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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Clinical

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

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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)

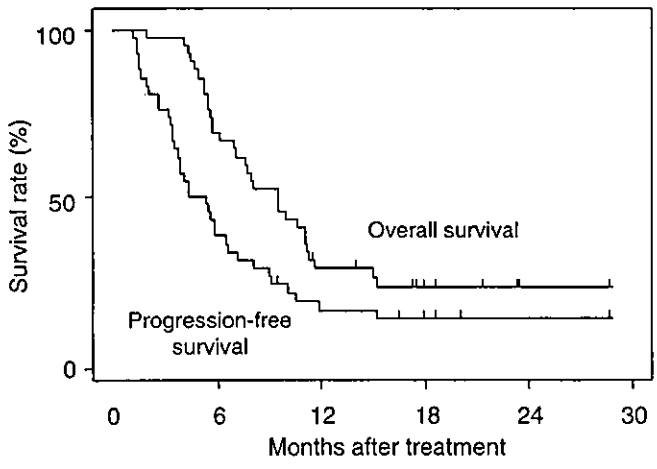

Figure 1 Progression-free survival and overall survival curves of patients with locally advanced pancreatic cancer receiving radiotherapy with gemcitabine.

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),

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 Study of Hyperfractionated Radiation Therapy with Protracted 5-Fluorouracil Infusion in Patients with Locally Advanced Pancreatic Cancer

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Key Words
Chemoradiotherapy · 5-Fluorouracil · Hyperfractionation · Pancreatic cancer · Phase I study · Radiation therapy

Abstract
Objective: This study investigated the maximum-tolerated dose of hyperfractionated radiation therapy with protracted 5-fluorouracil (5-FU) infusion in patients with locally advanced, unresectable pancreatic cancer. ***Methods:*** Five cohorts of patients were scheduled to receive escalating doses of hyperfractionated radiation therapy (range, 45.6–64.8 Gy). All patients received two fractions of 1.2 Gy each (separated by 6 h) per day for 5 days a week, and received protracted 5-FU infusion (200 mg/m^2/day) during the radiation course. The maximum-tolerated dose was defined as one dose level below the dose at which more than one third of 3–6 patients experienced dose-limiting toxicity. ***Results:*** Twenty-nine patients were enrolled in this study. The most common toxicities were nausea/vomiting and anorexia. Although 1 patient developed bleeding from a gastric ulcer 3 months after the completion of chemoradiotherapy, the maximum-tolerated dose was not reached even at the highest dose level (level 5, 64.8 Gy). The median survival time was 12.2 months and the 1-year survival rate was 55.0%. ***Conclusion:*** The toxicity associated with our regimen was tolerable up to dose level 5 (64.8 Gy). We are currently conducting a phase II study of this hyperfractionated radiation therapy with protracted 5-FU infusion at a dose of 64.8 Gy.

Introduction

Because of the difficulty in diagnosing pancreatic cancer early, the vast majority of patients have unresectable disease at the time of diagnosis. About 30–50% of the unresectable cases have localized disease without distant metastases. In the treatment of locally advanced, unresectable pancreatic cancer, radiotherapy with concomitant chemotherapy has been the treatment of choice since it offers better survival rates when compared to treatment by radiotherapy or chemotherapy alone [1, 2]. However, improvement in chemoradiotherapy for pancreatic cancer is necessary because chemoradiotherapy has achieved only modest improvements in median survival and minimal increases in long-term survival [3].

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Hyperfractionation, the administration of a larger number of smaller doses per fraction, is one of the promising and tempting alternatives to conventional radiation therapy. One possible advantage of hyperfractionation is that this approach may permit an improvement in tumor control by increasing the total tumor dose without increasing the risk of late complications [4]. Several encouraging results of this therapeutic modality have been reported in patients with head and neck cancer or lung cancer [5, 6]. However, only limited information about hyperfractionated radiation therapy is available for pancreatic cancer. Therefore, we conducted a phase I study of hyperfractionated radiation therapy with 5-fluorouracil (5-FU) in patients with locally advanced pancreatic cancer. In the present study, 5-FU was administered by protracted infusion during the radiation course to intensify the anti-tumor effect of chemotherapy. The primary objective of this study was to assess the toxicity of hyperfractionated radiation therapy with protracted 5-FU infusion and to determine the maximum-tolerated dose of radiation in this combined treatment.

