 were assigned to GEM. Five patients (one in GS and 4 in GEM) did not receive allocated treatment: one patient in the GEM arm due to deterioration in general condition and the other 4 patients due to withdrawal of consent. Baseline characteristics were well balanced between arms (Table 1).

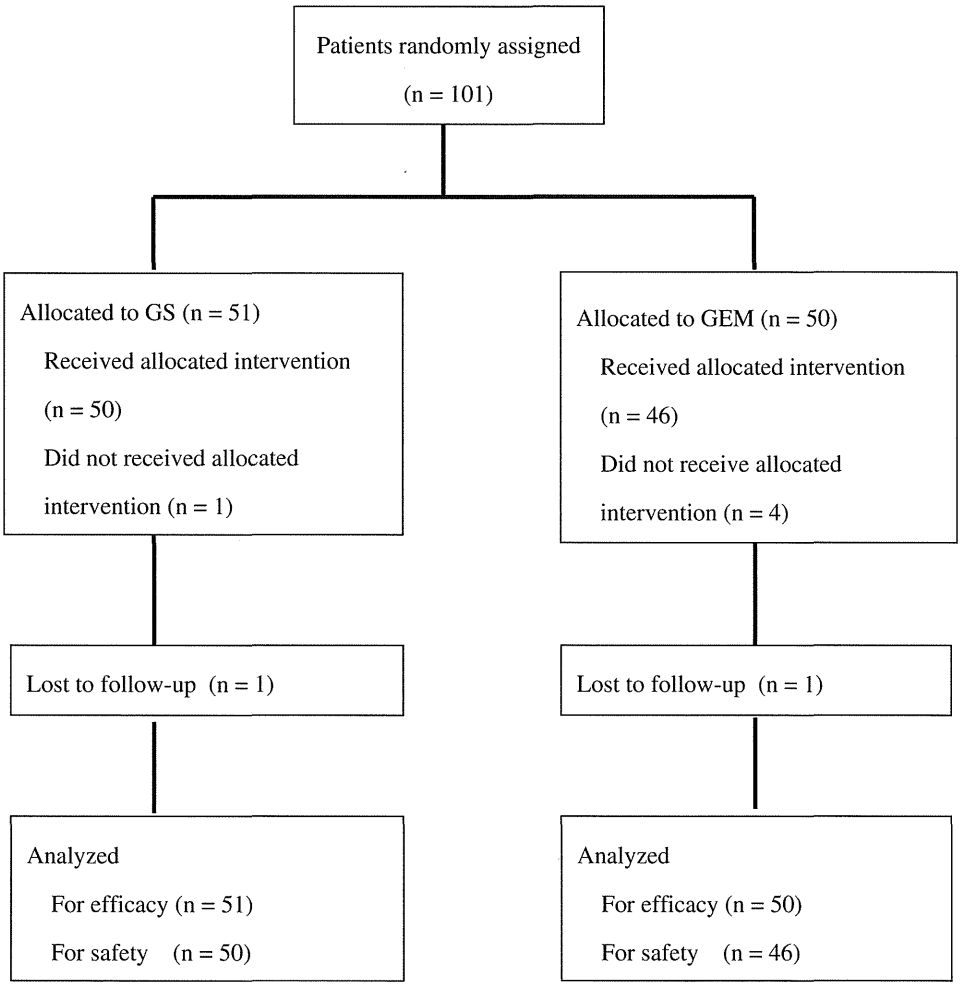

Fig. 1 CONSORT diagram of study design. One hundred and one patients were randomly assigned to GS ($n = 51$) or GEM alone ($n = 50$). Analyses for efficacy were done by intention to treat

