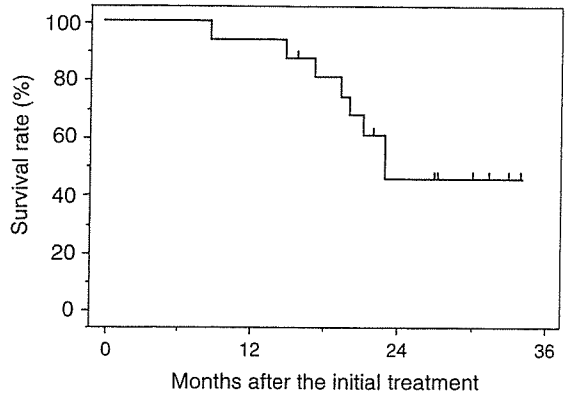

Figure 2. Survival curve for HCC patients who received intra-arterial chemotherapy using SM-11355.

Table 2. Hematologic toxicities (per patient)

	Grade			
	1	2	3	4
Hemoglobin	2 (13%)	1 (6%)	0 (0%)	0 (0%)
Leucocytes	6 (38%)	2 (13%)	0 (0%)	0 (0%)
Neutrophils	6 (38%)	1 (6%)	3 (19%)	0 (0%)
Platelets	2 (13%)	5 (31%)	0 (0%)	0 (0%)
Eosinophils >500/mm^3	16 (100%)			

were over 100 ng/ml before treatment, three patients (75%) showed at least 50% reduction in the level within 1 month after treatment.

Survival

The overall survival curve is shown in Figure 2, with a median follow-up period of 23.1 months (range, 8.7–34.0 months). Of the sixteen patients studied, eight had died of cancer at the time of analysis. Eight patients were still alive 15.7–34.0 months after the initial treatment. The 1-year and 2-year survival rates and median survival time were 94%, 45%, and 23 months, respectively.

Toxicity

Hematological toxicity per patient is summarized in Table 2. It was relatively mild and transient, although three patients (19%) showed grade 3 neutropenia. All 16 patients showed an increase of the eosinophil count to more than 500/mm^3; the maximum eosinophil count was 502–4743 (median 817) /mm^3, which was observed 2–3 weeks after the initial treatment. However, the eosinophil counts in all patients recovered to initial levels. While experiencing eosinophilia, fourteen patients (88%) developed grade 1–2 fever and three patients (19%) showed deterioration of performance status (ECOG performance status: 1–2). After the second treatment, five of twelve patients (42%) had an increase of the eosinophil count to more than 500/mm^3. The maximum count was 214–2030 (median 405)/mm^3, and occurred 1–2 weeks after the second treatment. Of these five patients, one showed grade 2 fever and declining performance status temporarily when eosinophilia was observed.

A summary of nonhematological toxicity in each patient is shown in Table 3. Grade 3 toxicity was observed as elevated total bilirubin in three patients (19%), as elevated AST in seven patients (44%), and as elevated ALT in three patients (19%). Among 13 patients who showed grade 1 or worse hepatic toxicity, the peaks of the toxicity were achieved within 2 weeks after the treatment in six patients (46%), 3–5 weeks in three patients (23%), and 9–11 weeks in four patients (31%). The liver function returned to the initial level within 8 weeks after the peak in all patients except one whose total bilirubin improved but did not attain to the initial level during his follow-up period (4 weeks after the peak). None of the patients showed grade 4 toxicity. Fifteen patients (94%) developed grade 1–3 fever after the initial treatment, although it was alleviated within a week. Grade 3 fever, which was observed in one patient, was caused by bacteremia induced from the indwelling intravenous catheter. This was unlikely to be related to the treatment and was not classified as a toxicity. Fourteen of the fifteen patients redeveloped grade 1–2 fever 7 days or later after the initial treatment while experiencing eosinophilia. Among the 12 patients who underwent the second treatment, fever occurred immediately after the treatment in 10 patients (83%), and recurred 7 days or later after the treatment in 1 patient (8%). All serum IgE levels, which were measured serially in 10 patients, were normal.

Pharmacokinetics

Plasma samples for pharmacokinetic studies were obtained from all 16 patients. Figure 3 shows changes in the plasma total platinum on a log scale. The median *C*max and *T*max were 9.95 ng/ml (range, 6.3–22.0) and 28 (range, 18–37) days, respectively, after the initial treatment, and 16 ng/ml (range, 8.2–54.0) and 21 (range, 7–34) days, respectively,

Table 3. Nonhematologic toxicities (per patient)

	Grade				
	1	2	3	4	
Nausea, vomiting	0 (0%)	4 (25%)	0 (0%)	–	(25%)
Diarrhea	3 (19%)	2 (13%)	0 (0%)	0 (0%)	(31%)
Stomatitis	1 (6%)	0 (0%)	0 (0%)	0 (0%)	(6%)
Total bilirubin	–	2 (13%)	3 (19%)	0 (0%)	(31%)
AST*1	0 (0%)	2 (13%)	7 (44%)	0 (0%)	(56%)
ALT*2	2 (13%)	2 (13%)	3 (19%)	0 (0%)	(44%)
Alkaline phosphatase	3 (19%)	4 (25%)	0 (0%)	0 (0%)	(44%)
Abdominal pain	6 (38%)	2 (13%)	0 (0%)	0 (0%)	(50%)
Serum creatinine	4 (25%)	0 (0%)	0 (0%)	0 (0%)	(25%)
Proteinuria	1 (6%)	2 (13%)	0 (0%)	0 (0%)	(19%)
Rash	0 (0%)	1 (6%)	0 (0%)	0 (0%)	(6%)
Fever	2 (13%)	13 (81%)	0 (0%)	0 (0%)	(94%)

*1aspartate aminotransferase.
*2alanine aminotransferase.

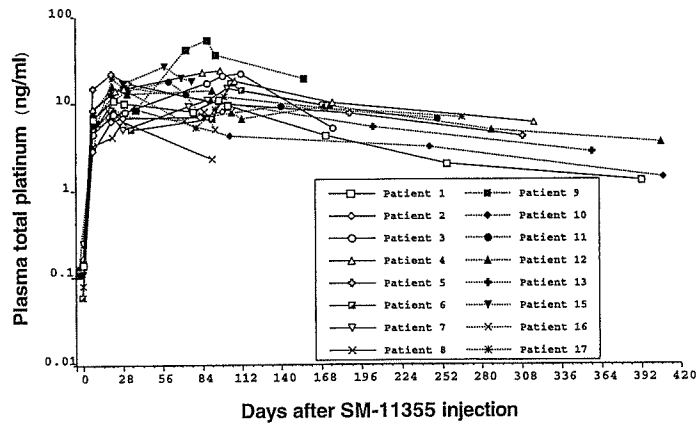

Figure 3. Plasma concentration of total platinum after administration of SM-11355.

after the second treatment. The plasma total platinum concentrations gradually decreased after *C*max was reached: it represented $47.3 \pm 12.5\%$, $31.0 \pm 6.4\%$, and $17.1 \pm 3.7\%$ of the *C*max at 12–15 weeks, 6–8 months, and 10–14 months after the final administration of SM-11355, respectively.

One patient underwent hepatic resection 3 months after the second treatment (Figure 4). In this patient, the dose of SM-11355 was 40 mg/body in the first treatment and 20 mg/body in the second treatment. The total platinum concentration was 250 μg/g tissue in the central part of tumor, 190 μg/g tissue in the peripheral part of the tumor, and 29 μg/g tissue in the nontumorous tissue.

Discussion

Several intra-arterial chemotherapy regimens using adriamicin [1], fluorouracil [2], fluorodeoxyuridine (FUDR) [3], mitomycin C [4], cisplatin [5], epirubicin [6], and mitoxantrone [7] administered singly or in combination [8] have been reported as treatments for HCC. Although some regimens have shown a high response rate, most of them resulted in only short survival or had significant adverse effects. Accordingly, the optimum regimen for intra-arterial chemotherapy for HCC is still unknown.