Patients and Methods

Patients

Eligibility criteria included (1) locally advanced unresectable pancreatic cancer; (2) histologically or cytologically confirmed adenocarcinoma of the pancreas; (3) 20–74 years of age; (4) an Eastern Cooperative Oncology Group performance status of 0–2, and (5) no prior anti-cancer treatment. Required pretreatment laboratory data included white blood cell count ≥4,000/μl, hemoglobin level ≥10 g/dl, platelet count ≥100,000/μl, normal serum creatinine level, serum total bilirubin level ≤2.0 mg/dl, serum albumin level ≥3.0 g/dl and serum transaminase level ≤2.5 × upper normal limit. Exclusion criteria were: 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. A chest X-ray and abdominal computed tomography (CT) were performed on all patients before treatment. The disease was considered locally advanced if abdominal CT revealed celiac trunk and/or superior mesenteric artery encasements with no evidence of systemic metastasis. Diagnostic laparoscopy was not performed. Histological and/or cytological confirmation was obtained by needle biopsy. Endoscopic or percutaneous biliary drainage was performed before treatment in patients with obstructive jaundice. This protocol was approved by the Institutional Review Board of the National Cancer Center. All patients received a full explanation of this study and gave written informed consent before entry into the study.

Treatment

The study design consisted of a sequential dose escalation of radiation therapy. The radiation dose level was planned in five cohorts as shown in table 1. The starting dose of radiation was 45.6 Gy, deemed safe based on the results of previous studies of hyperfractionation for pancreatic cancer [7–9]. Dose escalations at 4.8-Gy increments were planned if the previous dose had been tolerated. All patients received two fractions of 1.2 Gy each (separated by 6 h) per day for 5 days a week using 10–14 MV X-rays from a microtron (MM22, Scanditronix, Uppsala, Sweden). Treatment planning was determined by a three-dimensional treatment planner (FOCUS, Computerized Medical Systems, St. Louis, Mo., USA). Contours of the clinical target volume, which included the primary tumor, regional lymph nodes detected by CT, and paraaortic regions at celiac and supramesenteric axes were manually outlined on serial CT images displayed on a monitor. The definition of the regional lymph nodes followed the 6th edition of the UICC TNM Classification. Paraaortic lymph node metastasis was considered distant metastasis. A planning target volume which included a 10-mm margin of normal tissue surrounding the clinical target volume was defined on each CT image and on the craniocaudal dimension. Four field techniques (anterior, posterior and opposed lateral fields) were used. Spinal cord dose was maintained below 45 Gy, ≥50% of liver was limited to ≤30 Gy, and ≥50% of both kidneys were limited to ≤20 Gy. Chemotherapy consisted of protracted infusion of 5-FU at a dose of 200 mg/m^2/day, which began on the first day of radiation and continued through the entire radiation course. One week after the completion of chemoradiotherapy, maintenance chemotherapy of 5-FU (500 mg/m^2, drip infusion) was given weekly until disease progression or unacceptable toxicity.

The toxicity of the treatment was scored according to the criteria of the Japan Society for Cancer Therapy [10], which are fundamentally similar to the National Cancer Institute common toxicity criteria. Both radiation therapy and chemotherapy were suspended for grade 3 hematological toxicity or grade 2 non-hematological toxicity excluding nausea/vomiting and anorexia during the treatment course, and treatment was restarted when toxicity was resolved. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematological toxicities (excluding nausea/vomiting and anorexia) or grade 4 hematological toxicity occurring during chemoradiotherapy or within 4 weeks after completing treatment. If both radiation therapy and chemotherapy were suspended for more than 10 days due to adverse effects, the adverse effects were considered DLT.