Table 1 Patient characteristics

	GS ($n = 51$)	Gemcitabine ($n = 50$)	P value
Gender, *n* (%)			
Men	27 (52.9 %)	34 (68 %)	0.122
Women	24 (47.1 %)	16 (32 %)	
Age, years			
Median (range)	66 (50–77)	67 (45–73)	0.865
ECOG PS, *n* (%)			
0	35 (68.6 %)	35 (70 %)	0.948
1	16 (31.4 %)	15 (30 %)	
CA19-9, IU/L			
Median (range)	1,243 (1–907,657)	896 (0.1–220,423)	0.107
Site of tumor, *n* (%)			
Head	22 (43.1 %)	18 (36 %)	0.463
Body-tail	29 (56.9 %)	32 (64 %)	
Extent of disease, *n* (%)			
Metastatic	33 (64.7 %)	31 (62 %)	0.778
Locally advanced	18 (35.3 %)	19 (38 %)	
Site of metastasis, *n* (%)			
Liver	23 (45.1 %)	19 (38 %)	0.469
Lung	4 (7.8 %)	6 (12 %)	0.714
Peritoneum	9 (17.6 %)	9 (18 %)	0.831

GS gemcitabine and S-1, *ECOG PS* Eastern Cooperative Oncology Group performance status

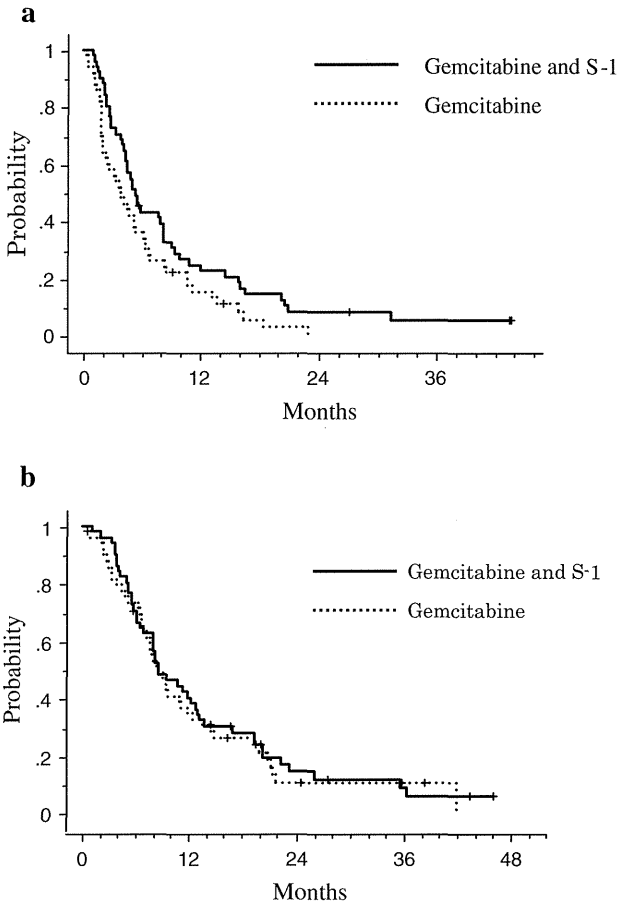

Fig. 2 Kaplan–Meier Estimates of (**a**) progression-free survival (PFS) and (**b**) overall survival (OS). GS therapy significantly improved PFS compared to GEM alone. (HR 0.65; 95 % CI 0.43–0.98; $P = 0.039$; median, 5.3 vs 3.8 months). There was no significant difference between arms in OS (HR 0.93; 95 % CI 0.61–1.41; $P = 0.714$; median, 8.6 vs 8.6 months)

About one-third of the patients had locally advanced unresectable disease and two-thirds had metastatic disease. No patient had received pancreatic resection, adjuvant chemotherapy or radiotherapy before entry into this study. Information about pathological diagnosis was missing for seven patients (4 in GS and 3 in GEM). A total of 455 cycles (median 6, range 1–45) were administered in the GS arm and 278 cycles (median 4, range 1–21) in the GEM arm.

Survival

PFS was significantly longer in the GS arm with an estimated HR of 0.65 (95 % CI 0.43–0.98; log-rank $P = 0.039$; Fig. 2). The median PFS was 5.3 months for GS and 3.8 months for GEM. The median survival was 8.6 months for GS and 8.6 months for GEM (Fig. 2). There was no statistically significant difference in OS between arms (HR 0.93; 95 % CI 0.61–1.41; log-rank $P = 0.714$).

Objective response and CA19-9 status

The ORR was 21.6 % for GS (95 % CI 10.3–32.9 %) and 6 % for GEM (95 % CI 0–12.6 %). The difference was statistically significant ($P = 0.048$; Table 2). Forty-six patients (90 %) in the GS arm and 37 patients (74 %) in the GEM arm had elevated serum CA19-9 levels. Among these patients, marked decrease (≥50 %) of serum levels of CA 19-9 was observed more frequently in the GS arm (56.5 vs 29.7 % $P = 0.015$).