Among the anticancer drugs noted above, cisplatin is one of the most promising agents for

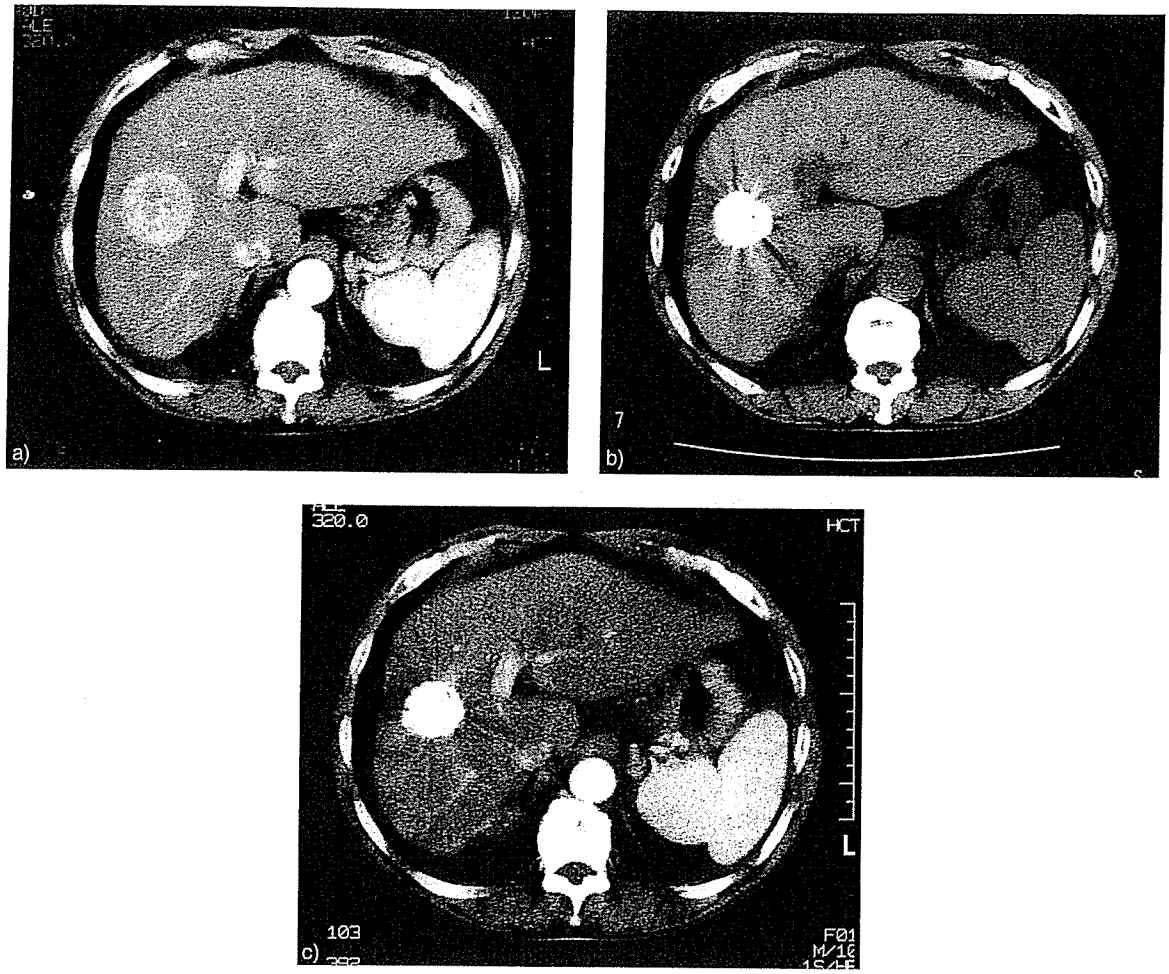

Figure 4. (a) CT scan before SM-11355 injection showed a hyperenhancing tumor in the right lobe of the liver; (b) CT scan which was performed 3 months after the second treatment showed dense accumulation of lipiodol throughout the whole tumor; (c) CT scan which was carried out 5 months after the second treatment showed maintenance of the lipiodol accumulation.

intra-arterial chemotherapy against HCC. A remarkable antitumor response was reported in patients who received cisplatin–lipiodol suspension intra-arterially [5]. However, cisplatin is rather hydrophilic and barely soluble in lipiodol (which is a carrier of anticancer agents for targeting chemotherapy for HCC) even when cisplatin is prepared as a powder to increase its solubility in lipiodol. Therefore, only a small volume of cisplatin remains in the tumor for a long period, and most of the agent is released briefly into bloodstream in the systemic circulation and cause systemic side effects such as nausea/vomiting and renal dysfunction. SM-11355 has been developed as a lipophilic platinum complex in an effort to produce a superior antitumor effect for HCC and lower toxicity than cisplatin [15,26]. SM-11355–lipiodol suspension is a stable and colloidal emulsion that is deposited within HCCs and releases active derivatives of SM-11355 there gradually [17]. SM-11355 itself, unlike cisplatin, is not an active agent against HCC, but SM-11355–lipiodol has greater stability and longer sustained release of active platinum compounds that bind to nuclear DNA in comparison with cisplatin–lipiodol [17,26,27]. In a rat intra-arterial chemotherapy model, SM-11355–lipiodol showed higher antitumor activity and lower hepatic toxicity than cisplatin–lipiodol [27].

In the present study, intra-arterial chemotherapy with SM-11355 had a remarkable antitumor effect in terms of both tumor necrosis and tumor reduction. Tumor necrosis was evaluated by lipiodol accumulation as revealed by CT in this study, because the

lipiodol accumulation area in the tumor corresponds to the tumor necrotic area [21,22]. In a previously conducted phase II study for styrene maleic acid neocarzinostatin (SMANCS) (zinostatin stimalamer), which is now the only commercially available lipophilic agent for HCC in Japan, only 27% of patients achieved CR [9]. A phase II study of TAE with SMANCS and gelatin sponge showed a CR rate of 56% [13]. In intra-arterial chemotherapy with cisplatin, approximately 40–50% of the patients showed reduction in tumor size more than 50% [5,28]. These results indicate that SM-11355, which showed a CR rate of 56% and produced tumor size reduction of more than 50% in 44% of the patients in the present study, may have equivalent efficacy to that of cisplatin or SMANCS plus gelatin sponge.

The toxicity profile in the present study was mild and acceptable. The major toxicities with this treatment were neutropenia and liver dysfunction, but neither grade 4 toxicities nor episodes of febrile neutropenia were observed. The hepatic toxicity of SM-11355 was relatively milder than that of TAE; elevation of the serum total bilirubin level was more frequent with SMANCS plus gelatin sponge compared with SM-11355 (68% vs. 31%) [13]. This study also showed favorable results in terms of renal toxicity (0%) and nausea/vomiting (25%), whereas intra-arterial chemotherapy using cisplatin causes vomiting in 62% patients (the incidence of renal toxicity was ambiguous) [5]. Eosinophilia was observed 7 days or later after the treatment, concomitantly with fever, which was likely due to drug allergy to SM-11355, but the precise mechanism remains unknown.

Our pharmacokinetic study revealed that the plasma concentration of total platinum in patients receiving SM-11355 was very low: the *C*max was approximately 300-fold lower than that reported in a study of intra-arterial administration of cisplatin at 40–100 mg/body [5]. The *T*max ranged from 18–37 days, which was much longer than the 10–60 min in the cisplatin study. In a preclinical study in laboratory animals, more than 80% of the administered total platinum dose was delivered to the liver both 24 h and 168 h after intra-arterial administration of SM-11355 (unpublished data). In the patients who underwent hepatic resection, the platinum concentration in the tumor tissue was more than six times higher than that in the nontumorous tissue. These results indicate that SM-11355 suspended in lipiodol selectively targeted liver tumors, and released platinum into the bloodstream gradually.

Cyclohexane-1,2-diamineplatinum(II) dichloride (DPC) is one of the platinum compounds released from SM-11355, which is presumed to have active antitumor activity [17], but analytical techniques have not been developed to measure DPC concentration under physiological conditions.

In conclusion, intra-arterial chemotherapy with SM-11355 was effective and well tolerated in patients with advanced HCC. This agent appeared to show a marked antitumor effect and reduced toxicity. A large-scale Phase II trial is now being conducted to confirm the results found in this study.