Table 1. Dose-escalation scheme for maximum-tolerated doses in hyperfractionated radiation therapy

Study cohort	Dose/fraction Gy	Total fractions	Total dose, Gy	Treatment duration, days
1	1.2	38	45.6	25
2	1.2	42	50.4	29
3	1.2	46	55.2	31
4	1.2	50	60.0	33
5	1.2	54	64.8	37

Treatment duration is given from the first day to the last day of radiation.

Radiation dose escalation was scheduled to proceed as follows. Initially, 3 patients were to be studied in cohort 1. If none of the initial 3 patients in a cohort experienced DLT, the radiation dose was to be increased in the next 3 patients according to the schedules listed in table 1. If 1 or 2 of the initial 3 patients in a cohort experienced DLT, a maximum of 3 additional patients were entered into the cohort. If only 1 or 2 of 6 patients experienced DLT, dose escalation would continue. If 3 or more patients experienced DLT at a given dose level, then the previous dose level would be considered maximum-tolerated dose. Dose escalation to the next cohort was allowed after observing a previous cohort for a minimum of 4 weeks after the completion of chemoradiotherapy.

Follow-up CT was performed every 2 months to assess objective tumor response according to World Health Organization criteria [11]. Progression-free and overall survival were measured from the 1st day of study entry, and the survival rate was calculated by the Kaplan-Meier method. Serum CA 19-9 levels were measured monthly by radioimmunometric assay using the Centocor radioimmunoassay kit (Centocor, Malvern, Pa., USA).

Table 2. Patient characteristics (n = 29)

Characteristics	Patients	
	n	%
Gender		
Men	17	59
Women	12	41
Performance status		
0	5	17
1	24	83
Biliary drainage	7	24
Tumor location		
Head	9	31
Body-tail	20	69

Median carcinoembryonic antigen was 2.9 ng/ml (range: 0.9–42.1) and median CA 19-9 429 U/ml (range: 1–16,680). Median age of the patients was 59 years (range 32–74).

Results

Patient Characteristics

Between April 1999 and May 2001, 29 patients with locally advanced, unresectable pancreatic cancer were enrolled in the study at the National Cancer Center Hospital, Tokyo, Japan. The demographic characteristics of the 29 patients are listed in table 2. Relatively many patients with pancreatic body-tail cancer were enrolled in the study. All patients were in stage III according to the UICC TNM Classification (ed 6).

Toxicities

All 29 patients were assessable for toxicity. Two of the 29 patients failed to complete chemoradiotherapy for reasons other than toxicity: 1 patient at dose level 1 abandoned treatment after 25.2 Gy because of disease progression, and another patient at dose level 3 refused to continue treatment after 50.4 Gy, although there were no clinically significant adverse effects. Of the 27 patients evaluable for DLT, 22 (81%) completed the scheduled course of chemoradiotherapy. However, the remaining 5 had to abandon treatment because of adverse effects: nausea/vomiting and anorexia (3 patients), alanine aminotransferase elevation (1 patient) and thrombocytopenia (1 patient). Table 3 shows the toxicities that occurred during chemoradiotherapy or within 4 weeks after completing treatment. Hematological toxicity was relatively mild and reversible. Two patients exhibited grade 3 neutropenia, but these toxicities recovered immediately after interruption of chemoradiotherapy. Although thrombocytopenia was a rare toxicity, 1 patient at level 5 showed grade 4 thrombocytopenia after 52.8 Gy. Since this thrombocytopenia persisted after discontinuation of chemoradiotherapy, bone marrow aspiration was performed, and the patient was diagnosed with myelodysplastic syndrome. The most common non-hematological toxicities were nausea/vomiting and anorexia, which were observed in 27 (93%) and 24 patients (83%), respectively. These adverse effects were generally mild to moderate, but 5 patients required temporary treatment interruption (median, 2 days; range, 2–5 days) and 3 patients abandoned chemoradiotherapy because of prolonged toxicities. Other non-hematological toxicities included diarrhea and liver dysfunction, but these were also generally mild and transient. During the median follow-up period of 8.2 months (range, 1.7–26 months), late radiation-related toxicity was observed in only 1 patient, who developed bleeding from a gastric ulcer 3 months after the completion of chemoradiotherapy (level 1, 45.6 Gy) and then recovered from the ulcer by conservative treatment. There were no life-threatening toxicities, and no treatment-related deaths occurred. Table 4 summarizes the DLT observed in the current study. The maximum-tolerated dose of this phase I study was not reached even at the highest dose level (level 5, 64.8 Gy).