Table 2 Objective response rate

	GS ($n = 51$)	Gemcitabine ($n = 50$)	P value
Response, *n*			
Complete response	1	0	
Partial response	10	3	
Stable disease	24	24	
Objective response rate			
No. (%)	11 (21.6 %)	3 (6 %)	
95 % CI	10.3–32.9	0–12.6	0.048

GS gemcitabine and S-1, *CI* confidence interval

Three patients in the GS arm underwent surgery with curative intent after marked response to chemotherapy ($n = 2$) or long-term disease stabilization ($n = 1$). One patient achieved complete response and underwent surgery 23 months after the start of GS therapy. Another patient achieved marked response to GS therapy, but subsequently showed an increase in serum CA19-9 levels without radiographic evidence of tumor progression. This patient underwent surgery as part of salvage treatment. The remaining patient underwent surgery after long-term (45 months) disease stabilization. Among the three patients, two achieved R0 resection.

Safety

Fifty patients in the GS arm and 46 in the GEM arm were evaluable for adverse events. Grade 3–4 adverse events observed during treatment are summarized in Table 3. GS therapy was generally well tolerated. Grade 3–4 neutropenia was significantly frequent in the GS arm (44 vs 19.6 %, $P = 0.011$). And grade 3–4 thrombocytopenia was also frequent in the GS arm (26 vs 8.7 %, $P = 0.051$). However, the incidence of febrile neutropenia, severe infection or gastrointestinal hemorrhage was similar in both groups. There were two deaths of unknown cause in the GS arm. The cause of death was possibly due to cancer complications, but a causal relationship with therapy could not be definitely ruled out.

Table 3 Summary of grade 3/4 adverse events

Event, *n* (%)	GS ($n = 50$)	Gemcitabine ($n = 46$)	*P* value
Hematological toxicity			
Leukocytopenia	10 (20 %)	8 (17.4 %)	0.744
Neutropenia	22 (44 %)	9 (19.6 %)	0.011
Anemia	9 (18 %)	6 (13 %)	0.699
Thrombocytopenia	13 (26 %)	4 (8.7 %)	0.051
Non-hematological toxicity			
Anorexia	6 (12 %)	5 (10.9 %)	0.883
Nausea/vomiting	6 (12 %)	3 (6.5 %)	0.569
Diarrhea	1 (2 %)	2 (4.3 %)	0.941
Constipation	1 (2 %)	0	0.967
Stomatitis	1 (2 %)	0	0.967
Rash	2 (4 %)	0	0.512
Fatigue	0	1 (2.2 %)	0.967
Creatinine	0	1 (2.2 %)	0.967
Infection	6 (12 %)	7 (15.2 %)	0.872
Febrile neutropenia	1 (2 %)	1 (2.2 %)	0.512
Thrombosis	2 (4 %)	0	0.512
GI hemorrhage	4 (8 %)	2 (4.3 %)	0.752

GS gemcitabine and S-1, *GI* gastrointestinal

Second-line therapy

Second-line therapy after the allocated treatment is shown in Table 4. Sixty-four percent of patients in the GEM arm received S-1-based chemotherapy, while most patients in the GS arm had few options for second-line treatment.

Discussion

In the current study, combination chemotherapy with GS showed significantly better PFS compared with GEM monotherapy. The study met its primary endpoint.

ORR and CA19-9 response were significantly higher in the GS arm. Three patients in the GS arm underwent surgery with curative intent after marked response to chemotherapy or long-term disease stabilization, and two achieved R0 resection. Meanwhile, no patient in the GEM arm underwent surgery. This is probably due to the higher response rate of GS therapy. As shown in Table 5, other two studies have also reported the superiority of GS with respect to ORR [15, 16].