Appendix

Efficacy and safety evaluation committee

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Hiroki Inoue	Kagoshima University School of Medicine
Shoji Fukushima (*chairperson)	Kobe Gakuin University

Judgment committee

Yasuhiko Kubo*	Omuta City General Hospital
Shuichi Okada	National Cancer Center Hospital
Toshio Nakanishi	Hiroshima University School of Medicine
Shigetoshi Fujiyama	Kumamoto University School of Medicine
Junji Shibata (*chairperson)	Shibata Clinic

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Systemic Chemotherapy for Pancreatic Cancer

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Abstract: Surgical resection offers the only curative strategy for pancreatic cancer. Yet, because early detection of pancreatic cancer is so difficult and diagnosis is delayed, pancreatic cancer in most patients is surgically unresectable. Even in patients with resectable disease, the long-term outcome remains unsatisfactory due to early recurrence after resection. Early appearance of distant metastasis suggests that systemic treatment, such as chemotherapy, should play a major role in improving patient survival. Although the recently developed gemcitabine has renewed interest in clinical research for pancreatic cancer, other currently available chemotherapeutic agents have little impact on survival. Studies to identify more effective agents or treatment regimens must have the highest priority. The expanding understanding of molecular and genetic biology should facilitate research to develop novel molecule-targeted agents and to establish individualized therapy regimens for this disease.

Key Words: pancreatic cancer, chemotherapy, gemcitabine, S-1, thymidylate synthase inhibitor 5-fluorouracil

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Pancreatic cancer is a virulent disease with an extremely poor prognosis. Of all the treatment modalities for pancreatic cancer, only resection offers the opportunity for cure. However, because of local extension and/or metastatic disease, only a small minority of pancreatic cancer patients are candidates for resection with curative intent. Moreover, even for selected patients, prognosis remains unsatisfactory because of postoperative recurrence, indicating that resection alone has only limited value in treating pancreatic cancer. Accordingly, to improve the overall survival of patients with pancreatic cancer, there is an urgent need to develop effective nonsurgical treatments, including chemotherapy, for this disease. In this article, chemotherapies for pancreatic cancer in Japan are discussed. This review focuses on pancreatic ductal adenocarcinoma because it is the most common form of pancreatic cancer in Japan, accounting for approximately 90% of pancreatic cancer cases.[1]

RESULTS IN PATIENTS WITH UNRESECTABLE AND RECURRENT DISEASE

Although a variety of chemotherapeutic regimens have been tried and evaluated in advanced pancreatic cancer in Japan, most studies demonstrated little objective evidence of significant activity against this disease. Few agents repeatedly documented high response rates and meaningful impact on patient survival or quality of life. However, the recent development of gemcitabine has renewed an interest in clinical research for pancreatic cancer due to its significant clinical benefit and survival improvement.

Fluoropyrimidine-Based Chemotherapy

Of all chemotherapeutic drugs, the thymidylate synthase inhibitor 5-fluorouracil (5-FU) has been the most extensively evaluated and most widely used agent for pancreatic cancer in Japan. However, despite numerous trials of 5-FU, the optimal dose and administration schedule have yet to be defined. Moreover, results with this agent, regardless of schedule, remain dismal, with reported response rates ranging up to 20%.[2] Based on accumulated clinical evidence suggesting that protracted venous infusion of 5-FU may induce greater antitumor activity than bolus infusion, continuous venous infusion of 5-FU was investigated in a small phase 2 study for advanced pancreatic cancer patients.[3] A dose of 500 mg/m^2 of 5-FU was given for 7 days by continuous venous infusion over a 24-hour period and then followed by a dose of 170 mg/m^2 for more than 28 days. The administration schedule of 5-FU in this study was feasible, but the result of this regimen was disappointing; none of the patients achieved objective response.

There have been various attempts at biochemical modulation of 5-FU through different agents to enhance antitumor activity. We examined sequential administration of methotrexate and 5-FU for metastatic pancreatic cancer patients that showed high response rates in several malignant diseases.[4] Methotrexate (100 mg/m^2) was given, followed by a 600-mg/m^2 infusion of 5-FU. Partial responses were achieved in 4 of the 31 patients (12.9%), with a median survival time of 4.0 months. The antitumor activity of this regimen, therefore, seemed marginal.

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UFT, an orally administered drug, is a combination of tegaful, a prodrug of 5-FU, and uracil, a competitive inhibitor of dihydropyrimidine dehydrogenase. A Japanese phase 2 study conducted in the early 1980s of UFT administered at a daily dose of 300–600 mg exhibited a 25% tumor response in 16 evaluable patients with advanced pancreatic cancer.[5] Recently, we conducted a confirmatory phase 2 study of UFT at a dose of 360 mg/m^2/d, but this study failed to confirm the initial response finding; none of 21 patients achieved an objective tumor response.[6]

S-1 is an oral anticancer drug that consists of tegafur (FT) as a prodrug of 5-FU, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo). The drug was developed in Japan to improve the tumor-selective toxicity of 5-FU by 2 biochemical modulators, CDHP and Oxo. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase involved in degrading 5-FU and maintains efficacious 5-FU concentrations in plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits phosphorylation of 5-FU in the gastrointestinal tract and reduces the serious gastrointestinal toxicity of 5-FU. S-1 has already demonstrated a potent antitumor effect on various solid tumors in clinical studies.[7–12] We conducted an early phase 2 study of S-1 in patients with metastatic pancreatic cancer,[13] and our study showed promising results, with a 21% response rate in 19 evaluable patients, and a manageable toxicity profile of this agent. We are conducting a multiinstitutional late-phase 2 study of S-1 for metastatic pancreatic cancer to confirm the results in this study.

There has been hope that improved therapeutic results might be obtained with 5-FU–based multiagent chemotherapy since several agents having at least some activity have been identified. We performed a phase 2 trial of combined chemotherapy using 5-FU and cisplatin, a potential modulator of 5-FU, which itself showed some antitumor activity against pancreatic cancer.[14] 5-FU was administered at 500 mg/m^2/d by continuous intravenous infusion for 5 days and cisplatin was administered at 80 mg/m^2 intravenously on the first day of every 28 days. The therapy on this schedule had limited antitumor activity, with only an 8% response rate in 37 patients. With this treatment, 4 (21%) of the 21 patients obtained remarkable symptom relief.[15] Based on laboratory data suggesting a profound schedule dependency for cytotoxicity of this combination, Tsuji et al[16] conducted a phase 2 trial of continuous-infusion 5-FU and low-dose consecutive cisplatin for 39 patients with advanced pancreatic cancer. 5-FU (160 mg/m^2/d) was continuously infused over 24 hours for 7 consecutive days, and cisplatin (3 mg/m^2/d) was administered over 30 minutes for 5 days, followed by a 2-day rest every 4 weeks. The objective response rate was 28.2%, with a clinical benefit response rate of 48.7% and a median survival time of 6.5 months.

Most studies of 5-FU–based, multiagent chemotherapy have documented little reproducible impact on patient survival, while all of these regimens have exhibited great toxicity. Takada et al[17] failed to demonstrate a survival benefit of the combination chemotherapy consisting of 5-FU, doxorubicin, and mitomycin for Japanese patients with unresectable pancreatic and biliary cancer. Based on the results to date, 5-FU–based chemotherapy cannot be recommended outside clinical trials.

Chemotherapy Using Agents Other Than Fluoropyrimidine

Various agents other than fluoropyrimidine, including drugs developed in Japan, have also been studied in advanced pancreatic cancer patients. CPT-11, a semisynthetic, water-soluble derivative of the plant alkaloid camptothecin, has been tested for this disease. Sakata et al[18] reported a 11.4% response rate in a phase 2 trial employing 100 mg/m^2 given weekly or 150 mg/m^2 given biweekly. However, only 35 of the 57 eligible patients were evaluable for efficacy in this study. A confirmatory phase 2 study is now underway in Japan.

Docetaxel, a semisynthetic taxane, has also been evaluated. In a French study, Rougier et al[19] reported 5 objective responses (29%) in 17 advanced pancreatic cancer patients in the initial report, and 6 responses (15%) in 40 patients in the final report. However, subsequent trials, including a Japanese study, could not confirm the favorable results. None of the 21 patients in the Japanese trial showed a response.[20]

Gemcitabine is a deoxycytidine analog that is capable of inhibiting DNA replication and repair. Gemcitabine has the potential for great activity against various solid tumors, including pancreatic cancer, because of its prolonged inhibition of both cell synthetic function and progression through the cell cycle. In the randomized trial comparing gemcitabine with 5-FU, gemcitabine showed significantly better results in clinical benefit response and survival.[21] Accordingly, gemcitabine has been accepted as first-line chemotherapy for advanced pancreatic cancer. In the phase 1 trial conducted in Japan before this randomized trial, the recommended dose schedule of gemcitabine was 800 mg/m^2 weekly × 3, followed by 1 week of rest, with leukocytopenia as dose-limiting toxicity.[22] However, in most trials of gemcitabine for pancreatic cancer, including the previous randomized study, a dose of 1000 mg/m^2 has been employed and approved in Western countries. Therefore, we conducted a phase 1 trial to confirm the tolerability of weekly scheduled gemcitabine at a dose of 1000 mg/m^2 in Japanese patients with advanced pancreatic cancer.[23] This study showed low incidence of dose-limiting toxicity, suggesting that 1000 mg/m^2 gemcitabine weekly × 7, followed by 1 week rest and again weekly × 3 every 4 weeks may be tolerated in Japanese patients with advanced pancreatic cancer. In this trial, a partial response was obtained in 2 (18%) of the 11 enrolled patients with metastatic pancreatic cancer and a clinical benefit response was achieved in 2 (29%) of the 7 evaluable patients. Based on the consistency in response and toxicity of

this study with those of previous Western trials, gemcitabine was approved for pancreatic cancer treatment in Japan in 2001.