Therapeutic Results and Patient Outcome

Six patients (21%) achieved a partial response, 19 (66%) remained stable and 4 (14%) showed progressive disease demonstrated by the development of distant metastases. The serum CA 19-9 level was reduced more than

Table 3. Treatment-related toxicity (n = 29)

Toxicities	Study cohort														
	1 45.6 Gy (n = 6)			2 50.4 Gy (n = 3)			3 55.2 Gy (n = 7)			4 60.0 Gy (n = 6)			5 64.8 Gy (n = 7)		
	1, 2	3	4	1, 2	3	4	1, 2	3	4	1, 2	3	4	1, 2	3	4
Hematological															
Anemia	1	0	0	0	0	0	4	0	0	0	0	0	0	0	0
Leukocytopenia	3	0	0	3	0	0	6	1	0	3	0	0	4	0	0
Neutropenia	3	0	0	2	0	0	2	2	0	2	0	0	1	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0	2	0	0	0	0	1
Non-hematological															
Anorexia	2	3	0	2	0	0	4	3	0	1	3	0	3	3	0
Nausea/vomiting	5	0	0	3	0	0	7	0	0	3	2	0	7	0	0
Diarrhea	1	0	0	1	0	0	1	1	0	1	0	0	3	0	0
Stomatitis	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
AST/ALT	3	0	0	1	0	0	3	0	0	1	1	0	2	0	0
Alkaline phosphatase	1	0	0	0	0	0	1	0	0	2	0	0	0	0	0
Skin rash	1	0	0	0	0	0	2	0	0	1	0	0	0	0	0
Abdominal pain	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Fatigue	3	1	0	2	0	0	5	0	0	4	0	0	5	0	0
Weight loss	0	0	0	1	0	0	2	0	0	2	0	0	1	0	0

AST = Aspartate aminotransferase; ALT = alanine aminotransferase.

Table 4. Dose-limiting toxicity (n = 27)

Study cohort	Patients	Patients with DLT	DLT	Total dose at DLT, Gy
1 (45.6 Gy)	6[a]	1	suspension of treatment for >10 days[b]	31.2
2 (50.4 Gy)	3	0		
3 (55.2 Gy)	6	2	suspension of treatment for >10 days[b]	36.0
			grade 3 diarrhea	55.2
4 (60.0 Gy)	6	2	suspension of treatment for >10 days[b]	31.2
			grade 3 ALT elevation	46.8
5 (64.8 Gy)	6	1	grade 4 thrombocytopenia	52.8

ALT = Alanine aminotransferase.
[a] One patient developed gastric ulcer 3 months after the completion of chemoradiotherapy.
[b] Due to nausea/vomiting and anorexia.