However, GS therapy had little impact on OS, though this study was not designed to evaluate whether GS improved OS. Similar tendency that GS improved PFS but not OS was also shown in other randomized studies including a large-scale phase III study (Table 5) [16, 17]. One possible explanation is that high rate of crossover to S-1 after GEM failure in the GEM arm may affect the results though there has been no confirmed evidence that recommends the use of S-1 after GEM failure. As shown in the GEST study, S-1 is non-inferior to GEM in OS for unresectable pancreatic cancer [16], and previous phase II studies of S-1 in patients with GEM resistant pancreatic cancer have shown a moderate activity (ORR 9.5–15 %, MST 4.5–6.3 months) [8, 9]. S-1 has been approved for the treatment for pancreatic cancer since 2006 in Japan and commonly used in patients with GEM resistant pancreatic cancer. In fact, sixty-four percent of patients received second-line treatment using S-1 after GEM failure in our cohort of patients.

Table 4 Second-line therapy

Treatment, *n* (%)	GS ($n = 46$)	Gemcitabine ($n = 45$)
S-1	4 (8.7 %)	25 (55.6 %)
S-1 + gemcitabine	–	2 (4.4 %)
S-1 + irinotecan	0	2 (4.4 %)
Gemcitabine	7 (15.2 %)	–
Cisplatin + irinotecan	3 (6.5 %)	0
Other	5 (10.9 %)	1 (2.2 %)

GS gemcitabine and S-1

Table 5 Randomized study of GS versus GEM for unresectable pancreatic cancer

Author	Design	Endpoint	Treatment arm	*n*	Treatment schedule of GS	ORR (%)	PFS (M)	MST (M)
Ueno	PIII	Superiority of GS and non-inferiority of S-1 to GEM in OS	GS	275	S-1 60, 80, 100 mg/body d 1–14	29[a]	5.7[a]	10.1
			GEM	277	GEM d 1, 8 every 3 weeks	13	4.1	8.8
			S-1	280		21[a]	3.8[b]	9.7[b]
Ozaka	rPII	ORR	GS	53	S-1 80 mg/m^2 d 1–14	28.3[a]	6.15[a]	13.7[a]
			GEM	59	GEM d 1, 8 every 3 weeks	6.8	3.78	8.0
Nakai	rPII	PFS	GS	53	S-1 80 mg/m^2 d 1–15	18.9	5.4[a]	13.5
			GEM	53	GEM d 1, 15 every 4 weeks	9.4	3.6	8.8

GS gemcitabine and S-1, *GEM* gemcitabine, *ORR* objective response rate, *PFS* progression-free survival, *MST* median survival time, *OS* overall survival, *PIII* phase III study, *rPII* randomized phase II study, *d* day

[a] Statistically significantly better than GEM

[b] Statistically significant for non-inferiority to GEM

As for toxicity, grade 3–4 neutropenia and thrombocytopenia were more frequent in the GS arm, but the incidence of severe infection or hemorrhage was similar in both groups. Grade 3 rash was seen only in the GS arm, which was the most frequent non-hematological toxicity in our phase II study of GS therapy. Interstitial pneumonia or other severe toxicities were uncommon in both arms. The current study demonstrated the feasibility and acceptable toxicity profile of GS therapy.

In this study, we administered GEM on days 8 and 15 with S-1 from days 1 to 15 every 3 weeks based on a theoretical basis that the maximum synergistic effect was observed when the thymidylate synthase inhibitors such as 5-FU or S-1 preceded GEM [14, 18]. We have investigated this S-1 pretreatment schedule of GS therapy through phase I and II study [12, 13]. On the other hand, Lee et al. and Ueno et al. [19, 20] investigated a different schedule of GS therapy that consisted of GEM administration on days 1 and 8 with S-1 from days 1 to 14 every 3 weeks. No standard schedule of GS therapy has been confirmed. However, Satouchi et al. [21] conducted a randomized phase II study of the above two different schedule of GS therapy in patients with non-small cell lung cancer and concluded that they selected the former, S-1 pretreatment schedule of GS therapy for further studies based on the efficacy data. Our study is the first randomized trial that investigated the S-1 pretreatment schedule of GS therapy in comparison with GEM for unresectable pancreatic cancer.

The major limitation of this study is the change in primary endpoint from OS to PFS because of poor accrual. The sample size was recalculated, and further accrual was continued. Although some studies chose PFS or time to progression as their primary endpoint in pancreatic cancer [22, 23], OS is a generally accepted primary measure in this patient population. Therefore, the results of this study seem to be inconclusive as to whether GS therapy can be added to the standard therapy for unresectable pancreatic cancer.