Despite worldwide agreement on the role of gemcitabine as a first-line treatment in advanced pancreatic cancer, therapies that can achieve more significant survival advantages are needed because prognosis for patients with this disease still remains very poor. Based on preclinical and clinical data showing favorable antitumor effects of gemcitabine in combination with other cytotoxic agents, additional trials of gemcitabine-based regimens, including gemcitabine plus S-1, are in progress in Japan. Several trials of new agents arising from our increased understanding of the pathobiology of pancreatic cancer are also underway to identify compounds with activity against this disease.

RESULTS IN PATIENTS WITH RESECTABLE DISEASE

Although surgical resection has offered the only curative strategy for pancreatic cancer, the long-term outcome after resection remains poor. Chemotherapy can play a role as an adjuvant treatment after resection for pancreatic cancer; there is hope that postoperative local recurrence and metastasis will be reduced with addition of chemotherapy, resulting in improved survival.

Takada et al[24] conducted a randomized, controlled trial to evaluate postoperative adjuvant chemotherapy with mitomycin C and 5-FU in patients with resected pancreaticobiliary cancer. In this trial, patients were stratified according to disease and institution. One-hundred fifty-eight patients with resected pancreatic cancer were then randomly assigned to adjuvant chemotherapy (81 patients) or surgery alone (77 patients). The 5-year survival rate in pancreatic cancer patients was 11.5% in the adjuvant group and 18.0% in the no-adjuvant group, with no significant difference noted between the groups.

A multicenter randomized trial in 89 Japanese patients with resected pancreatic cancer compared adjuvant cisplatin and 5-FU for 2 courses after pancreatectomy with surgery alone. No statistical differences in survival were seen between the 2 groups, although the 5-year survival rate for patients with adjuvant therapy was somewhat better than for those treated with surgery alone (unpublished data). Given gemcitabine's favorable results in patients with advanced pancreatic cancer, we are now conducting an additional cooperative group study comparing adjuvant chemotherapy using gemcitabine and observation alone after pancreatic resection. Ten centers are participating in this study, which began accrual in 2002. Final analysis of the study is expected in 2006.

CONCLUSION

Pancreatic cancer is a major cause of cancer-related mortality in Japan and remains the most virulent disease in the world. At present, chemotherapy is of limited value in the treatment of pancreatic cancer, although gemcitabine has been accepted as first-line chemotherapy for advanced pancreatic cancer. However, various trials are being attempted that we hope will result in improving patient survival. Clinical trials of novel agents or gemcitabine-based regimens may be mandatory for the further development of chemotherapy for pancreatic cancer. Moreover, the evolving understanding of molecular and genetic biology should facilitate research to develop novel target-based agents and to establish individualized therapy regimens for this disease.

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New approaches for pancreatic cancer in Japan

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Abstract Pancreatic cancer is the fifth leading cause of cancer-related mortality in Japan, with an estimated annual incidence rate of approximately 20,000 cases. Even in patients with resectable disease, the long-term outcome remains unsatisfactory due to early recurrence after resection. However, surgical resection has offered the only curative strategy for pancreatic cancer. Currently available chemotherapeutic agents have little impact on survival, although the development of gemcitabine has renewed interest in clinical research for pancreatic cancer. To further improve the prognosis of patients with pancreatic cancer, the development of more effective nonsurgical treatment is essential. Studies to identify more effective treatments, such as chemotherapy, interventional therapy and gene therapy, are ongoing in Japan. The expanding understanding of molecular and genetic biology should facilitate research to develop novel molecular-targeted agents and to establish individualized therapy regimens for this disease.

Keywords Pancreatic cancer · Chemotherapy · Gemcitabine · Gene therapy

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Introduction

Pancreatic cancer is the fifth leading cause of cancer-related mortality in Japan. The estimated annual incidence is approximately 20,000 cases, which is similar to its mortality [26]. Of all the treatment modalities for pancreatic cancer, only resection offers the opportunity for cure. However, because of local extension and/or metastatic disease, only a small minority of pancreatic cancer patients are candidates for resection with curative intent. Moreover, even for these selected patients, the prognosis remains unsatisfactory because of postoperative recurrence, indicating that surgery alone has limited value in the treatment of pancreatic cancer. Accordingly, to improve the overall survival of patients with pancreatic cancer, there is an urgent need to develop effective nonsurgical treatment for this disease. Various studies have been conducted to identify more effective nonsurgical treatments for pancreatic cancer in Japan. This review focuses on new approaches for chemotherapy in patients with advanced pancreatic cancer, and introduces other approaches including nonmyeloablative allogeneic stem cell transplantation and gene therapy.

Fluoropyrimidine-based chemotherapy in Japan

Of all chemotherapeutic drugs, the thymidylate synthase inhibitor fluorouracil (5-FU) has been the most extensively evaluated and most widely used agent for pancreatic cancer in Japan. Since the results with this agent remain poor, with reported response rates reaching 20% [17], there have been various attempts at biochemical modulation to enhance the antitumor activity of 5-FU through different agents. In Japan, sequential administration with methotrexate and 5-FU has been examined, but the antitumor activity of this regimen appears to be only marginal [9]. UFT is an orally administered drug developed in Japan that is a combination of tegafur, a prodrug of 5-FU, and uracil,

a competitive inhibitor of dihydropyrimidine dehydrogenase. Unfortunately, clinical trials of this agent have demonstrated little superiority in therapeutic effect to 5-FU alone against advanced pancreatic cancer [22, 31].

S-1 is an oral anticancer drug, which consists of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo). The drug was developed in Japan to improve the tumor-selective toxicity of 5-FU by two biochemical modulators, CDHP and Oxo. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase involved in degradation of 5-FU, and maintains efficacious 5-FU concentrations in plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits phosphorylation of 5-FU in the gastrointestinal tract and reduces the serious gastrointestinal toxicity of 5-FU. S-1 has already demonstrated a potent antitumor effect in various solid tumors in clinical studies [7, 11, 12, 16, 25, 27]. We conducted an early phase II study of S-1 in patients with metastatic pancreatic cancer [19]. This study showed promising results with a 21% response rate in 19 evaluable patients and a manageable toxicity profile of this agent. We are conducting a multi-institutional late phase II study of S-1 for metastatic pancreatic cancer to confirm these results.

There has been hope that improved therapeutic results might be obtained with 5-FU-based multiagent chemotherapy, since several agents having at least some activity have been identified. Cisplatin has been the most extensively used agent as a potential modulator of 5-FU, and has itself demonstrated some antitumor activity against pancreatic cancer. The combination of continuous infusion of 5-FU and bolus administration of cisplatin has been found to have limited antitumor activity, with only an 8% response rate in 37 Japanese patients [15]. With this treatment, 4 (21%) of 21 patients obtained remarkable symptom relief [20]. Based on laboratory data suggesting a profound schedule dependency for the cytotoxicity of this combination, Tsuji and colleagues conducted a phase II trial of continuous-infusion 5-FU and low-dose consecutive cisplatin in 39 patients with advanced pancreatic cancer [30]. 5-FU (160 mg/m^2 per day) was continuously infused over 24 h for seven consecutive days and cisplatin (3 mg/m^2 per day) was administered over 30 min for 5 days followed by a 2-day rest period, every 4 weeks. The objective response rate was 28.2%, with a clinical benefit response rate of 48.7% and a median survival time of 6.5 months.

Most studies of 5-FU-based multiagent chemotherapy have documented little reproducible impact on patient survival, while all of these regimens exhibit great toxicity. Takada and coworkers failed to demonstrate a survival benefit for combination chemotherapy consisting of 5-FU, doxorubicin and mitomycin for Japanese patients with unresectable pancreatic and biliary tract cancer compared to palliative surgery alone [29]. Based on the results to date, 5-FU-based multiagent chemotherapy cannot be recommended outside clinical trials.