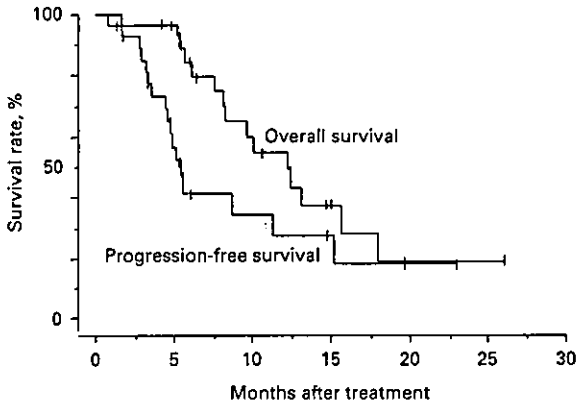

Fig. 1. Overall survival curve and progression-free curve of 29 patients who received hyperfractionated radiotherapy with protracted 5-FU infusion for locally advanced pancreatic cancer. Vertical lines indicate censored cases.

Table 5. Patterns of initial disease progression

Progression	Patients	
	n	%
None	10	34
Local	2	7
Distant	15	52
Liver	8	
Lymph nodes	3	
Peritoneum	1	
Liver and peritoneum	2	
Lung and peritoneum	1	
Local and distant[a]	2	7

[a] Peritoneum.

50% in 12 (55%) of 22 patients who had a pretreatment level of 100 U/ml or greater. Disease progression and death from cancer were documented in 19 and 13 patients, respectively, at the time of analysis. The initial sites of disease progression are listed in table 5. Distant metastases predominated over local progression. The median progression-free time and 1-year progression-free rate were 5.4 months and 20.2%, respectively. The median survival time (MST) and 1-year survival rate were 12.2 months and 55.0%, respectively (fig. 1).

Discussion

Based on previous randomized trials, concurrent external-beam radiotherapy and chemotherapy have been the treatment of choice for locally advanced, unresectable pancreatic cancer [1, 2]. Nevertheless, there is substantial room for improvement in chemoradiotherapy for pancreatic cancer because chemoradiotherapy has achieved only modest improvements in median survival and minimal increase in long-term survival to date [3]. Therefore, there is a clear need to establish more effective chemoradiotherapy for locally advanced pancreatic cancer.

Since local relapse of disease after chemoradiotherapy remains high, local tumor control and systemic chemotherapy are necessary for locally advanced pancreatic cancer. To intensify local tumor control, numerous clinical trials have been performed with specialized radiotherapy techniques, including intraoperative radiotherapy, brachytherapy, high-dose conformal radiotherapy and hyperfractionated radiation therapy [7–9, 12–15]. It is noteworthy that relatively good local tumor control and survival were achieved in these trials in which a higher dose was given using external-beam radiotherapy combined with either intraoperative radiotherapy or brachytherapy. These findings suggest the efficacy of dose-intensive radiotherapy for locally advanced pancreatic cancer.

Hyperfractionation is expected to produce a differential effect between the response in tumor and normal tissues. The basic rationale of hyperfractionation is that the use of small dose fractions allows higher total doses to be administered within the tolerance of late-responding normal tissues and that this translates to a higher biologically effective dose to the tumor [4]. Other rationales for hyperfractionation are radiosensitization through redistribution and reduced dependence on oxygen effect [4, 16, 17]. Clinical trials have demonstrated that hyperfractionated radiotherapy has a favorable treatment efficacy in some types of tumors, including head and neck cancer and lung cancer [5, 6].

With regard to pancreatic cancer, however, only limited information about hyperfractionated radiation is available. In 1990, the Gastrointestinal Tumor Study Group reported on hyperfractionated radiation therapy in patients with locally advanced pancreatic cancer [7]. In this study, 18 patients received two fractions of 1.2 Gy each per day (total 50.4 Gy) and bolus 5-FU infusion (350 mg/m^2) on the first 3 and last 3 days of radiation therapy. However, the study results were not encouraging: the MST and 1-year survival rate were 35 weeks and

Table 6. Comparison of toxicity, response rate and MST

Toxicity and response	Patients, n (%)	
	current study (n = 29)	conventional regimen (n = 20)
≥ Grade 2 toxicity		
Leukocytopenia	8 (28)	4 (20)
Thrombocytopenia	1 (3)	0 (0)
Nausea/vomiting	21 (72)	3 (15)
Diarrhea	2 (7)	0 (0)
Stomatitis	0 (0)	3 (15)
ALT elevation	5 (17)	2 (10)
Response rate	6 (21)	2 (10)

MST was *12.2* months in the current study and *10.4* months in patients treated with the conventional regimen. ALT = Alanine aminotransferase.

