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Giardiasis in the Pancreas Accompanied by Pancreatic Cancer

To the Editor:

In the last 30 years, parasitic diseases have been considered to be successfully controlled in Japan. However, there has been a steady increase in the number of patients who had a diagnosis of parasitic diseases in Japan.[1,2] *Giardia lamblia*, a protozoan pathogen that commonly affects the upper intestine and biliary tract but rarely affects the pancreas, causes *G. lamblia* infection (giardiasis), which is the most important parasitic disease affecting people worldwide.[3] Pancreatic cancer has currently become an interesting topic of research because of its increasing incidence and particularly poor prognosis. Early diagnosis of pancreatic cancer is necessary for better prognosis and for a thorough understanding of the risk factors and environmental causes of pancreatic cancer and the mechanism underlying its development.[4] We had an experience with a case of giardiasis in the pancreas accompanied with pancreatic cancer. We discussed a case in which parasites and cancer cells can coexist; the case may provide information that can be used to resolve one of the problems involved in the pathophysiology of pancreatic cancer.

CASE REPORT

A 69-year-old Japanese man was admitted to our hospital for the diagnosis and treatment of a pancreatic tail mass. This patient had given up smoking 10 years ago; furthermore, he was not a heavy drinker and had no family history of pancreatic cancer. A multidetector computed tomographic scan showed the existence of a 35-mm low-density area in the pancreatic tail with no liver metastasis. The levels of hemoglobin A_{1c}, serum pancreatic enzyme, and tumor markers were within the reference range. Endoscopic retrograde cholangiopancreatography revealed occlusion of the main pancreatic duct in the tail. Numerous pear-shaped binucleate flagellated organisms that were morphologically consistent with the trophozoites of *G. lamblia* were identified in the aspirated pancreatic juice (Fig. 1). Endoscopic ultrasound-guided fine-needle aspiration biopsy specimen showed a cystic mass, suggesting dilation of the pancreatic duct by the obstruction above the solid mass. Furthermore, cytologic examination confirmed class-V adenocarcinoma. Clusters of similar trophozoites were simultaneously seen. Fluorodeoxyglucose positron emission tomography did not reveal any hot spot except for one that corresponded to the pancreatic tail mass (standardized uptake value level, 3.8). Histopathological findings of the pancreatic tail tumor after distal pancreatectomy showed a well-differentiated–to–moderately differentiated adenocarcinoma (scirrhous type), and resection of the omental bursa revealed metastatic carcinoma cells, indicating stage IV disease. In addition, microorganisms

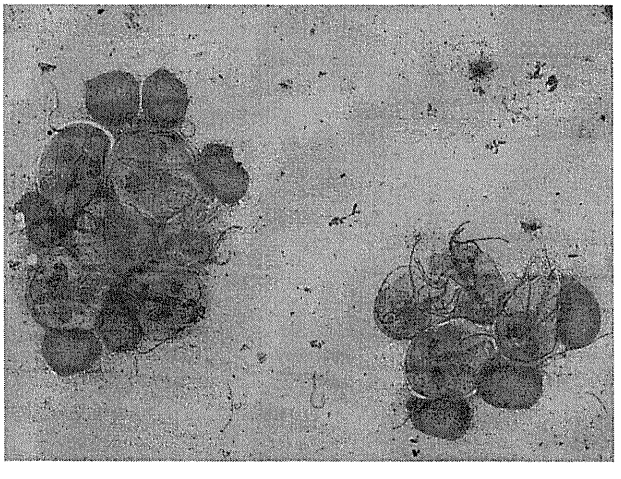

FIGURE 1. Numerous pear-shaped binucleate flagellated organisms morphologically consistent with trophozoites of *G. lamblia* were identified by endoscopic retrograde cholangiopancreatography in aspirated pancreatic juice.

that were suggestive of *G. lamblia* were seen in the pancreatic duct.

DISCUSSION

Giardiasis, which is caused by the protozoan parasite *G. lamblia*, is considered the most common protozoan infection in humans.[5] Symptoms of giardiasis include abdominal pain, nausea, anorexia, diarrhea, vomiting, flatulence, eructation, and fatigue. Signs include weight loss, abdominal distension and tenderness, pale watery stools, and malodorous flatulence. The aforementioned symptoms usually range from mild to severe in intensity; however, a large number of the infected individuals may also remain asymptomatic.[6]

Transmission of *G. lamblia* to humans usually occurs through the ingestion of cysts in contaminated water or food or via direct fecal-oral contact.[5] In our case, the patient had been boiling water from a natural spring near his house and using this boiled water for cooking and drinking. A public health center certified this spring water to be free of known parasite. Giardiasis is often detected in specific groups such as male homosexuals and people traveling to developing countries.[7,8] Our patient did not belong to any of these groups. Recently, there have been reports of suspected cases of giardiasis in humans from a canine source[9]; however, this patient did not keep dogs as pets. Therefore, the transmission route of the pathogen in this case remained unidentified.

Till date, giardiasis in the pancreas has often been overlooked; however, the frequency of diagnosis of this condition may increase in the future. To our knowledge, there are no reports of coexistence of giardiasis and cancer cell. Our patient had no known risk factors of pancreatic cancer, such as heavy smoking history, family history of cancer, and diabetes mellitus. Hence, it was difficult to establish a definite causal relationship between the existence of *G. lamblia* infection and pancreatic cancer. Furthermore, the carcinogenesis could not be attributed to parasitic infection because the resected tissues did not show chronic pancreatitis or inflammation of the pancreatic duct around the cancer tissue. Because trophozoites do not usually penetrate the epithelium, infection generally occurs within the lumen and invades the surrounding tissues.[10] Although the relationship between pancreatic giardiasis and pancreatic cancer is presently unknown, the coexistence of these 2 diseases motivates us to explore the mechanism of carcinogenesis in the pancreas. Investigation of giardiasis-induced inflammatory changes in the pancreatic duct may help overcome the difficulties involved in studying the pathophysiologic mechanism of pancreatic cancer. Further investigation in this regard is necessary.

Masayuki Furukawa, MD
Lingaku Lee, MD
Toru Ikegami, MD
Takashi Maeda, MD
Department of Gastroenterology
National Kyushu Cancer Center
Fukuoka, Japan
Kenichi Nishiyama, MD
Department of Pathology
National Kyushu Cancer Center
Fukuoka, Japan
Souichi Itaba, MD
Department of Medicine
and Bioregulatory Science
Graduate School of Medical Sciences
Kyushu University
Fukuoka, Japan
Akihiro Funakoshi, MD
Department of Gastroenterology
National Kyushu Cancer Center
Fukuoka, Japan
akfunako@nk-cc.go.jp

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Case Reports in Oncology

Case Rep Oncol 2011;4:534–541
DOI: 10.1159/000334704

Published online: November 22, 2011

ISSN 1662–6575
www.karger.com/cro

Paclitaxel-Based Chemotherapy for Advanced Pancreatic Cancer after Gemcitabine-Based Therapy Failure: A Case Series of 5 Patients

Hisato Igarashi[a] Tetsuhide Ito[a] Terumasa Hisano[a]
Nao Fujimori[a] Yusuke Niina[a] Mikihiko Yasuda[a]
Toyoma Kaku[a] Susumu Matsuo[a] Takamasa Oono[a]
Masahiro Yoshinaga[b] Hiroyuki Sakai[b]
Ryoichi Takayanagi[a]

[a]Department of Medicine and Bioregulatory Science, Graduate School of Medical Science, Kyushu University, Fukuoka, and [b]Department of Gastroenterology, National Hospital Organization, Beppu Medical Center, Beppu, Japan

Key Words
Pancreatic cancer · Paclitaxel · Chemotherapy · Gemcitabine failure · Second-line therapy