Chemotherapy using gemcitabine

Gemcitabine is a deoxycytidine analog that is capable of inhibiting DNA replication and repair. Gemcitabine has the potential for great activity against various solid tumors including pancreatic cancer. This is because of gemcitabine's prolonged inhibition of both cell synthetic function and progression through the cell cycle. In a randomized trial comparing gemcitabine with 5-FU, gemcitabine showed significantly better results in terms of clinical benefit and survival [3]. Accordingly, gemcitabine has been accepted as first-line chemotherapy for advanced pancreatic cancer. In the phase I trial conducted in Japan before this randomized trial, the recommended dose schedule of gemcitabine was 800 mg/m^2 weekly ×3 followed by 1 week of rest, with leukocytopenia as the dose-limiting toxicity [28]. However, in most trials of gemcitabine for pancreatic cancer including the previous randomized study, a dose of 1000 mg/m^2 has been employed and approved in Western countries. Therefore, we conducted a phase I trial to confirm the tolerability of a weekly schedule of gemcitabine at a dose of 1000 mg/m^2 in Japanese patients with advanced pancreatic cancer [18]. This study showed a low incidence of dose-limiting toxicity, suggesting that gemcitabine at 1000 mg/m^2 weekly ×7 followed by 1 week rest and weekly ×3 every 4 weeks may be tolerated in Japanese patients with advanced pancreatic cancer. In this trial, a partial response was obtained in 2 (18%) of the 11 enrolled patients with metastatic pancreatic cancer and a clinical benefit response was achieved in 2 (29%) of the 7 evaluable patients. Based on the consistency in response and toxicity of this study with those of previous Western trials, gemcitabine was approved in Japan for the treatment of pancreatic cancer in 2001.

Despite worldwide agreement on the role of gemcitabine as a first-line treatment in advanced pancreatic cancer, only a minority of patients obtain clear benefits such as symptom relief and prolongation of survival from the administration of gemcitabine. Accordingly, it is important to establish effective methods for estimating individual drug response and toxicity. We are currently conducting a pharmacogenomics study for gemcitabine to identify polymorphisms of genes encoding drug-metabolizing enzymes and membrane-transporter proteins for gemcitabine and its metabolites, and their correlation with pharmacokinetics, toxicity and tumor response in pancreatic cancer patients. In this study, evidence for functional single-nucleotide polymorphisms responsible for gemcitabine metabolism is accumulating. This gene-based information has the potential to aid in the establishment of individualized therapy regimens using gemcitabine for pancreatic cancer.

Based on preclinical and clinical data showing the favorable antitumor effects of gemcitabine in combination with other cytotoxic agents, additional trials of gemcitabine-based regimens including gemcitabine plus S-1 are in progress in Japan.

Other new agents

Several novel chemotherapeutic agents developed in Japan, such as irinotecan, exatecan, UCN-01, NK911, capecitabine and S-1, have been evaluated in clinical trials for pancreatic cancer in Japan and/or other countries. It is hoped that improved therapeutic results might be obtained using these agents either singly or in combination with gemcitabine. This section focuses on irinotecan and NK911, clinical trials of which are ongoing for pancreatic cancer patients in Japan.

Irinotecan, a semisynthetic, water-soluble derivative of the plant alkaloid camptothecin, induces antitumor activity by inhibition of topoisomerase I. The single-agent antitumor activity of irinotecan in pancreatic cancer has been demonstrated in two phase II studies [24, 33]. In the first study conducted in Japan, administration of irinotecan at 100 mg/m^2 weekly or 150 mg/m^2 every other week to previously untreated patients resulted in a response rate of 11% in the 35 assessable patients treated [24]. In the second study, conducted by the European Organization for Research and Treatment of Cancer (EORTC), an irinotecan regimen of 350 mg/m^2 every 3 weeks induced partial responses in 9% of the 32 assessable patients [33]. A confirmatory phase II study is now underway in Japan. While no significant survival improvement with the combination of irinotecan and gemcitabine over gemcitabine alone has been reported recently [23], this agent may have the potential to be used in gemcitabine-refractory patients.

A new agent, developed based on the pathobiology of pancreatic cancer, is also being studied in a clinical trial for treatment of this disease. NK911 is a doxorubicin-encapsulated polymeric micellar nanoparticle [10]. The polymeric micelle carrier of NK911 consists of a block copolymer of polyethyleneglycol and polyaspartic acid. Polyethyleneglycol is expected to be in the outer shell of the micelle. NK911 has a highly hydrophobic inner core, and therefore can entrap a sufficient amount of doxorubicin. After the NK911 is extravasated from the tumor vessels, doxorubicin is released from NK911. It is suggested that pegylated liposomal doxorubicin (known as Doxil) can deliver doxorubicin to a solid tumor, via the enhanced permeability and retention (EPR) effect, more efficiently than NK911. This is because pegylated liposomal doxorubicin is more stable in the bloodstream. However, it is expected that NK911 can distribute more doxorubicin into cancer cells distant from the tumor vessel than can pegylated liposomal doxorubicin, once NK911 is extravasated from the tumor vessel. It is, therefore, suggested that NK911 may be more effective against cancers where the tumor vessel network is rough due to an abundant collagen-rich matrix, e.g. pancreatic cancer. In a phase I trial, NK911 was well tolerated and produced only moderate nausea and vomiting at myelosuppressive dosages. A partial response was obtained in one patient with gemcitabine refractory pancreatic cancer [13]. A phase II study of NK911 is ongoing in Japan.

A novel arterial infusion chemotherapy

Homma and coworkers have reported a novel arterial infusion chemotherapy for advanced pancreatic cancer [8]. To restrict the blood flow into the pancreas, the peripancreatic blood vessels were embolized superselectively with microcoils. The catheter tip for continuous arterial infusion of 5-FU and cisplatin is placed in the splenic artery just proximal to the branching of the great pancreatic artery for treatment of the primary tumor, and in the common hepatic artery for treatment of metastatic liver lesions. In 31 patients with advanced pancreatic cancer, 2 achieved a complete response and 16 showed a partial response. The median survival period of all patients was 18.3 months. They concluded that this treatment is effective against both primary tumor and metastatic lesions in unresectable pancreatic cancer patients.

Other approaches in Japan

Allogeneic stem-cell transplantation has been proven to have potent antitumor effects not only in patients with hematologic malignancies but also in those with solid tumors [6, 32]. Successful nonmyeloablative allogeneic peripheral blood stem-cell transplantation has been reported in patients with metastatic renal cell carcinoma, and the results with this treatment are consistent with a graft-versus-tumor effect [4, 5]. Omuro and colleagues described a patient who showed continuous regression of unresectable pancreatic tumor following nonmyeloablative allogeneic peripheral blood stem-cell transplantation, which was considered to be attributed to a graft-versus-tumor effect [21]. Based on the results of the report and those for other malignancies, clinical trials of nonmyeloablative allogeneic peripheral blood stem-cell transplantation are being conducted with pancreatic cancer patients in several institutes in Japan.

Increased understanding of the biology of pancreatic cancer could provide the potential to develop entirely novel treatment options. One innovative approach for therapy is a combination of interferon α and antisense K-ras [14]. We have shown that interferon α gene transduction into pancreatic cancer cells induces growth suppression and cell death in the cells; an effect that appears to be more prominent when compared with other types of cancers and normal cells. Another strategy developing for pancreatic cancer targets its characteristic genetic aberration, K-ras point mutation. It has been reported that the expression of antisense K-ras RNA significantly suppresses the growth of pancreatic cancer cells [1, 2]. When these two gene therapy strategies are combined, the expression of antisense K-ras

RNA significantly enhances interferon α-induced cell death (1.3- to 3.5-fold), and suppresses subcutaneous growth of pancreatic cancer cells in mice. Because the 2′,5′-oligoadenylate synthetase/RNaseL pathway, which is regulated by interferon and induces apoptosis of cells, is activated by double-strand RNA, it is plausible that the double-strand RNA formed by antisense and endogenous K-ras RNA enhances the antitumor activity of interferon α. This study suggested that the combination of interferon α and antisense K-ras RNA is a promising gene therapy strategy against pancreatic cancer.