GS therapy significantly improved PFS compared with GEM but has little impact on OS in the current study. Although the sample size was not large enough to detect the difference in OS between both arms in this study, we conclude that GS therapy would not be accepted as a standard treatment option for unresectable pancreatic cancer. GS therapy did not improve OS compared to GEM in a large-scale phase III study (GEST study) [16]. Similarly, other GEM and fluoropyrimidine combinations such as GEM/5-FU or GEM/capecitabine have failed to show an improvement in OS in patients with unresectable pancreatic cancer [24–26]. Based on currently available evidence, GEM plus erlotinib, GEM plus nab-paclitaxel and Folfirinox are accepted treatment options for metastatic pancreatic cancer [2, 3, 27]. However, we consider that favorable PFS, high response rate and acceptable toxicity profile may warrant further evaluation of GS therapy in selected patient populations. In an effort to assess whether GS therapy can improve treatment efficacy, meta-analysis may be necessary using the data of randomized studies. Furthermore, taking into account the high response rate of GS therapy and the result of this study that two patients achieved R0 resection after GS therapy, its use for borderline resectable or locally advanced disease seems to be an attractive strategy in future trials.

In conclusion, this study demonstrated that GS therapy significantly improved PFS compared to GEM with higher response rate and acceptable toxicity in patients with unresectable pancreatic cancer.

Acknowledgments This study was performed according to the guidelines of the Declaration of Helsinki. The protocol was approved by the institutional review board of participating institutions. Written informed consent was obtained from all patients before their inclusion into the study. This manuscript has not been published and is not under consideration for publication elsewhere.

Conflict of interest No financial support for this study was provided. The authors report no conflict of interest.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(2)139–145
doi:10.1093/jjco/hys211
Advance Access Publication 28 December 2012

Safety and Effectiveness of Gemcitabine in 855 Patients with Pancreatic Cancer under Japanese Clinical Practice Based on Post-marketing Surveillance in Japan

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Received September 12, 2012; accepted November 20, 2012

Objective: When gemcitabine was approved as an anti-cancer drug, there were limited data for Japanese patients treated with gemcitabine. Generally, advanced or metastatic pancreatic cancer patients experience poor prognosis and suffer from debilitating disease-related symptoms. Reports and information on gemcitabine use within a large patient pool will be beneficial to aid physicians. Therefore, this post-marketing surveillance was conducted as a non-interventional, observational study on the use of gemcitabine in a clinical practice setting in Japan.

Methods: Patients had no previous treatment with gemcitabine and were diagnosed with pancreatic cancer by an attending physician. Patients were registered between May 2001 and December 2003 in Japan. The patients were treated with gemcitabine. Data such as patient background, treatment details, adverse events, tumor response, serum CA19-9 levels and drug-related symptom improvement were assessed.

Results: Of the 890 patients registered for the study, 855 were included in the analysis of gemcitabine for safety. Four hundred and forty-three (51.9%) patients reported drug-related adverse events, with 97 patients (11.4%) experiencing serious adverse events. The incidence of interstitial lung disease was 0.7% (six patients). Six hundred patients were evaluated for tumor response. The overall response rate was 6.0% and the disease control rate was 54.0%. CA19-9 decreased in 63.6% of the 335 evaluable patients, with a $\geq$75% decrease seen in 19.4% of the total group. Drug-related symptom improvement was observed in 27.0% of the 686 evaluable patients.

Conclusions: This large-scale surveillance could confirm the safety of gemcitabine for Japanese pancreatic cancer patients as well as elucidate the efficacy profile, measured by drug-related symptom improvement, for Japanese pancreatic cancer patients.

Key words: gemcitabine – pancreatic cancer – interstitial lung disease (ILD)

INTRODUCTION

Patients with advanced pancreatic cancer (PC) experience poor prognosis and suffer debilitating disease-related symptoms. Because most patients of PC are in advanced stages at the initial visit, only 15–20% of patients can be candidates for curative surgery. A 5-year survival rate is found in <5% of patients and complete remission with chemotherapy is extremely rare.