Abstract
Background/Objectives: Gemcitabine (GEM) is a gold-standard chemotherapy agent for advanced pancreatic cancer. Because of the malignant character of the disease, nearly all patients show disease progression despite treatment with GEM-based chemotherapy; therefore, second-line chemotherapy may be beneficial for these patients. We report a retrospective analysis of 5 patients with advanced pancreatic cancer, treated with a paclitaxel-containing regimen as second-, third- or fourth-line chemotherapy after various therapies, such as a GEM-based regimen, S-1 regimen, and chemoradiation. We retrospectively analyzed the efficacy and adverse events, and evaluated the paclitaxel-containing regimens. A review of the literature is also discussed.
Results: The median overall survival from the start of salvage therapy was 10.7 months. The disease control rate of the paclitaxel-containing regimen according to RECIST criteria was 60%, including complete response in 0 patients, partial response in 3, and stable disease in 2. Two patients had malignant ascites at the start of this salvage therapy, and in both of them

Hisato Igarashi, MD, PhD
Department of Medicine and Bioregulatory Science
Graduate School of Medical Science, Kyushu University
3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 (Japan)
Tel. +81 92 642 5285, E-Mail igaras@med.kyushu-u.ac.jp

Case Rep Oncol 2011;4:534–541
DOI: 10.1159/000334704
Published online: November 22, 2011

ISSN 1662–6575
www.karger.com/cro

the ascites and clinical complaints improved. Grade 3 and 4 hematological adverse events were observed in 2 patients and 1 patient, respectively.
Conclusion: Salvage paclitaxel-based therapy could be beneficial to advanced pancreatic cancer patients who maintain good performance status after several chemotherapy failures.

Introduction

Pancreatic cancer is the fifth highest cause of cancer-related death in Japan [1]. Because pancreatic cancer is often diagnosed late in the course of the disease with metastatic spread, the development of effective medical therapy is needed. Gemcitabine (GEM) is a gold-standard chemotherapy agent for advanced pancreatic cancer; it shows a more significant improvement of clinical symptoms and a modest survival benefit as compared with 5-fluorouracil (5-FU) [2]. With the malignant character of advanced pancreatic cancer, most patients show disease progression despite treatment with GEM-based chemotherapy. The median progression-free survival (PFS) and median overall survival (MST) have been reported as 2–4 and 4.9–8.2 months, respectively [3].

Second-line chemotherapy after GEM treatment failure may be beneficial for patients with good performance status (PS) and tolerability of additional chemotherapy. Although a number of phase II and III second-line chemotherapy trials have been completed, sufficient evidence for efficacy has not been obtained [2]. In Japan, S-1, an oral agent containing a mixture of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxalate, has been approved for pancreatic cancer treatment [4]. Furthermore, the results of several phase II studies using S-1 as a second-line chemotherapeutic regimen after GEM failure have been reported [3, 5].

Paclitaxel is a semisynthetic taxane that interferes with mitotic spindles, inhibits the depolymerization of microtubules and blocks the mitotic cell cycle [6]. Recently, 3 reports of second-line chemotherapy using paclitaxel for advanced pancreatic cancer refractory to GEM or GEM-based regimens have been published, 2 with weekly administration of paclitaxel [7, 8], and 1 with a 5-FU/paclitaxel combination [9].

In this study, we treated 5 patients with advanced pancreatic cancer with paclitaxel-containing regimens as second-, third-, or fourth-line chemotherapy after various therapies, including GEM-based regimens, S-1 regimens, and chemoradiation. We retrospectively analyzed the efficacy and adverse events, and evaluated these paclitaxel-containing regimens.

Patients and Methods

This study included 5 patients with inoperable advanced pancreatic cancer who underwent paclitaxel therapy at our hospital or a related institution between November 2005 and January 2010. All patients had adenocarcinoma diagnosed by biopsy or cytology. They had been previously treated with various therapies as described below, and those patients in whom cancer was exacerbated or in whom the tumor tended to increase and tumor marker levels were elevated according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria) underwent paclitaxel-based therapy. Informed written consent was obtained. Eastern Cooperative Oncology Group PS of the patients ranged from 0 to 2, and their bone marrow, hepatic and renal functions were good.

Case Rep Oncol 2011;4:534–541
DOI: 10.1159/000334704
Published online: November 22, 2011

ISSN 1662–6575
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Previously, the patients had undergone GEM therapy, S-1 therapy, chemoradiotherapy (CRT), a combination of GEM and tegafur-uracil (UFT), and/or a combination of GEM and S-1 according to their symptoms. The patients who could not continue or were refractory to these therapies received paclitaxel-based chemotherapy. The therapeutic protocols were as follows: (1) GEM therapy: GEM (1,000 mg/m^2) was administered on days 1, 8, and 15, followed by a 1-week rest; this was defined as one course of treatment. (2) S-1 therapy: S-1 [80 mg/(m^2·day)] was administered for 4 weeks followed by a 2-week rest; this was defined as one course of treatment [4]. Alternatively, S-1 [80 mg/(m^2·day)] was administered for 2 weeks followed by a 1-week rest; repeated every 21 days. (3) GEM/UFT combination (GF) therapy: GEM (1,000 mg/m^2) was administered on days 1 and 8, and UFT [400 mg/(m^2·day)] was administered for 2 weeks (days 1–14), and both drugs were discontinued in week 3; this was defined as one course of treatment [10]. (4) GEM/S-1 combination (GS) therapy: GEM (1,000 mg/m^2) was administered on days 1 and 8, and S-1 [80 mg/(m^2·day)] was administered for 2 weeks (days 1–14), followed by a 1-week rest; this was defined as one course of treatment [11]. (5) CRT: as reported by our department, 2.0 Gy/day was administered for 5 days, for a total of 40–50 Gy. GEM (40 mg/m^2) was administered twice a week as a sensitizer [12]. The above-mentioned regimens were the basic protocols, and the dosages and schedules were adjusted according to the development of adverse reactions.

Paclitaxel/cisplatin/S-1 combination (PCS): Paclitaxel (60 mg/m^2), cisplatin (7 mg/m^2), and S-1 [60 mg/(m^2·day)] were administered on day 1, days 1 and 5, and days 1–5, respectively, for 3 weeks followed by a 1-week rest; this was defined as one course of treatment.

Tumor response was defined according to the RECIST criteria. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Results

Table 1 shows patient characteristics. The median age at the first visit was 65 years (range 41–70). The female-to-male ratio was 2:3. The Union for International Cancer Control (UICC) classifications at the first visit were stage III in 2 patients and stage IV in 3 patients. Symptoms at diagnosis included abdominal pain and jaundice in 1 patient, abdominal pain in 2 patients, ileus in 1 patient, and weight loss and diabetes exacerbation in 1 patient. The median period from initial chemotherapy to the start of paclitaxel therapy was 13.1 months (range 6.5–19.5). Table 2 shows the prior therapies of the 5 patients; all 5 patients received multiple prior therapies. PS at the initiation of PCS was 0 in 2 patients, 1 in 2 patients and 2 in 1 patient. Reasons for starting PCS were as follows: development of malignant ascites in 2 patients, appearance of distant metastases to the liver in 2 patients and progression of primary site in 1 patient (table 3). The disease control rate of paclitaxel therapy according to the RECIST criteria was 60%, including complete response in 0 patients, partial response (PR) in 3 patients, and stable disease in 2 patients. Malignant ascites improved in the 2 affected patients, and subjective symptoms, such as abdominal pain, improved in all 3 affected patients. The median survival after the start of PCS was 10.7 months (range 9.1–27.6), and the MST from the start of initial chemotherapy was 25.2 months (range 11.6–47.1). All subjects developed alopecia and myelosuppression of grade 2 (2 patients), grade 3 (2 patients), or grade 4 (1 patient) as adverse reactions.

