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H．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

研究成果の刊行に関する一覧表

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切除不能膵がんに対する治療法の確立に関する研究

平成１６～１８年度　研究成果の刊行物・別刷

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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.