A global phase III study comparing gemcitabine with 5-FU demonstrated that gemcitabine was associated with a significantly better clinical response rate (24 versus 5%) and 1-year survival rate (18 versus 2%), although there were no confirmed objective responses in either group (1). In Japan, however, gemcitabine was approved for the treatment of PC in 2001 after a phase I clinical trial involving 11 patients with advanced PC confirmed the tolerability of gemcitabine at 1000 mg/m^2 weekly for 3 weeks, followed by a 1 week rest (2). Hence, the number of Japanese PC patients treated with gemcitabine was limited at the time of its approval. Safety and effectiveness needed to be confirmed in clinical practice settings with a larger number of patients.

The primary purpose of this study was to confirm the safety profile of gemcitabine in Japanese PC patients. In addition, the effectiveness was studied as a secondary objective in this surveillance.

METHODS

This survey was a multi-center, prospective, non-interventional observational study assessing the use of gemcitabine in patients with PC in daily clinical practice settings.

Registration

This survey was conducted in compliance with the Japanese regulatory requirements stipulated in the Good Post-Marketing Study Practice (GPMSP) guidelines. Patients were registered by attending physicians through a central registration system with Eli Lilly Japan K.K. The registration period was from 1 May 2001 to 30 December 2003.

Patients and treatment

The subjects of the study were patients who had not been treated by gemcitabine and diagnosed as PC by an attending physician. Four patients turned out to have other diseases than PC after obtaining their case report forms (CRFs). They were included in the safety analysis because they received at least one gemcitabine treatment. The approved dosage for PC is 1000 mg/m^2 as gemcitabine is administered by intravenous infusion for 30 min on Days 1, 8 and 15, in a 28-day cycle.

Observational period

The observational period was from first treatment of gemcitabine to 4 weeks after the 9th treatment or to 4 weeks after its discontinuation. Survey data were collected after the observational period via the CRFs completed by the attending physicians. Although monitoring was not conducted, the sponsor confirmed inconsistent data with a query sheet. This observational survey was conducted under the discretion of clinical practice. All treatment decisions were made by the attending physician.

Safety assessment

Data of adverse events (AEs) were collected regardless of causality to the drug. The actual events described were based on each investigator's judgment. An AE was serious if it met at least one of the following criteria: (i) resulted in death, (ii) was life-threatening, (iii) required inpatient hospitalization or prolongation of existing hospitalization, (iv) resulted in persistent or significant disability/incapacity, (v) led to a congenital anomaly/birth defect or (vi) another medically important condition. In line with the Japanese regulations, an adverse drug reaction (ADR) was defined as an AE for which the causality to the drug cannot be ruled out.

Effectiveness assessment

Tumor response was assessed by each attending physician according to the *Guidelines to Evaluate the Response to Treatment in Solid Tumors* by Japan Society of Clinical Oncology in 1986, Nihon Gan Chiryou Gakkai Shi (3). The overall tumor response rate was defined as the number of patients with documented partial response or complete response divided by the number of patients who had tumor response reports from physicians. Analysis of serum CA19-9 was conducted in patients who showed above 74 U/ml (twice the normal limit) of CA19-9 within 14 days before the first treatment, and who had both CA19-9 measurement before and after treatment. The decreasing rate of CA19-9 was calculated using the CA19-9 value within 2 weeks prior to gemcitabine therapy as a baseline and the best data (lowest data) during the observational period.

In order to measure disease-related symptom improvement (DRSI) (4), four kinds of data were collected in the study: strength of pain, usage of analgesic, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and change of body weight.

DRSI was evaluated at the third, fourth, sixth, seventh, ninth treatment and 4 weeks after the last gemcitabine treatment. Patients were classified as DRSI responders, if compared with the baseline value, they had an improvement in one or more of the four parameters mentioned above (without worsening in any other).

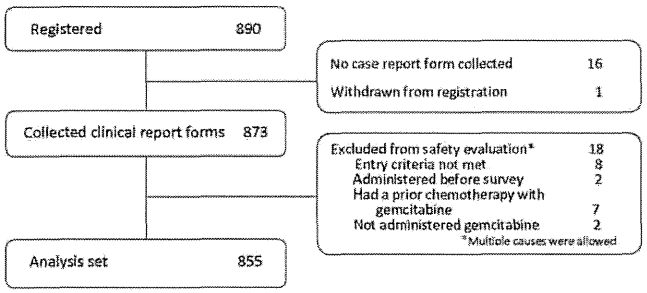

Figure 1. Patient disposition.