Case Report

Case 1 was a 70-year-old man with a history of alcoholic liver cirrhosis. A tumor 3.4 cm in diameter, associated with invasion of the superior mesenteric artery and found in the pancreatic head, was determined as UICC stage III pancreatic cancer (fig. 1a). GF therapy was started, but the size of the tumor increased; therefore, GF therapy was replaced with GS therapy. However, grade 3 thrombocytopenia developed, so GEM was administered every other week. Due to thrombocytopenia, GEM could not be continued; therefore, it was replaced with S-1 therapy 8 months after the start of

Case Rep Oncol 2011;4:534–541
DOI: 10.1159/000334704
Published online: November 22, 2011

ISSN 1662–6575
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initial chemotherapy (fig. 1b). Thereafter, abdominal pain gradually increased, which required a higher dose of narcotic. The tumor size further increased, and 10 months after the start of initial chemotherapy, ascites developed (fig. 1c). Cytodiagnosis of ascites revealed adenocarcinoma cells; therefore, malignant ascites was diagnosed. Ascites improved and tumor size decreased after 1 course of PCS therapy, and the dose of narcotic was decreased by 20% of the maximal dose. An abdominal CT 6 months after the start of PCS (fig. 1d) showed complete resolution of ascites and PR of the tumor. The patient died 19.2 months after the start of PCS, which was 30.1 months after the start of initial chemotherapy.

Discussion

For more than 10 years, GEM has been the standard chemotherapy for advanced pancreatic cancer; however, the response rate is low, and chemoresistance occurs early. There have been very few randomized trials in GEM-refractory patients, and there is no widely accepted standard of care [13]. To obtain a better prognosis for advanced pancreatic cancer, effective second-line chemotherapy should be developed for patients with good PS after GEM failure.

In Japan, S-1 has been commonly used as second-line chemotherapy for patients with advanced pancreatic cancer after GEM failure. Morizane et al. [5] performed a phase II study of this agent in a second-line setting in patients with GEM-refractory metastatic pancreatic cancer. The response rate was 16%, the median PFS and MST were 2.0 and 4.5 months, respectively, and the 1-year survival rate was 14%. Furthermore, Todaka et al. [3] reported a retrospective study of 84 patients who received S-1 monotherapy as second-line treatment after GEM failure. Fifty-two patients were selected for the analysis, and the median PFS and MST were 2.1 and 5.8 months, respectively.

There have been several reports of paclitaxel as a second-line chemotherapeutic agent in patients with advanced pancreatic cancer refractory to GEM or GEM-based regimens. Oettle et al. [14] reported that weekly administration of paclitaxel at 50 mg/m^2, increasing up to 85 mg/m^2, in advanced pancreatic cancer patients after pre-treatment with GEM and/or in combination with 5-FU and folinic acid, was effective with a low toxicity profile. In this study, the disease control rate was 33.3%, including complete response in 1 patient, and the MST was 17.5 weeks [14]. Recently, Kim et al. [9] reported a phase II study of another second-line paclitaxel-containing regimen in 28 pancreatic cancer patients after GEM-based regimen failure. On days 1, 2 and 3, 5-FU (1,000 mg/m^2) was infused, and on day 1, paclitaxel (175 mg/m^2) was administered every 4 weeks. Of the 20 evaluated patients, 10% obtained PR, 20% had stable disease, and the MST was 7.6 months. Maeda et al. [8] presented results from a retrospective study of weekly administration of paclitaxel (80 mg/m^2 a week for 3 weeks followed by a 1-week rest) as second- or third-line treatment in patients with GEM-based regimen-refractory pancreatic cancer. Thirty patients were retrospectively analyzed, and the MST was 6.7 months. The response rate was 10% and the disease control rate was 46.7%. The authors found a significant correlation between the disease control rate and tumor marker decline within 2 months of paclitaxel treatment ($p = 0.01$) [8].

In this study, we evaluated 5 patients with advanced inoperable pancreatic cancer after various therapies such as chemotherapy using GEM, GF therapy, GS therapy, and S-1 monotherapy, or CRT. The median time from initial chemotherapy to the start of

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DOI: 10.1159/000334704
Published online: November 22, 2011

ISSN 1662–6575
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paclitaxel therapy was 10.1 months. The idea for using a PCS regimen, a weekly paclitaxel regimen combined with low-dose FP (5-FU/cisplatin), came from a previous case series in Japan [15]. The background of each patient in this study differed at the initiation of paclitaxel therapy, the number of patients was small, and it was just a retrospective evaluation; therefore, the actual effectiveness of this regimen requires further investigation. However, it is possible that PCS could be a salvage chemotherapy candidate for patients with advanced inoperable pancreatic cancer with good PS after pretreatment failure.

The prognosis of patients with advanced pancreatic cancer refractory to GEM is poor due to metastases to the liver, lung, and bone, or peritoneal dissemination. Peritoneal dissemination causes massive ascites resulting in abdominal pain, fullness, constipation and/or malnutrition, and these patients' quality of life becomes poor. Recently, Shukuya et al. [7] reported the effectiveness of weekly paclitaxel after GEM failure in pancreatic cancer with malignant ascites in a retrospective study. They evaluated 23 patients who received weekly paclitaxel (80 mg/m^2 administered on days 1, 8, and 15 every 4 weeks); ascites decreased in 30% of the patients, and the ascites control rate was 61% [7]. In our study, 2 patients harbored malignant ascites at the initiation of paclitaxel therapy, and ascites and clinical complaints improved in both of them. Therefore, a chemotherapeutic regimen including paclitaxel after GEM failure could also provide a clinical benefit for pancreatic cancer patients with peritoneal dissemination.

Conclusion

In conclusion, for patients with advanced pancreatic cancer after several chemotherapy failures, including GEM, salvage paclitaxel-based therapy could be a candidate for second-, third-, or fourth-line chemotherapy, especially in patients maintaining good PS. However, a more detailed randomized study is required for further evaluation.

Disclosure Statement

The authors have no potential conflicts of interest.

Case Rep Oncol 2011;4:534–541
DOI: 10.1159/000334704
Published online: November 22, 2011

ISSN 1662–6575
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Table 1. Patient profiles at the diagnosis of advanced pancreatic cancer

Case No.	Age years	Sex	UICC stage	Symptom at diagnosis
1	70	M	III	Abdominal pain
2	65	M	IV	Abdominal pain, jaundice
3	41	M	III	Ileus
4	68	F	IV	Weight loss, diabetes exacerbation
5	65	F	IV	Abdominal pain

Table 2. Prior therapy regimens

Case No.	Contents of prior therapy
1	GF, GS, S-1
2	GF, GS, CRT, S-1
3	Bypass surgery, GEM, GS, CRT, S-1
4	GF, GS
5	GEM, GS

Table 3. Patient profiles at the start of paclitaxel therapy and results

Case No.	Time from initial chemotherapy to start of PCS therapy, months	PS at PCS therapy	Reason for introducing PCS therapy	Survival after initiation of PCS, months
1	10.9	1	Appearance of malignant ascites	19.2
2	13.1	1	Appearance of distant metastases	9.1
3	19.5	0	Progression of primary site	27.6
4	14.5	0	Appearance of distant metastases	10.7
5	6.5	2	Appearance of malignant ascites	5.1

Case Rep Oncol 2011;4:534–541
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Published online:
November 22, 2011