Conclusion

Pancreatic cancer is a major cause of cancer-related mortality in Japan. At present, nonsurgical therapy is of limited value in the treatment of pancreatic cancer, but various approaches are being attempted that we hope will result in improved patient survival. The evolving understanding of molecular and genetic biology should facilitate research to develop novel target-based agents and to establish individualized therapy regimens for this disease.

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Phase II study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer

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Clinical

Gemcitabine has been reported to be a potent radiosensitiser in human pancreatic cell lines. This study was conducted to evaluate the efficacy and toxicity of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. In all, 42 patients with pancreatic cancer that was unresectable but confined to the pancreatic region were treated with external-beam radiation (50.4 Gy in 28 fractions over 5.5 weeks) and weekly gemcitabine (250 mg m^{-2}, 30-min infusion). Maintenance gemcitabine (1000 mg m^{-2} weekly × 3 every 4 weeks) was initiated 1 month after the completion of the chemoradiotherapy and continued until disease progression or unacceptable toxicity. Of the 42 patients, 38 (90%) completed the scheduled course of chemoradiotherapy. The major toxicity was leucopenia and anorexia. There was one death attributed to duodenal bleeding and sepsis. The median survival time was 9.5 months and the 1-year survival rate was 28%. The median progression-free survival time was 4.4 months. In 35 patients with documented disease progression at the time of analysis, 34 (97%) showed distant metastasis as the cause of the initial disease progression. The chemoradiotherapy used in this study has a moderate activity against locally advanced pancreatic cancer and an acceptable toxicity profile. Future investigations for treatment with more systemic effects are warranted.
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Pancreatic cancer is the fourth leading cause of cancer death in the United States and the fifth leading cause in Japan. The statistics indicate a rapid increase in the number of deaths and the death rate due to pancreatic cancer in Japan, but the precise reasons are not clear, except for smoking. Pancreatic cancer in most patients is surgically unresectable at the time of diagnosis because of the difficulty of early detection of this disease. For patients with locally advanced pancreatic cancer, chemoradiotherapy has been accepted as standard treatment because the results of previous randomised trials have indicated that concurrent external-beam radiation therapy and 5-fluorouracil (5-FU) therapy results in a significantly longer survival time than radiotherapy (Moertel *et al*, 1969; Gastrointestinal Tumor Study Group, 1981) or chemotherapy alone (Gastrointestinal Tumor Study Group, 1988). In attempts to improve the efficacy of the treatment, numerous trials using modified approaches of chemoradiotherapy have been conducted (Chakravarthy and Abrams, 1997; Okada, 1999). However, there has not yet been a regimen that has demonstrated superiority over conventional chemoradiotherapy performed in randomised controlled trials.

Gemcitabine is a novel deoxycytidine analog, which has demonstrated significant clinical benefit and survival improvement compared with 5-FU in patients with advanced pancreatic cancer (Burris *et al*, 1997). Gemcitabine has also been shown to be a potent radiosensitiser in human pancreatic and other solid tumour cell lines (Lawrence *et al*, 1996; Shewach and Lawrence, 1996; van Putten *et al*, 2001), suggesting that the combination of radiotherapy and gemcitabine may improve survival in patients with locally advanced disease. A phase I trial that was conducted in our hospital determined the recommended dose of weekly gemcitabine for the phase II chemoradiotherapy trial to be 250 mg m^{-2} (Ikeda *et al*, 2002). We report our results of the phase II study that was conducted to clarify the efficacy and toxicity of concomitant chemoradiotherapy with gemcitabine in patients with locally advanced pancreatic cancer.

PATIENTS AND METHODS

Patients eligible for this study had locally advanced pancreatic cancer for which they had not received any anticancer treatment. Each patient was required to meet the following eligibility criteria: pathological proof of adenocarcinoma of the pancreas; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate bone marrow reserve (white blood cell count $\geqslant$4000 mm^3, platelet count $\geqslant$100 000 mm^3, haemoglobin level $\geqslant$10 g dl^{-1}); adequate renal function (normal serum creatinine and blood urea nitrogen levels, and a creatinine clearance level $\geqslant$60 mg min^{-1}); a serum aspartate aminotransferase (AST) level $<$2.5 times upper normal limit (UNL); a serum alanine aminotransferase (ALT) level $<$2.5 times UNL; and written informed consent. Patients with obstructive jaundice were

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required to have a serum total bilirubin level of less than 2.0 mg dl^{-1} after biliary drainage. Pretreatment staging included ultrasonography and dynamic computed tomography (CT) scans of both the abdomen and the chest. The possibility for resection of the local tumour was assessed by dynamic CT and/or angiography. Obstruction or bilateral invasion of the portal vein and/or tumour encasement of the celiac or superior mesenteric arteries was considered to be unresectable. Patients were excluded if they met the following criteria: concomitant malignancy, pleural and/or peritoneal effusion, active ulcer of the gastrointestinal tract, active infection, severe heart disease, pregnant or lactating females, or other serious medical conditions. The goal was set at 40 eligible patients. This number of patients was planned using a design based on the assumptions that the median survival time in conventional chemoradiotherapy was 10 months, expected median survival time was 14 months, type I error was 5% (one-tailed) and statistical power was 70%.

Radiotherapy was delivered via a racetrack microtron (MM50, Scanditronix, Upsala, Sweden) with a 25 MV X-rays. A total dose of 50.4 Gy was delivered in 28 fractions over 5.5 weeks. All patients had treatment planning, CT scans (X-vision, Toshiba, Tokyo) and FOCUS (version 3.2.1, CMS, St Louis, MO, USA) was used as a radiotherapy treatment planning system. Clinical target volume (CTV) included the primary tumour, nodal involvement detected by CT scan and regional draining and paraaortic lymph nodes, which included the peripancreatic nodes, celiac and superior mesenteric axes. Planning target volume was defined as CTV plus a 10-mm margin. Four field techniques (anterior, posterior and opposed lateral fields) were used. Spinal cord dose was maintained below 45 Gy and $\geqslant$50% of liver was limited to $\leqslant$30 Gy, $\geqslant$50% of both kidneys were limited to $\leqslant$20 Gy.

Gemcitabine at a dose of 250 mg m^{-2} was given intravenously over 30 min starting 2 h before radiotherapy weekly for 6 weeks. This schedule was based on an *in vitro* study which revealed that gemcitabine induced its radiosensitising effect in cells within 2 h (Lawrence *et al*, 1997). Toxicity was assessed according to the National Cancer Institute – Common Toxicity Criteria version 2.0. When grade 3 haematological toxicity, serum creatinine of 1.5–2.0 times UNL, total bilirubin level of 3.0–5.0 times UNL, serum AST/APT of 5.0–10 times UNL and/or grade 2 nonhaematological toxicity (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration) were observed, gemcitabine administration was omitted and postponed to the next scheduled treatment day. The radiotherapy was also suspended, and then resumed when the toxicities recovered. In patients who experienced the above adverse effects, dose reduction of gemcitabine to 200 mg m^{-2} was allowed in subsequent administrations. The combined treatment was discontinued when grade 3 leucopenia and/or neutropenia with high fever, grade 4 haematological toxicities after dose reduction of gemcitabine, serum creatinine of $>$2.0 times UNL, total bilirubin level of $>$5.0 times UNL, serum AST/APT of $>$10 times UNL, grade 3 or 4 nonhaematological toxicities (excluding nausea, vomiting, anorexia, fatigue, constipation, alopecia and dehydration), grade 4 vomiting, a total of 2 weeks of delay due to toxicity for any reason or tumour progression were observed. At 1 month after the completion of chemoradiotherapy, maintenance chemotherapy of gemcitabine at a dose of 1000 mg m^{-2} was administered as a 30-min intravenous infusion weekly for 3 weeks with 1-week rest until disease progression or unacceptable toxicity. Follow-up CT was performed within 1 week after the completion of chemoradiotherapy, and thereafter every 2 months to evaluate tumour response according to the WHO criteria (World Health Organization, 1979).

Progression-free and overall survival times were calculated from the first day of treatment using the Kaplan–Meier method (Kaplan and Meier, 1958). Serum CA 19-9 levels were measured monthly by a radioimmunometric assay using the Centocor radioimmunoassay kit (Centocor, Inc., Malvern, PA, USA).