39%, respectively. Prott et al. [8] treated 32 patients with locally advanced pancreatic cancer by hyperfractionated radiation therapy (total 44.8 Gy) along with 5-FU and leucovorin (MST, 12.7 months), and Luderhoff et al. [9] conducted a pilot study using a combination of hyperfractionated radiation (total 45–50 Gy) and continuous infusion of 5-FU in 13 patients (MST, 36 weeks). Summarizing these three trials, although toxicities seemed to be acceptable, improved survival was unfortunately not achieved. However, the total dose of radiation used in these trials might have been insufficient to obtain adequate local tumor control. Therefore, in the current study, we conducted a phase I study, and concluded that the toxicity associated with our regimen was tolerable up to a total dose of 64.8 Gy. Our conclusions were consistent with the results of the recent phase I–II study for locally advanced pancreatic cancer, in which Ashamalla et al. [18] reported that the use of hyperfractionated radiotherapy (2 fractions of 1.1 Gy each per day) to a dose of 63.8 Gy combined with weekly paclitaxel was tolerated. They also reported that good local control was observed following their regimen; complete relief of pain was achieved in 10 of 14 patients, and objective response was achieved in 5 of 17 evaluable patients.

The adverse effects associated with our regimen seemed to be tolerable. There were no life-threatening toxicities, and no treatment-related deaths occurred. However, acute reactions such as gastrointestinal toxicity were more severe compared with conventional regimens of chemoradiotherapy. Table 6 shows a comparison of adverse effects between our hyperfractionated chemoradiotherapy and the conventional chemoradiotherapy previously performed in our hospital, which consisted of protracted 5-FU infusion (200 mg/m^2/day) with current radiation therapy (50.4 Gy in 28 fractions over 5.5 weeks) [19]. Although hematological toxicity did not significantly differ between these two regimens, nausea/vomiting were more frequently observed in the hyperfractionated chemoradiotherapy. As a result, 8 of 29 (28%) patients treated by hyperfractionated chemoradiotherapy required treatment interruption due to gastrointestinal toxicities, and 3 of the 8 patients abandoned chemoradiotherapy. It is interesting that these 3 patients developed such gastrointestinal toxicities before reaching a total radiation dose of 40 Gy (31.2, 36.0, and 31.2 Gy, respectively). Therefore, although this schedule of hyperfractionated radiation therapy was acceptable for most patients with pancreatic cancer, some patients developed severe and/or prolonged acute toxicities at a relatively low total radiation dose. There was no significant association between the gastrointestinal toxicities and pretreatment factors including gender, age, performance status, and tumor location (data not shown).

In the current study, relatively good local tumor control was obtained: 6 patients (21%) achieved a partial response and 19 (66%) remained stable. At the time of analysis, local disease progression had occurred in only 4 (14%) patients. In addition, the MST of 12.2 months was equal or superior to that of previous studies using conventional fractionation [1, 2, 19]. These findings have encouraged us to conduct further trials of hyperfractionated chemoradiotherapy. However, the incidence of distant metastasis did not decrease after treatment in the present study. Therefore, more effective systemic therapy will be necessary to reduce distant metastases and subsequently improve long-term survival.

In conclusion, the toxicity associated with our regimen was tolerable up to dose level 5 (64.8 Gy). Hoping to demonstrate a superior survival benefit for patients with locally advanced pancreatic cancer, we are currently conducting a phase II trial of this hyperfractionated radiation therapy with protracted 5-FU infusion at a dose of 64.8 Gy.

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