ISSN 1662–6575
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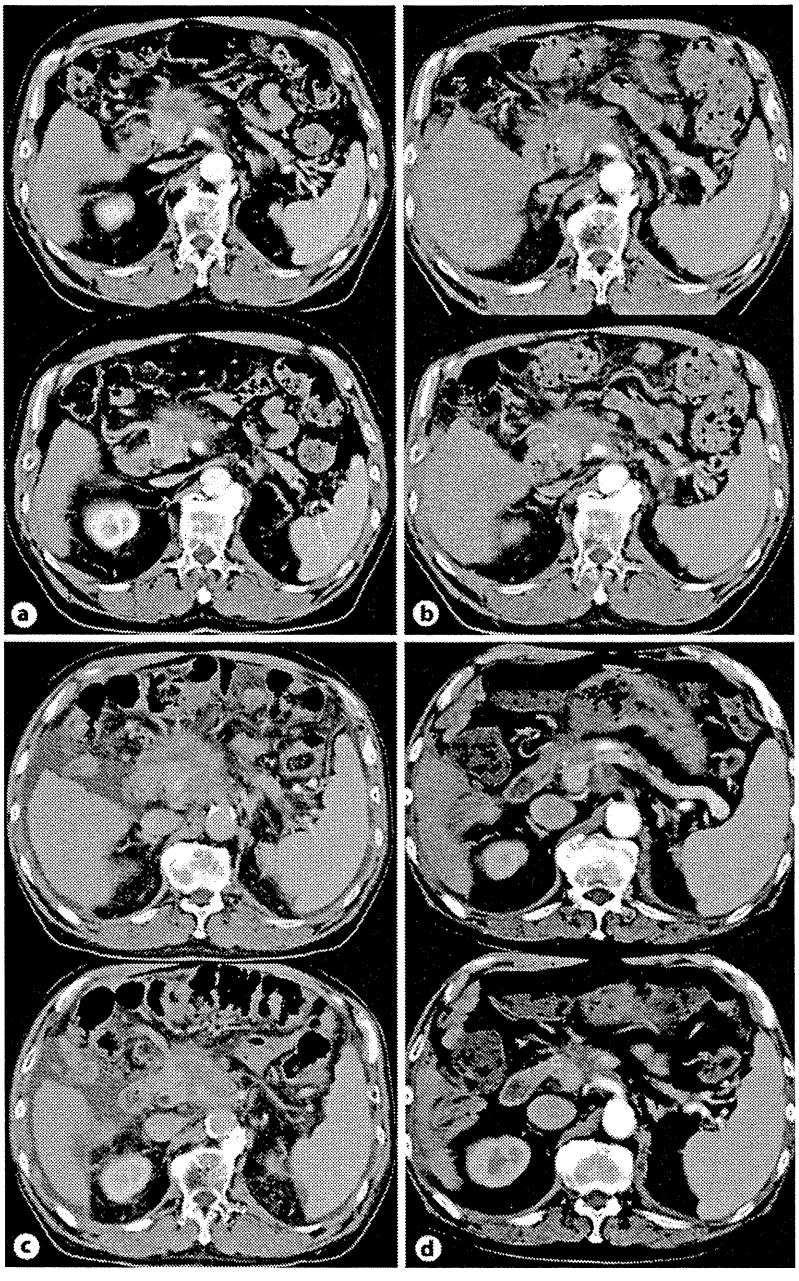

Fig. 1. Abdominal CT findings of case 1. **a** CT at admission. **b** CT 8 months after initial treatment. **c** CT 10 months after initial treatment. **d** CT 6 months after introduction of PCS regimen.

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DOI: 10.1159/000334704
Published online: November 22, 2011

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International Journal of
Radiation Oncology
biology • physics

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Clinical Investigation

Concurrent Radiotherapy and Gemcitabine for Unresectable Pancreatic Adenocarcinoma: Impact of Adjuvant Chemotherapy on Survival

Kazuhiko Ogawa, M.D.,* Yoshinori Ito, M.D.,† Naoki Hirokawa, M.D.,‡ Keiko Shibuya, M.D.,¶ Masaki Kokubo, M.D.,§ Etsuyo Ogo, M.D., Hitoshi Shibuya, M.D.,†† Tsutomu Saito, M.D.,‡‡ Hiroshi Onishi, M.D.,¶¶ Katsuyuki Karasawa, M.D.,§§ Kenji Nemoto, M.D.,*** Yasumasa Nishimura, M.D.†††, and the Japanese Radiation Oncology Study Group Working Subgroup of Gastrointestinal Cancers**

**Department of Radiology, University of the Ryukyus, Okinawa, Japan; †Department of Radiation Oncology, National Cancer Center, Tokyo, Japan; ‡Department of Radiology, Sapporo Medical University, Sapporo, Japan; ¶Department of Radiation Oncology and Image-Applied Therapy, Kyoto University, Kyoto, Japan; §Department of Radiation Oncology, Institute of Biomedical Research and Innovation Hospital, Kobe, Japan; **Department of Radiation Oncology, Kurume University, Kurume, Japan; ††Department of Radiology Tokyo Medical and Dental University, Tokyo, Japan; ‡‡Department of Radiation Oncology, Nihon University Itabashi Hospital, Tokyo, Japan; ¶¶Department of Radiology, Yamanashi University, Yamanashi, Japan; §§Department of Radiation Oncology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; ***Department of Radiation Oncology, Yamagata University, Yamagata, Japan; and †††Department of Radiation Oncology, Kinki University School of Medicine, Osaka, Japan*

Received Apr 5, 2011, and in revised form May 25, 2011. Accepted for publication Jul 1, 2011

Summary

This retrospective study looked at patients with unresectable pancreatic cancer treated with different combinations of chemotherapy and radiation. When concurrent chemo-radiotherapy using gemcitabine was used, a relatively favorable local control rate was seen. When adjuvant chemotherapy was given,

Purpose: To retrospectively analyze results of concurrent chemoradiotherapy (CCRT) using gemcitabine (GEM) for unresectable pancreatic adenocarcinoma.

Methods and Materials: Records of 108 patients treated with concurrent external beam radiotherapy (EBRT) and GEM were reviewed. The median dose of EBRT in all 108 patients was 50.4 Gy (range, 3.6–60.8 Gy), usually administered in conventional fractionations (1.8–2 Gy/day). During radiotherapy, most patients received GEM at a dosage of 250 to 350 mg/m^2 intravenously weekly for approximately 6 weeks. After CCRT, 59 patients (54.6%) were treated with adjuvant chemotherapy (AC), mainly with GEM. The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months).

Results: Initial responses after CCRT for 85 patients were partial response: 26 patients, no change: 51 patients and progressive disease: 8 patients. Local progression was observed in 35 patients (32.4%), and the 2-year local control (LC) rate in all patients was 41.9%. Patients treated with total doses of 50 Gy or more had significantly more favorable LC rates (2-year LC rate, 42.9%) than patients treated with total doses of less than 50 Gy (2-year LC rate,

Reprint requests to: Dr. Kazuhiko Ogawa, Department of Radiology, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa, 903-0215, Japan. Tel: 81-98-895-3331 (ext. 2401); Fax: 81-98-895-1420; E-mail: kogawa@med.u-ryukyu.ac.jp

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–7, 2011
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.07.013

a small survival benefit became evident. Adjustments in the sequencing of chemotherapy and radiation thus have the potential to improve outcomes.

29.6%). Regional lymph node recurrence was found in only 1 patient, and none of the 57 patients with clinical N0 disease had regional lymph node recurrence. The 2-year overall survival (OS) rate and the median survival time in all patients were 23.5% and 11.6 months, respectively. Patients treated with AC had significantly more favorable OS rates (2-year OS, 31.8%) than those treated without AC (2-year OS, 12.4%; $p < 0.0001$). On multivariate analysis, AC use and clinical T stage were significant prognostic factors for OS.

Conclusions: CCRT using GEM yields a relatively favorable LC rate for unresectable pancreatic adenocarcinoma, and CCRT with AC conferred a survival benefit compared to CCRT without AC.. © 2011 Elsevier Inc.

Keywords: Chemotherapy, Gemcitabine, Pancreatic neoplasms, Radiotherapy, Unresectable

Introduction

Pancreatic cancer is one of the leading causes of cancer death worldwide. The prognosis for patients with this disease remains extremely poor, with a 5-year survival rate after diagnosis of less than 5% (1, 2). Most patients with pancreatic cancer already have advanced disease at the time of diagnosis, and among patients with unresectable pancreatic cancer, nearly half of patients have advanced but localized disease (2).