RESULTS

Patients and treatments

In all, 42 patients were enrolled in the study between July 2001 and July 2002. Patient characteristics are listed in Table 1. A total of 38 patients (90%) received the full regimen of chemoradiotherapy, and the remaining four patients (10%) discontinued the treatment after 18.0–45.0 Gy. The reasons for the treatment discontinuation were elevated serum ALT of $>$10 times UNL (two patients), duodenal bleeding (one), and patient's refusal of treatment due to general fatigue (one). After discontinuation of the chemoradiotherapy, the two patients who showed the ALT elevation suspected as gemcitabine-related toxicity received chemoradiotherapy using 5-FU, and the other two patients underwent only supportive care. Of 241, 30 (12%) planned gemcitabine injections (0.7 injections per patient) were omitted owing to adverse events including grade 3 or more leucopenia and/or neutropenia, grade 2 fever, grade 2 skin rash and patient's refusal due to nausea, vomiting or fatigue. In three patients who showed grade 4 leucopenia and/or neutropenia, the dose of gemcitabine was modified in subsequent injections. Maintenance chemotherapy was initiated in 23 of the 38 patients who completed the full regimen of chemoradiotherapy. Of the remaining 15 patients, seven showed deterioration of general condition due to disease progression before initiating the chemotherapy, seven refused the treatment due to appetite loss (4) or general fatigue (3) and one transferred to another hospital (1).

Response and survival

Tumour response was determined in 40 patients. Two patients were excluded from the protocol efficacy analysis because their treatment was switched over to chemoradiotherapy using 5-FU before the response evaluation due to the ALT elevation. Nine patients (21%) achieved a partial response, 26 (62%) remained stable and five (12%) showed progressive disease demonstrated by the development of distant metastases. No patients could undergo tumour resection even after the completion of chemoradiotherapy because of infiltration of the adjacent large vessels. In 22 (76%) of the 29 patients with a pretreatment serum CA19-9 (carbohydrate antigen 19-9) level of 100 U ml^{-1} or greater, the level was reduced more than 50% within 14 weeks after initiation of treatment.

Table 1 Patient characteristics

Number of patients	42
Gender	
Male	19 (45%)
Female	23 (55%)
Age (years)	
Median (range)	59 (43–73)
ECOG performance status	
0	12 (29%)
1	30 (71%)
Tumour location	
Head	21 (50%)
Body–tail	21 (50%)
CEA (ng ml^{-1})	
Median (range)	11 (1.0–62.7)
CA19-9 (U ml^{-1})	
Median (range)	2775 (1–15 620)

ECOG = Eastern Cooperative Oncology Group; CEA = carcinoembryonic antigen; CA19-9 = carbohydrate antigen 19-9.

A total of 35 patients documented disease progression at the time of analysis. The initial sites of disease progression are listed in Table 2. The pattern of failure was distant metastases in 33 patients (94%), local–regional recurrence in one patient (3%) and both in one patient (3%). The median progression-free interval and the median survival time were 4.4 and 9.5 months, respectively. The overall 1- and 2-year survival rates were 28 and 23%, respectively (Figure 1).

Toxicity

The acute toxicity is summarised in Table 3. The haematological toxicity was relatively brief and reversible in most patients. Grade 3–4 leucopenia and neutropenia occurred in 22 (52%) and 14 (33%) of the patients, respectively. Grade 3 thrombocytopenia occurred in one patient (2%) on the day after the chemoradiotherapy completion. The patient, who showed grade 4 anaemia, suffered catastrophic duodenal bleeding requiring embolisation under angiography. She exhibited cholangitis and sepsis subsequently and died on day 63.

The most common nonhaematological toxicity was anorexia, which was observed in 38 patients (90%). In total, 14 patients (33%) required intravenous hyperalimentation. In all, 33 patients (79%) complained of fatigue and one of them refused continuation of the chemoradiotherapy. Nine patients (21%) experienced grade 3 nausea. Liver function abnormality was another major adverse effect. Four patients (10%) showed grade 3 elevation of serum transaminase levels. Two of them discontinued the treatments after 19.8 and 21.6 Gy, respectively, due to serum ALT elevation of 10 times UNL according to the protocol criteria (maximum level: 452 and 435 IU l^{-1}), although the serum ALT levels of both recovered to the grade 1 levels 4 days after discontinuation of the treatment. We suspected that the ALT elevation in these two patients was gemcitabine-related toxicity because it was never reproduced after their treatment was switched over to chemoradiotherapy using 5-FU. One patient suffered unexpected acute abdominal pain requiring morphine 2 months after the completion of the chemoradiotherapy and was diagnosed with perforation of pancreatic pseudocyst into the duodenum. This pain disappeared completely by only medical management within 1 week. No patients experienced any symptoms considered to be late toxicity as of the time of analysis.

Table 2 Patterns of initial disease progression

Local	No. (%)
Distant metastasis	33 (94)
Peritoneum	17 (49)
Liver	15 (43)
Lymph node	1 (3)
Ovary	1 (3)
Bone	1 (3)
Local and distant metastasis	1 (3)

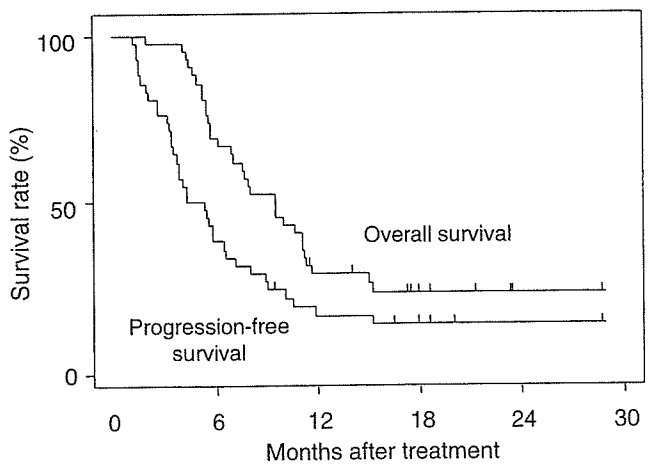

Figure 1 Progression-free survival and overall survival curves of patients with locally advanced pancreatic cancer receiving radiotherapy with gemcitabine.

Table 3 Acute toxicity

Grade	1 (%)	2 (%)	3 (%)	4 (%)
Haematological toxicity				
Leucocytopenia	3 (7)	17 (40)	21 (50)	1 (2)
Neutropenia	9 (21)	15 (36)	11 (26)	3 (7)
Thrombcoytopenia	22 (52)	2 (5)	1 (2)	0 (0)
Anaemia	21 (50)	17 (40)	0 (0)	1[a] (2)
Nonhaematological toxicity				
Total bilirubin	10 (24)	5 (12)	1 (2)	0 (0)
AST	14 (33)	5 (12)	1 (2)	0 (0)
ALT	15 (36)	11 (26)	4 (10)	0 (0)
ALP	15 (36)	5 (12)	0 (0)	0 (0)
Creatinine	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	9 (21)	5 (12)	10 (24)	14 (33)
Nausea	11 (26)	11 (26)	9 (21)	0 (0)
Vomiting	10 (24)	7 (17)	0 (0)	0 (0)
Diarrhoea	1 (2)	1 (2)	0 (0)	0 (0)
Mucositis	0 (0)	0 (0)	0 (0)	0 (0)
Duodenal ulcer	0 (0)	0 (0)	0 (0)	1[a] (2)
Fatigue	17 (40)	14 (33)	2 (5)	0 (0)
Skin rash	0 (0)	1 (2)	0 (0)	0 (0)
Infection	0 (0)	0 (0)	0 (0)	1[a] (2)

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase. [a]One patient died of duodenal bleeding and sepsis.

DISCUSSION

Based on previous randomised trials (Moertel *et al*, 1969; Gastrointestinal Tumor Study Group, 1981; Gastrointestinal Tumor Study Group, 1988), concurrent external-beam radiotherapy and 5-FU have been generally accepted as the standard treatment for locally advanced carcinomas. To intensify the treatment efficacy, various anticancer agents and radiation schedules are being investigated in clinical trials of chemoradiotherapy (Roldan *et al*, 1988; Seydel *et al*, 1990; Wagener *et al*, 1996; Thomas *et al*, 1997; Prott *et al*, 1997; Okusaka *et al*, 2001). However, marked improvement in their survival has not been observed. In an attempt to optimise radiosensitisation, radiotherapy with protracted 5-FU infusion has been examined recently, but the median survival times were similar to those observed in previous studies (Ishii *et al*, 1997).