Table 1. Demographic and disease characteristics of patients

Characteristics		*n* (%)
Number of patients	All	855 (100.0)
Gender	Male	526 (61.5)
	Female	329 (38.5)
Age	<40	12 (1.4)
	40–49	46 (5.4)
	50–59	203 (23.8)
	60–69	338 (39.5)
	70–79	235 (27.5)
	80≤	21 (2.5)
Stage of disease in patients for primary pancreatic cancer ($n = 796$)	I	4 (0.5)
	II	18 (2.3)
	III	44 (5.5)
	IVa	222 (27.9)
	IVb	496 (62.3)
	Unknown	12 (1.5)
Performance status (PS)	0	302 (35.3)
	1	343 (40.1)
	2	101 (11.8)
	3	33 (3.9)
	4	6 (0.7)
	Unknown	70 (8.2)
Comorbidity	No	338 (39.5)
	Yes	517 (60.5)
	Hepatic function disorder[a]	210 (40.6)
	Renal function disorder[a]	17 (3.3)
	Blood disorder[a]	94 (18.2)
	Others[a]	402 (77.8)
Reason for gemcitabine usage	Primary pancreatic cancer	796 (93.1)
	Recurrent pancreatic cancer	55 (6.4)
	Others[b]	4 (0.5)
Histology of pancreatic cancer ($n = 851$[c])	Tubular adenocarcinoma	413 (48.3)
	Adenocarcinoma	63 (7.4)
	Papillary adenocarcinoma	24 (2.8)
	Adenosquamous carcinoma	6 (0.7)
	Acinar cell adenocarcinoma	5 (0.6)
	Others and unknown	340 (40.0)
Metastasis in primary pancreatic cancer ($n = 796$)	No	286 (35.9)
	Yes	499 (62.7)
	Unknown	11(1.4)
Primary chemotherapy	No	788 (92.2)
	Yes	67 (7.8)
Concomitant medication (anti-tumor drug)	No (monotherapy)	679 (79.4)
	Yes	176 (20.6)
Serum CA19-9 levels (U/ml) before first gemcitabine treatment ($n = 617$)	0≤ to ≤37	164 (26.6)
	37< to ≤100	66 (10.7)
	100< to ≤1000	174 (28.2)
	1000< to ≤10 000	134 (21.7)
	10000<	79 (12.8)

[a]Multiple answers allowed.
[b]Including one rectal cancer, two biliary carcinoma and one cholangiocellular carcinoma.
[c]Excluded four cases which had other cancer than PC.

Statistics

The percentage of patients who experienced ADRs was calculated.

The effectiveness analysis excluded the collected CRF of patients who were administered gemcitabine as a treatment for non-pancreatic cancers. Tumor response rate and disease control rate were evaluated based on all tumor response reported from attending physicians regardless of their day of assessment. Regarding DRSI, 'improvement' is defined as patients having at least one improvement with no aggravation in three symptoms (strength of pain, usage of analgesics and PS) and 7% weight gain. Time to treatment failure (TTF) was calculated for the days from the first administration to the 9th or last administration.

RESULTS

A total of 890 patients were registered by physicians and the CRFs of 873 patients were utilized for this surveillance (Fig. 1). Eighteen of the 873 patients were excluded, 855 patients from 125 institutions were evaluable for the safety analysis of gemcitabine. The types of PC and disease stages

Table 2. Dose administration for evaluable patients

Items	Results ($n = 855$)
Dosage (times)	
Median	9
Range	1–9
TTF[a] (days)	
Median	73
Range	1–295
Mean dosage (mg/m^2)	
Median	909.1
Range	10.0–1159.4
Total dosage (mg/m^2)	
Median	5960.3
Range	90.0–104 34.8

[a]Time to treatment failure.

were classified according to the sixth edition of *General Rules for the Study of Pancreatic Cancer* by Japan Pancreas Society.