In the 1980s, the Gastrointestinal Tumor Study Group reported the survival benefit of 5-fluorourcil (5-FU)-based concurrent chemoradiotherapy (CCRT) over that of external beam radiotherapy (EBRT) alone in patients with unresectable pancreatic cancer (3). Until recently, CCRT has been the standard approach to treating surgically unresectable, localized disease. More recently, therapy using the drug gemcitabine (GEM), a nucleoside analogue, has been reported to confer marginally superior clinical benefit and survival compared with that with 5-FU (4). GEM has also been shown to be a potent radiosensitizer in pancreatic cancer (5). Therefore, concurrent radiotherapy and GEM may be a promising strategy for treating unresectable localized pancreatic cancer. However, optimal management of concurrent EBRT and GEM for unresectable disease has not been fully investigated.

In the current study, we reviewed a retrospective and multi-institutional series of 108 patients with nonmetastatic unresectable pancreatic cancer, who were treated with concurrent radiotherapy using GEM, and evaluated the efficacy and safety of this treatment for these tumors.

Methods and Materials

The Japanese Radiation Oncology Study Group (JROSG) conducted a nationwide questionnaire survey of patients with nonmetastatic pancreatic adenocarcinoma who were treated with radiotherapy. The questionnaire elicited detailed information regarding patient characteristics, treatment characteristics, and outcomes of treatments. Details of the JROSG survey have been described elsewhere (6–8). Briefly, 34 radiation oncology centers belonging to the JROSG agreed to participate in this survey, and detailed information for 870 patients was accumulated. Of these patients, 223 patients with unresectable disease were treated with concurrent EBRT and GEM. Histology finding for 108 patients was adenocarcinoma; 3 patients had other histological findings, such as anaplastic carcinoma and undifferentiated carcinoma; and 112 patients had no histological information. These last 115 patients were excluded from this study, and the remaining 108 patients with histological diagnosis of adenocarcinoma were the subjects of the current study. Their tumors were judged to be unresectable by the respective physicians at each institution. Of these 108 patients, there were 3 patients with inoperable cancer, who were not fit for surgery, and the remaining 105 patients had unresectable tumors at presentation.

Patient and treatment characteristics for all 108 patients are shown in Table 1. The median age of patients was 63 years old (range, 40–83 years old), and the Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranged from 0 to 3 (median, 1). We used the tumor staging system devised by the Union Internationale Contre le Cancer (9). The median maximum tumor size was 3.9 cm (range, 1.4–10.0 cm), and the median serum concentration of carbohydrate antigen 19-9 (CA19-9) was 511 U/mL (range, 0–57,300 U/mL). Total doses of EBRT ranged from 3.6 to 60.8 Gy (median, 50.4 Gy), with a single fraction of 1.8 to 2 Gy given 5 days per week in most patients. On the other hand, 11 patients (10.2%) were treated with a single fraction of 2.2 to 2.5 Gy.

Chemotherapy schedules are described in Table 2. During radiotherapy, 8 patients received a dosage of 1,000 mg/m^2 GEM weekly for 3 weeks with a 1-week rest period, depending on their response and toxicity (using the standard dosage of GEM). The remaining 100 patients received GEM at a dosage of 250 to 350 mg/m^2 intravenously weekly during radiotherapy for approximately 6 weeks (low-dose GEM). After radiotherapy, 59 of 108 patients (54.6%) were treated with adjuvant chemotherapy (AC). Fifty-three of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at 1,000 mg/m^2 weekly for 3 weeks with a 1-week rest period, until disease progression or unacceptable toxicity was reached. Six patients received intravenous bolus infusions of 300 to 500 mg/m^2 5-FU, until disease progression or unacceptable toxicity was reached. For 5 patients, a combination compound of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium (S-1) was administered orally, and S-1 doses ranged from 50 to 80 mg/m^2.

In the current study, there were no definitive treatment policies for pancreatic cancer during the survey period; thus, treatment was determined by the respective physicians at each institution. We assigned 108 patients to two groups (patients treated with AC and those without AC treatment) and determined whether the AC influenced patient characteristics, such as age, tumor size, and clinical stage. There were no significant differences in age, gender, tumor site, tumor size, or clinical T stage and clinical N stage, except for CA19-9 levels, which varied according to the AC used (data not shown). Concerning PS, there were no significant differences according to the AC used, and 56 of 58 patients with

Table 1 Patient and disease characteristics

Characteristic	No. of patients	% of total
Age (median, 63 years old)		
<70	84	77.8
≥70	24	22.2
Gender		
Female	50	46.3
Male	58	53.7
Primary site		
Head	55	50.9
Body	48	44.4
Tail	4	3.7
Unknown	1	0.9
Maximum tumor size (median, 3.9 cm)		
<4.0 cm	48	44.4
≥4.0 cm	54	50.0
Unknown	6	5.6
ECOG performance status scale		
0	28	25.9
1	70	64.8
2	5	4.6
3	1	0.9
Unknown	4	3.7
CA19-9 (U/ml) (median, 248.2 U/ml)		
<1,000	56	51.9
≥1,000	43	39.8
Unknown	9	8.3
Clinical T stage (UICC 2002)		
2	3	2.8
3	15	13.9
4	90	83.3
Clinical N stage (UICC 2002)		
0	57	52.8
1	49	45.4
Unknown	2	1.8
EBRT total radiation dose (Gy) (median, 50.4 Gy)		
<40	6	5.6
40≤ to <50	9	8.3
50≤ to <60	89	86.4
≥60	4	3.7
Dose per fraction (Gy)		
1.8–2	97	89.8
2.2–2.5	11	10.2
Radiation field		
Primary plus LN	65	60.2
Primary only	43	39.8
CT-based treatment planning		
Yes	106	98.1
No	2	1.9
Conformal therapy		
Yes	91	84.3
No	17	15.7
GEM dose during EBRT		
Low dose (250–350 mg/m^2/week)	100	92.6
Standard dose (1,000 mg/m^2/week)*	8	7.4
Adjuvant chemotherapy use		
Yes	59	54.6
No	49	45.4

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CT = computed tomography; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; UICC = Union Internationale Contre le Cancer.

* Usually administered weekly for 3 weeks with a 1-week rest period.

AC therapy (96.6%) and 42 of 46 patients without AC (91.3%) had PS of 0 to 1 ($p = 0.2543$).

The median follow-up for all 108 patients was 11.0 months (range, 0.4–37.9 months). In the current study, local failure was defined as apparent primary tumor progression detected by computed tomography (CT) scans after CCRT. Assessment of initial response by CCRT was based on CT scans that were obtained within 3 months after CCRT. In the current study, complete response was defined as the complete disappearance of all visible tumor, and partial response (PR) was defined as a reduction of 50% to 99% in the product of the perpendicular diameters of the contrast-enhancing tumor. Progressive disease was defined as an increase of more than 25% in the product of the perpendicular diameters of the contrast-enhancing tumor or any new tumor seen on CT scans, and all other situations were defined as no change (NC). Overall survival (OS), progression-free survival (PFS), and local control (LC) rates were calculated actuarially according to the Kaplan-Meier method (10) and were measured starting from the day of initial treatment. Differences between groups were estimated using the chi-square test, Student's *t* test, and the generalized Wilcoxon test (11). Multivariate analysis was performed using the Cox regression model (12). A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using SPSS software (version 11.0; SPSS, Inc., Chicago, IL). Acute and late adverse effects were graded in accordance with the National Cancer Institute-Common Terminology Criteria (NCI-CTC) version 3.0.