Gemcitabine has been expected to be an agent that improves the outcome of chemoradiotherapy for locally advanced pancreatic cancer because it is a chemotherapeutic drug having meaningful palliative and prognostic impact against advanced pancreatic cancer, and it is also a potent radiosensitiser. Several experimental studies have shown that more than one mechanism leads to the potentiation of radiation-induced cell killing by gemcitabine (Lawrence *et al*, 1996; Shewach and Lawrence, 1996; van Putten *et al*, 2001). In clinics, various phase I studies for radiotherapy with gemcitabine have been conducted (McGinn *et al*, 2001; Pipas *et al*, 2001; Wolff *et al*, 2001; Ikeda *et al*, 2002; Poggi *et al*, 2002),

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although the efficacy and safety of this combination have not been fully elucidated in phase II trials. A phase I trial that was conducted in our hospital determined the recommended dose of weekly gemcitabine in the phase II chemoradiotherapy trial to be 250 mg m^{-2}, because three of the six patients give a dose of 350 mg m^{-2} of gemcitabine demonstrated dose-limiting toxicities involving neutropenia/leucopenia and elevated transaminase (Ikeda *et al*, 2002).

The toxicity associated with radiotherapy with gemcitabine was relatively severe in this phase II study. Grade 3–4 leucopenia and neutropenia were observed in 52 and 33% of the patients, respectively, although none of the patients showed neutropenic fever. Nausea and anorexia were the most serious non-haematological toxicities in this treatment; 73% of the patients experienced various degrees of nausea and 33% required intravenous hyperalimentation. In all, 78% of the patients complained of general fatigue and one patient (2%) refused continuation of the treatment because of this adverse effect. These troublesome toxicities observed in this study seem to be more frequent and more severe compared with those in 5-FU-based chemoradiotherapy (Ishii *et al*, 1997). There was one death attributed to duodenal bleeding, which was arrested by transcatheter arterial embolisation, but deterioration of the general condition and lethal sepsis were induced subsequently.

The present study, in which 42 patients with locally advanced pancreatic cancer were treated with radiotherapy and weekly gemcitabine, documented a marginal impact on patient survival; the median survival time of 9.5 months is comparable to that in patients receiving conventional chemotherapy using 5-FU. However, the incidence rate of distant metastasis at the time of disease progression was remarkably higher with this treatment (97%) as compared to that with 5-FU-based chemoradiotherapy, which was reported to be 50% in our previous study (Ishii *et al*, 1997). This suggests that gemcitabine at a dose of 250 mg m^{-2} is a potent radiosensitiser for controlling local disease, but its ability as a chemotherapeutic agent is insufficient to counteract systemic tumour spread. To improve prognosis for these patients, future investigations for treatment with more systemic effects are warranted.

In an effort to increase capacity for systemic therapy, reduction of the radiation field has been attempted. Investigators at the University of Michigan elected to radiate the primary tumour alone, without the inclusion of regional lymph nodes, and administer full-dose gemcitabine concurrently, because the use of full-dose gemcitabine requires reduction of the radiation dose, based on their prior clinical experience (McGinn *et al*, 2001; Muler *et al*, 2004). Reduction of the radiation field may be one of the strategies not only for intense systemic therapy but also for decreasing the troublesome gastrointestinal toxicity often observed in our study; our recent retrospective study showed that a larger planning target volume for irradiation was only a significant predictor of severe acute intestinal toxicity in patients treated with chemoradiotherapy using gemcitabine (Ito *et al*, 2003).

Crane *et al* (2002) retrospectively compared the toxicity and efficacy of concurrent gemcitabine-based chemoradiation with those of concurrent 5-FU-based chemoradiation in patients with unresectable pancreatic cancer treated in the University of Texas MD Anderson Cancer Center. In the study, there was a significantly higher severe toxicity rate in patients treated with gemcitabine than in those with 5-FU, although the median survival times were similar between the two arms (gemcitabine *vs* 5-FU: 11 *vs* 9 months). They concluded that concurrent gemcitabine and radiotherapy could be an extremely difficult combination to administer safely, with a very narrow therapeutic index. Recently, investigators in Taiwan reported favourable results for radiotherapy with concurrent gemcitabine administration (600 mg m^2 week^{-1} for 6 weeks) in a small randomised study (Li *et al*, 2003). The gemcitabine-based chemoradiotherapy showed a significantly better median survival time (14.5 months) and a comparable toxicity profile in comparison with the 5-FU-based chemoradiotherapy (7.1 months). However, the number of enrolled patients in this study was only 16–18 in each arm. The results need further confirmation by larger multi-institutional clinical trials.

In summary, the chemoradiotherapy used in this study has a moderate activity against locally advanced pancreatic cancer and an acceptable toxicity profile, but appears to have more frequent acute toxicities compared with conventional chemoradiotherapy using 5-FU. Most patients who underwent this therapy demonstrated rapid appearance of distant metastasis. To explore innovative approaches for locally advanced pancreatic cancer, future investigations for treatment with more systemic effects and less toxicity are needed.

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Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin

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NK911 is a novel supramolecular nanocarrier designed for the enhanced delivery of doxorubicin (DXR) and is one of the successful polymer micelle systems to exhibit an efficient accumulation in solid tumours in mice. The purpose of this study was to define the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLTs) of NK911 and to evaluate its pharmacokinetic profile in man. NK911 was given intravenously to patients with solid tumours every 3 weeks using an infusion pump at a rate of 10 mg DXR equivalent min^{-1}. The starting dose was 6 mg DXR equivalent m^{-2}, and the dose was escalated according to the accelerated titration method. A total of 23 patients participated in this study. Neutropenia was the predominant haematological toxicity, and grade 3 or 4 neutropenia was observed at doses of 50 and 67 mg m^{-2}. Common nonhaematological toxicities were mild alopecia, stomatitis, and anorexia. In the dose identification part of the study, DLTs were observed at a dose of 67 mg m^{-2} (grade 4 neutropenia lasting more than 5 days). Thus, this dosage level was determined to be the MTD. Infusion-related reactions were not observed in any cases. The $C_{5\,min}$ and area under the concentration curve parameters of NK911 exhibited dose-dependent characteristics. Among the 23 patients, a partial response was obtained in one patient with metastatic pancreatic cancer. NK911 was well tolerated and produced only moderate nausea and vomiting at myelosuppressive dosages. The recommended phase II dose was determined to be 50 mg m^{-2} every 3 weeks.

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Agents categorised as drug delivery systems (DDSs) have been developed based on the characteristic macroscopic features of solid tumours, such as hypervascularity, an irregular vascular architecture, the presence of several vascular permeability factors stimulating extravasation within the cancer, and the relatively poor drainage of macromolecules and particulates from cancer tissue. These characteristics, which are unique to solid tumours, constitute the basis of the enhanced permeability and retention (EPR) effect (Matsumura and Maeda, 1986; Maeda *et al*, 2000). Macromolecules have long plasma half-lives because they are too large to pass through normal vessel walls unless they are trapped by the reticuloendothelial system (RES) in the cells of various organs. Such macromolecular agents can diffuse out of tumour blood vessels, reach the solid tumour tissue, and be retained for a long period because of the EPR effect.

To maximise the EPR effect, several techniques have been developed to modify the structures of drugs and to construct drug carriers. Doxil is comprised of doxorubicin (DXR) encapsulated in STEALTH™ liposomes, which are composed of a phospholipid bilayer with surface-bound methoxypolyethyleneglycol. Doxil recently received the US Food and Drug Administration's (FDA) approval for use in the treatment of Kaposi sarcoma or ovarian cancer after the clinical benefits of this drug were clearly shown in recent clinical trials (Muggia *et al*, 1996; Stewart *et al*, 1998; Gordon *et al*, 2001).

Polymeric micelles have also been utilised as a drug carrier system. The original form of micellar DXR contained two trapped components: a DXR monomer and a DXR dimer in the inner core (Yokoyama *et al*, 1990a, b). However, the lyophilised micelle containing DXR dimers became insoluble after long periods of storage. To improve the solubility of this drug carrier system, a new type of polymeric micelle containing only the DXR monomer, known as NK911, has been developed (Nakanishi *et al*, 2001). The DXR monomers, rather than the DXR dimers, were thought to play a major role in the antitumour activity of the original micellar DXR drug preparation. The DXR dimers, on the other hand, were thought to stabilise the drug's conformation. Thus, NK911, which only contains DXR monomers, is less stable in aqueous media than the original form of micellar DXR (Nakanishi *et al*, 2001; Tsukioka *et al*, 2002).

Both polyethyleneglycol (PEG)-liposomal and micellar DXR have longer plasma half-lives, accumulate in tumours more effectively because of the EPR effect, and exhibit a stronger

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