Table 1 shows the characteristics of the 855 patients included in the safety analysis. Overall, patients were predominantly male (61.5%), ranging from 60 to 69 years of age (39.5%) and primarily in Stage IV (90.2%). About 75% of the patients had an ECOG PS of 0-1 and 11.8% had a PS of 2, suggesting that gemcitabine was mainly prescribed to favorable PS patients. For a majority of patients, gemcitabine was used as a first-line therapy, and tubular adenocarcinoma was the most common histology (48.3%). Of the 617 patients evaluated for serum CA19-9 levels for 14 days up to the first treatment, 174 of those (28.2%) were at the 100–1000 U/ml level and 134 (21.7%) at the 1000–10 000 U/ml level.

As shown in Table 2, 855 patients received gemcitabine a maximum of nine times over a median TTF of 73 days (range: 1–295 days). More than half of the patients received the full three cycles of gemcitabine. The median dose of gemcitabine per treatment was 909.1 mg/m^2 (range: 10.0–1159.4 mg/m^2) and the median amount of gemcitabine administered per patient was 5960.3 mg/m^2 (range: 90.0–104 34.8 mg/m^2).

In Table 3, ADRs with an incidence of $\geq$1% are summarized. Out of the total 855 evaluable patients, 444 patients (51.9%) experienced ADRs including 98 patients (11.5%) who experienced serious ADRs. Leukopenia and thrombocytopenia were the notable hematological toxicities and changes in the non-hematological parameters were rather insignificant. The maximum frequency of serious ADRs was 2.9% for leukopenia. Nausea and thrombocytopenia were also listed as ADRs with >1% incidence. Table 4 indicates the background information and outcome of ILD cases,

Table 3. Drug-related adverse events (incidence $\geq$1%)

Parameter	All, *n* (%)	Serious, *n* (%)
Evaluable patients	855 (100.0)	855 (100.0)
Patients with drug-related adverse events	444 (51.9)	98 (11.5)
Hematological toxicities		
Leukopenia	187 (21.9)	25 (2.9)
Thrombocytopenia	119 (13.9)	19 (2.2)
Neutropenia	52 (6.1)	6 (0.7)
Hemoglobin decreased	39 (4.6)	4 (0.5)
Anemia	38 (4.4)	2 (0.2)
Bone-marrow failure	36 (4.2)	8 (0.9)
Red-blood-cell count decreased	16 (1.9)	0 (0.0)
Hematocrit decreased	11 (1.3)	0 (0.0)
Non-hematological toxicities		
Nausea	63 (7.4)	11 (1.3)
Fever	40 (4.7)	7 (0.8)
Anorexia	40 (4.7)	7 (0.8)
Vomiting	28 (3.3)	5 (0.6)
Rash	27 (3.2)	2 (0.2)
Malaise	21 (2.5)	5 (0.6)
Hepatic dysfunction	20 (2.3)	3 (0.4)
Diarrhea	14 (1.6)	1 (0.1)
Hepatic disorder	11 (1.3)	0 (0.0)
Constipation	10 (1.2)	0 (0.0)
Rash, pruritic	9 (1.1)	0 (0.0)

which were reported from this study. All cases were over 60 years old. Sex, treatment line and tumor stage were reflected in the patient characteristics, and there was no correlation between treatment cycles, dosage or timing of ILD occurrence. Five of the six ILD cases recovered by using correct treatment, including steroid. There was one fatal case of a 69 years old male in poor performance status with stage IVa disease.

Table 5 showed the additional sub-group safety analysis. We examined the association between ADRs and patients characteristics, PS and age. The incidence of ADRs in PS $\geq$1 and PS 0 patients were 55.1 and 48.7%, respectively. The incidence of ADRs in patients $\leq$75 years old and >75 years old patients were 40.7 and 38.4%, respectively.

The tumor response of gemcitabine treatment was analyzed in 600 patients, taking complete response (CR), partial response (PR), minor response (MR), no change (NC) and progressive disease (PD) into consideration (Table 6). Although the overall response rate (CR+PR) was 6.0%, the disease control rate (CR + PR + MR + NC) was 54.0%. In order to evaluate the control of cancer-related symptoms, DRSI was also measured, as shown in Fig. 2. The number of patients responding was 185 (27.0%). Among four symptoms