Results

Data regarding initial responses after CCRT were available for 85 patients (Table 3). Of the 3 patients with inoperable tumors, 1 patient had a response of NC, and there was no information regarding tumor responses for the remaining 2 patients. At the time of this analysis, 95 patients (88.0%) had disease recurrence (local only in 29 patients; regional lymph nodes only in 1 patient; liver only in 24 patients; peritoneum only in 27 patients; other distant metastases, such as at bone or lung, only in 4 patients; and multiple sites in 10 patients). Among the 10 patients with multiple recurrences, 6 patients had simultaneous local recurrences. Therefore, local recurrences occurred in a total of 35 patients (32.4%). The 2-year actuarial LC rate for all 108 patients was 41.9%. Figure 1 shows the LC curves according to the total radiation dose. Patients treated with a total dose of 50 Gy or more had a significantly more favorable LC rate (2-year LC rate, 42.9%)

Table 2 Agents and chemotherapy schedules

Drug	No. of patients receiving a drug*	
	During RT	After RT
GEM	108	53†
5-FU	–	6†
S-1	–	5†

Abbreviations: 5-FU = 5-fluorouracil; GEM = gemcitabine; RT = radiotherapy; S-1 = combination of tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium.

* A total of 108 patients (100%) received a drug during RT, and 59 patients (54.6%) received a drug after undergoing RT.

† When combination chemotherapy was used, each drug in the combination was counted.

than patients treated with a total dose of less than 50 Gy (2-year LC rate, 29.6%; $p = 0.0292$). Concerning the regional lymph node recurrence, all 57 patients with clinical stage N0 disease had no regional lymph node recurrence, and only 1 of 49 patients with clinical N1 disease had regional lymph node recurrence.

Eighty-seven of 108 patients (84.5%) died during the period of this analysis. Of these 87 patients, 85 patients died of pancreatic cancer, and the remaining 2 patients died without any sign of clinical recurrence (both of these patients died of intercurrent disease). The 2-year actuarial PFS rate and the median time to progression for all 108 patients were 8.2% and 6.0 months, respectively. Concerning AC use, the 2-year PFS rates for patients treated with AC (10.8%) were significantly higher than those for patients treated without AC (7.8%; $p = 0.0187$). Univariate analysis showed that AC used, clinical T stage, and CA19-9 levels had a significant impact on PFS outcomes, and multivariate analysis showed that AC use and clinical T stage were significant prognostic factors (data not shown).

The 2-year actuarial OS rate and median survival time (MST) in all 108 patients were 23.5% and 11.6 months, respectively. Concerning AC use, 2-year OS rates for patients treated with AC (31.8%) were significantly higher than those for patients treated without AC (12.4%; $p = 0.0022$) (Fig. 2). Univariate analysis showed that AC use, clinical T stage, and CA19-9 levels had a significant impact on OS outcomes (Table 4). However, when we excluded patients with hyperbilirubinemia (more than 2 mg/dl), CA19-9 concentration was not a significant factor for OS, and the 2-year OS rate was 27.4% in patients with CA19-9 concentrations $<1{,}000$ U/ml and 24.8% in patients with CA19-9 concentrations $\geq 1{,}000$ U/ml ($p = 0.7104$). Multivariate analysis showed that the use of AC (relative risk, 2.475; 95% confidence interval [CI], 1.564–3.917; $p < 0.001$) and clinical T stage (relative risk, 0.374; 95% CI, 0.202–0.692; $p = 0.002$) were significant prognostic factors. Other factors, such as CA19-9 level, tumor size, and total radiation dose did not influence OS outcomes.

In the current study, there were significant differences in the frequencies of AC use according to the initial response ($p < 0.0001$) (Table 3), and patients with favorable responses had more frequently received AC than those with unfavorable responses. Therefore, we conducted subgroup analyses of OS according to initial responses. Concerning patients with an NC response, there was a significant survival benefit with AC use. On the other hand, patients with PR and those with progressive disease response had no significant survival benefit with AC use (Table 3).

Concerning adverse acute effects, 46 patients (42.6%) had Grade 3 to 4 leukopenia, 38 patients (35.2%) had Grade 3 to 4 appetite loss, and 16 patients (14.8%) had Grade 3 to 4 vomiting. Late adverse effects of Grade 3 or higher were observed in 1 patient (1.0%; Grade 3 gastrointestinal bleeding). Total radiation dose given to this patient was 50 Gy.

Discussion

The current study indicated that CCRT using GEM yields noticeably favorable LC for unresectable pancreatic cancer, with a 2-year LC rate of 41.9%. Concerning initial responses of the 85 available patients, 27 patients (31.8%) had PR, 50 patients (58.8%) had NC response, and only 8 patients (9.4%) had progressive disease response. Several other reports also have indicated the efficacy of EBRT plus GEM therapy for LC (13, 14). Mattiucci *et al.* (13) treated 40 patients with unresectable pancreatic cancer with CCRT using GEM (1,000 mg/m2), and the 2-year LC rate was 39.6% (13). Yamazaki *et al.* (14) indicated that locoregional progression was observed in only 5 of 13 patients with unresectable tumors treated with EBRT plus GEM (14). These results indicate that CCRT using GEM produces relatively favorable LC for patients with unresectable tumors.

Although the efficacy of CCRT using GEM produces relatively favorable LC, optimal use of EBRT, that is, factors such as total radiation doses and radiation field, has not been clarified. National Comprehensive Cancer Network (NCCN) guidelines have recommended that for primary definitive chemoradiotherapy, total doses of 50 to 60 Gy (1.8–2.0 Gy/day) should be administered (15). Several investigators report using total doses of approximately 50 Gy for these tumors when GEM is combined with radiotherapy (13, 14, 16). In the current study, patients treated with total doses of 50 Gy or more had a significantly favorable LC rate (2-year LC rate,

Table 3 Comparisons of initial responses and overall survival according to AC use

Initial response	Total no. of patients	No. of patients			2-year OS rate (%)		
		AC (+)	AC (–)	*p* value	AC (+)	AC (–)	*p* value*
PR	26	25	1	<0.0001	25.3	0	0.3560
NC	51	24	27		34.3	12.1	**0.0251**
PD	8	2	6		0	0	0.7423
Unknown	23	8	15		–	–	–
Total	108	59	49		–	–	–

Abbreviations: AC (+) = with adjuvant chemotherapy; AC (–) = without adjuvant chemotherapy; NC = no change; OS = overall survival; PD = progressive disease; PR = partial response.

* *p* value in boldface type indicates significant diffrence.

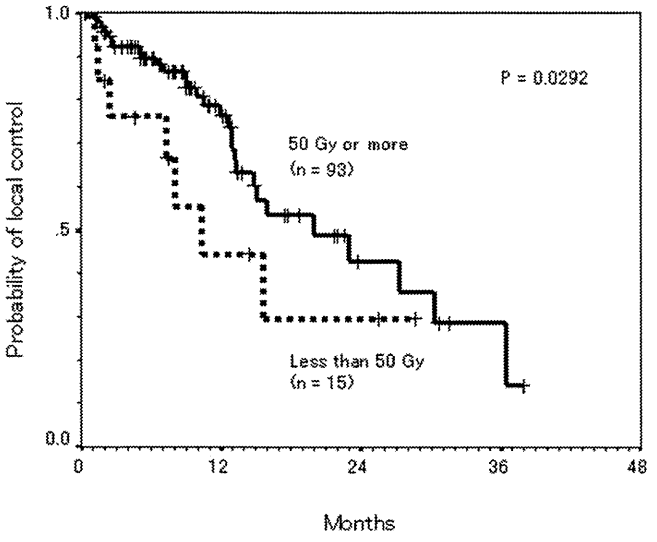

Fig.1. LC curves derived according to the total radiation dose in patients with unresectable pancreatic cancer are shown.

42.9%) compared to patients treated with total doses of less than 50 Gy (2-year LC rate, 29.6%). These results suggest that doses of 50 Gy or more are appropriate for these tumors.

