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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 $\times$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 $\times$7 followed by 1 week rest and weekly $\times$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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