Concerning radiation fields, NCCN practice guidelines have also recommended that when 5-FU-based chemoradiotherapy is used, treatment volumes should include the primary tumor location and regional lymph nodes (15). When GEM is added, some authors have used the radiation field encompassing the primary tumor along with regional lymph nodes for treating these tumors (13, 16). Recently, other investigators have tried to irradiate only the primary tumor site in order to reduce radiation volume, especially to the intestine (14, 17). Murphy *et al.* (17) indicated that in conjunction with full-dose GEM, the use of conformal fields encompassing only the gross tumor volume (GTV) does not result in marginal failures. In the current study, regional lymph node recurrence was found in only 1 patient (0.9%), and none of the 57 patients with clinical N0 disease had regional lymph node

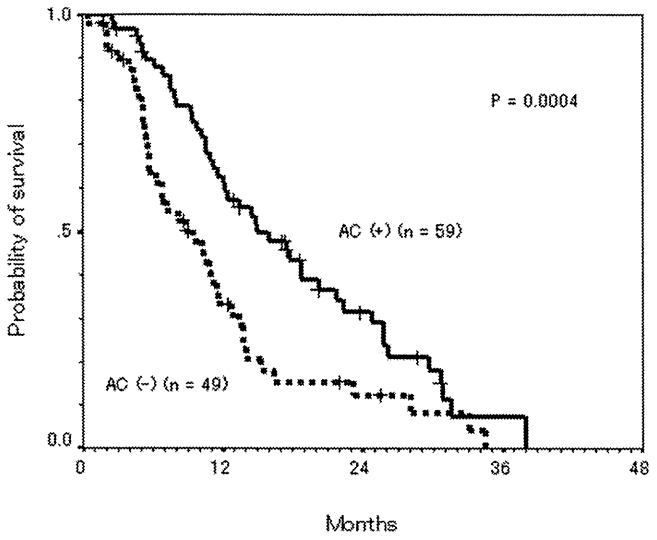

Fig.2. Actuarial OS curves according to administration of AC in patients with unresectable pancreatic cancer are shown.

recurrence. Therefore, when GEM is combined with radiation therapy, the treatment of choice may be to irradiate only the field of the primary tumor, especially for patients with stage N0 tumors. Further studies are required to confirm whether radiation only to the primary tumor field would be sufficient when CCRT with GEM is used.

When GEM is used as a single agent for treating patients with advanced cancer, the standard weekly dosage is approximately 1,000 mg/m^2, and this dosage is regarded as necessary to control occult distant metastases (4). Therefore, considering both the metastasis-prone and the radio-resistant nature of pancreatic cancer, CCRT using full-dose radiotherapy (50 Gy or more) and full-dosage GEM (1,000 mg/m^2 weekly) appears to produce the best outcome. Yamazaki *et al.* (14) indicated that when limited-field 50-Gy radiotherapy was applied, concurrent administration of 1,000 mg/m^2 GEM was safe for these patients. Murphy *et al.* (17) indicated that when conformal fields encompassing only the GTV were applied, CCRT with 1,000 mg/m^2 GEM was safe (17). On the other hand, several reports have pointed out that CCRT with 1,000 mg/m^2 GEM may be too toxic in clinical practice (18, 19). Crane *et al.* (18) indicated that patients receiving GEM-based CCRT developed significantly more severe acute toxicity during treatment than patients receiving 5-FU-based CCRT. Therefore, in order to reduce severe acute toxicity, several researchers conducted studies of CCRT using low-dose GEM (15, 18, 20–22). Shibuya *et al.* (19) conducted a phase II trial of radiotherapy (54 Gy in 28 fractions) with weekly administration of GEM (250 mg/m^2) and reported safe and promising results with a median survival time of 16.6 months and an acceptable level of toxicity (19). Huang *et al.* treated 55 patients with unresectable pancreatic cancer with concurrent 50.4-Gy EBRT and GEM, 400 mg/m^2 weekly, and found that this regimen can be safely administered (20). Further studies are required to investigate the optimal use of GEM for unresectable tumors.

Although CCRT using GEM provides relatively favorable LC rates, the role of this treatment in survival for these patients remains controversial. Several reports have indicated that when CCRT with GEM was administered, the 2-year OS rates and MSTs ranged from 11% to 25% and 10 to 16.6 months, respectively (13–20). In the current study, the 2-year actuarial OS rate and the median MST for all 108 patients were 23.5% and 11.6 months, respectively. These results indicate that despite the use of GEM, treatment outcomes are generally unfavorable for patients with these tumors. Therefore, it is important to investigate possible factors affecting the prognosis for patients treated with CCRT using GEM.

Several previous studies have suggested potential prognostic factors associated with PS and CA19-9 levels when CCRT is combined with GEM (20, 21). Recently, changes in CA19-9 levels after CCRT have emerged as a predictor for OS in patients with unresectable tumors (22). In the current study, we could not analyze changes in CA19-9 levels after CCRT due to limited information; however, it will be worthwhile to investigate more detailed analysis of CA19-9 levels in future studies. Our results indicated that AC use and clinical T stage were independent prognostic factors for OS. Several phase studies have used AC as a part of GEM-based CCRT (14, 20), and NCCN guideline recommend that (GEM-based) AC should be considered for patients with locally advanced disease who are receiving CCRT (15). Our results also indicated that CCRT with GEM-based AC conferred a survival benefit compared to CCRT without AC, and subgroup analysis indicated that patients with a response of NC

Table 4 Analysis of prognostic factors for OS in patients with unresectable pancreatic cancer treated with CCRT

Factor	No. of patients	Univariate analysis 2-y OS rate (%)	Univariate analysis p value[†]
Age (years)			
<70	84	22.8	0.9265
≥70	24	27.1	
Gender			
Female	50	28.1	0.7141
Male	58	18.7	
Primary site			
Head	55	30.3	0.8527
Body/tail	52	16.0	
Maximum tumor size			
<4.0 cm	48	31.0	0.6200
≥4.0 cm	54	23.0	
ECOG performance status scale			
0–1	98	21.6	0.7728
2–3	6	33.3	
CA19-9 level (U/ml)			
<1,000	56	24.5	**0.0135**
≥1,000	43	20.8	
Clinical T stage (UICC 2002)			
2–3	18	41.0	**0.0044**
4	90	20.0	
Clinical N stage (UICC 2002)			
0	57	22.9	0.1377
1	49	22.9	
EBRT dose (Gy)			
<50	15	17.8	0.1624
≥50	93	24.6	
Radiation field			
Primary plus LN	65	20.5	0.4224
Primary only	43	27.1	
GEM dose during EBRT			
Low dose (250–350 mg/m^2/week)	100	24.3	0.3199
Standard dose (1,000 mg/m^2/week*)	8	0	
Adjuvant chemotherapy used			
Yes	59	31.8	**0.0004**
No	49	12.4	

Abbreviations: CA19-9 = carbohydrate antigen 19-9; CCRT = concurrent chemoradiotherapy; EBRT = external beam radiotherapy; ECOG = Eastern Cooperative Oncology Group; GEM = gemcitabine; LN = lymph nodes; OS = overall survival; UICC = Union Internationale Contre le Cancer.

* Usually administered weekly for 3 weeks with a 1-week rest period.

† p values in boldface type indicate XXXX.

had significant clinical benefit with AC use. The possible reason for the clinical benefit of AC may be that AC delays the progression of residual primary tumor and/or development of distant metastasis. Therefore, from our results, AC should be administered after GEM-based CCRT, especially for patients with a response of NC. In the current study, 53 of 59 patients (89.8%) received GEM maintenance chemotherapy, usually given at 1,000 mg/m^2 weekly for 3 weeks with a 1-week rest period, and this regimen may be an attractive regimen for AC!! therapy. Further studies are required to investigate the optimal regimen of AC for these tumors.

Conclusions

In conclusion, our results indicated that CCRT using GEM had a relatively favorable LC rate for unresectable pancreatic adenocarcinoma. Our results also indicated that CCRT in addition to AC conferred survival benefit compared to CCRT without AC. Because CCRT using GEM can achieve relatively favorable LC and the addition of AC increased the OS, CCRT using GEM combined with AC appears to be an attractive strategy for treating patients with unresectable tumors. However, this study is a retrospective study with various treatment modalities, and further prospective studies are required to confirm our results.

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J Hepatobiliary Pancreat Sci (2011) 18:601–608
DOI 10.1007/s00534-011-0373-x

ORIGINAL ARTICLE

Predictive risk factors for clinically relevant pancreatic fistula analyzed in 1,239 patients with pancreaticoduodenectomy: multicenter data collection as a project study of pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

Manabu Kawai · Satoshi Kondo · Hiroki Yamaue · Keita Wada · Keiji Sano · Fuyuhiko Motoi · Michiaki Unno · Sohei Satoi · A-Hon Kwon · Takashi Hatori · Masakazu Yamamoto · Joe Matsumoto · Yoshiaki Murakami · Ryuichiro Doi · Masahiro Ito · Shuichi Miyakawa · Hiroyuki Shinchi · Shoji Natsugoe · Hisatoshi Nakagawara · Tetsuo Ohta · Tadahiro Takada

Published online: 14 April 2011

Abstract

Background/purpose It is important to predict the development of clinically relevant pancreatic fistula (grade B/C) in the early period after pancreaticoduodenectomy (PD). This study has been carried out as a project study of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) to evaluate the predictive factors associated with clinically relevant pancreatic fistula (grade B/C).

Method The data of 1,239 patients from 11 medical institutions who had undergone PD between July 2005 and June 2009 were retrospectively analyzed to review patient characteristics and perioperative and postoperative parameters.

Results A drain amylase level >4,000 IU/L on postoperative day (POD) 1 was proposed as the cut-off level to predict clinical relevant pancreatic fistula by the receiver operating characteristic (ROC) curve. The sensitivity, specificity, and accuracy of this cut-off level were 62.2, 89.0, and 84.8%, respectively. A multivariate logistic regression analysis revealed that male [odds ratio (OR) 1.7,

M. Kawai · H. Yamaue
Second Department of Surgery, School of Medicine, Wakayama Medical University, Wakayama, Japan

S. Kondo (✉) · J. Matsumoto
Department of Surgical Oncology, Hokkaido University Graduate School of Medicine, N15 W7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
e-mail: info@jshbps.jp

K. Wada · K. Sano
Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

F. Motoi · M. Unno
Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

S. Satoi · A.-H. Kwon
Department of Surgery, Kansai Medical University, Moriguchi, Osaka, Japan

T. Hatori · M. Yamamoto
Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, Tokyo, Japan

Y. Murakami
Division of Clinical Medical Science, Department of Surgery, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan

R. Doi
Department of Hepato-Biliary-Pancreatic Surgery and Transplantation, Kyoto University, Kyoto, Japan

M. Ito · S. Miyakawa
Department of Biliary Pancreatic Surgery, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

H. Shinchi · S. Natsugoe
Department of Surgical Oncology, Kagoshima University, Kagoshima, Kagoshima, Japan

H. Nakagawara · T. Ohta
Department of Gastroenterological Surgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Ishikawa, Japan

T. Takada
Japanese Society of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan

$P = 0.039$], intraoperative bleeding >1,000 ml (OR 2.5, $P = 0.001$), soft pancreas (OR 2.7, $P = 0.001$), and drain amylase level on POD 1 >4,000 IU/L (OR 8.6, $P < 0.001$) were the significant predictive factors for clinical pancreatic fistula.

Conclusion The four predictive risk factors identified here can provide useful information useful for tailoring postoperative management of clinically relevant pancreatic fistula (grade B/C).

Keywords Pancreatic fistula · Pancreaticoduodenectomy · Predictive risk factors · Drain amylase level

Introduction

In most patient series, the incidence of pancreatic fistula has been reported to vary between 5 and 20% after pancreaticoduodenectomy (PD) and to be associated with a high mortality rate [1–7]. In 2005, the International Study Group of Pancreatic Fistula (ISGPF) proposed a consensus definition and clinical grading of postoperative pancreatic fistula [8]. The most important issue currently being debated regarding pancreatic fistulas is whether it is possible to predict the development of clinically relevant pancreatic fistula (grade B/C) according to the ISGPF proposal in the early period after PD. The risk factors for developing a pancreatic fistula in previously reported studies may have been able to predict all grades of pancreatic fistulas but, unfortunately, could not predict the extent of severe clinically relevant pancreatic fistula (grade B/C) [9–13].

Molinari et al. [14] proposed that a drain amylase value on postoperative day (POD) 1 of >5,000 U/L was a significant predictive factor for the incidence of all grades of pancreatic fistula after PD. However, this amylase value could not distinguish clinically relevant pancreatic fistulas (grade B/C) from insignificant disease during the early postoperative period. Kawai et al. proposed that a combination of two predictive postoperative factors on POD 4, namely, serum albumin level ≤3.0 g/dL and leukocyte counts >9,800/mm^3, can predict the development of clinically relevant pancreatic fistula [15]. However, these two factors may also reflect serious systemic inflammation, such as that due to other intra-abdominal or respiratory complications. It therefore remains unclear which predictive risk factor(s) can be used to precisely distinguish the risk of clinically relevant pancreatic fistula (grade B/C) in the early postoperative period. In an attempt to clarify this situation, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHPBS) decided to perform a survey of high-volume PD centers in Japan to evaluate the predictive factors for the development of clinically relevant pancreatic fistula (grade B/C) in the early period after PD.

Methods

Patients

Data were collected by a questionnaire survey on all patients who underwent PD between July 2005 and June 2009 at one of 11 high-volume centers participating in the project study of the JSHPBS. The following patient characteristics and perioperative and postoperative parameters were reviewed: age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) class, preoperative laboratory data, such as hemoglobin, creatinine, HbA1c (glycated hemoglobin), albumin, total bilirubin, and amylase, preoperative biliary drainage, length of the surgery, intraoperative bleeding, blood transfusion, pancreatic texture (soft or hard), presence or absence of dilatation of the main pancreatic duct, histologic diagnosis (malignant or benign), and the serum C-reactive protein (CPR) and drain amylase levels on POD 1, 3, and 4. In total, data on 1,331 patients were collected from the 11 institutions. Of these 1,331 patients, 1,239 (749 men, 490 women; median age 67 years, age range 35–91 years) were enrolled in the study, and their data used for the analysis of the occurrence of pancreatic fistula using the ISGPF criteria.

Postoperative complications

The diagnosis of pancreatic fistula was made based on the ISGPF guidelines [8], namely, an amylase level in the drainage fluid on POD 3 of more than threefold the serum amylase level. Pancreatic fistulas were classified into three categories according to the ISGPF guidelines:

Grade A: Transient fistula. There is no clinical impact. The patient is fed orally and remains clinically well.
Grade B: Patients are usually supported with partial, total parenteral, or enteral nutrition. Antibiotics are usually used for signs of infections and a somatostatin analogue may also be required. Percutaneous drainage or persistent drainage for more than 3 weeks is usually required.
Grade C: A major change in clinical management or deviation from the normal clinical pathway. Total parenteral, enteral nutrition, antibiotics, or somatostatin analogue is often instituted in an intensive care unit (ICU) setting. Radiologic intervention or reoperation is required. The patients typically require an extended hospital stay with a major delay in hospital discharge and have life-threatening complications, such as intra-abdominal bleeding or sepsis. There is a real possibility of postoperative mortality[8].

Grades B + C were defined as "clinically relevant pancreatic fistula". Delayed gastric emptying (DGE) was