J Gastroenterol 2006; 41:70–76
DOI 10.1007/s00535-005-1724-7

Journal of
Gastroenterology

Comparison of standard-dose and low-dose gemcitabine regimens in pancreatic adenocarcinoma patients: a prospective randomized trial

Hiroki Sakamoto[1], Masayuki Kitano[1], Yoichirou Suetomi[1], Yoshifumi Takeyama[2], Harumasa Ohyanagi[2], Takuya Nakai[2], Chikao Yasuda[2], and Masatoshi Kudo[1]

[1] Department of Gastroenterology and Hepatology, Kinki University School of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama 589-8511, Japan
[2] Department of Surgery, Kinki University School of Medicine, Osaka, Japan

Background. A prospective, randomized study was performed to determine whether gemcitabine infusion at a low dose (250 mg/m^2) is comparable or superior to the standard-dose infusion (1000 mg/m^2) in terms of the survival period, clinical benefit, and frequency of adverse effects in patients with advanced pancreatic adenocarcinoma. ***Methods.*** Twenty-five patients who were histologically proven to have locally advanced pancreatic cancer or pancreatic cancer with distant metastases were initially enrolled in the present study. They were treated with gemcitabine infusion at either a dose of 1000 mg/m^2 over 30 min (the standard regimen) on days 1, 8, and 15 of every 4-week cycle or at a dose of 250 mg/m^2 over 30 min every week. Survival time, response rate, time to treatment failure, clinical benefit response, and adverse effects were compared between the two groups. ***Results.*** Twenty-one patients received gemcitabine for more than 1 month. The median survival period was 7.2 months for patients who received the low-dose infusion regimen, in contrast to 5.2 months for patients administered the standard-dose infusion regimen. The time to treatment failure was 5.6 months for patients in the low-dose infusion regimen, in contrast to 3.4 months for patients in the standard-dose infusion regimen. There were no significant differences in either survival time to time to treatment failure or clinical benefits between the two groups, but the incidence of adverse reactions in patients administered the low-dose therapy was significantly lower than that in patients receiving the standard-dose therapy ($P < 0.05$). In particular, patients in the standard infusion regimen group experienced more hematologic toxicity than those in the low-dose regimen. ***Conclusions.*** These findings suggest that the low-dose gemcitabine infusion regimen can be continuously administered to patients with locally advanced and systemically spreading pancreatic cancer because of its reduced toxicity, resulting in better quality of life and an improved safety profile as compared to the standard infusion treatment regimen.

Key words: gemcitabine, pancreatic adenocarcinoma, low-dose therapy

Introduction

Pancreatic cancer is the fifth leading cause of cancer deaths in Japan.[1] In 2001 in Japan, 18269 diagnosed cases of pancreatic cancer were reported, and 19397 pancreatic cancer patients died.[2] Despite development of imaging diagnosis techniques for early detection of pancreatic cancer, the 5-year survival rate of newly diagnosed pancreatic cancer patients is still as low as 13%.[2] This poor survival rate may be attributable to both the high incidence of metastatic diseases at the time of diagnosis and the resistance of this tumor to existing chemotherapeutic agents. Enhancing the efficacy of currently available chemotherapeutic regimens may improve the prognoses of pancreatic cancer patients.

Gemcitabine, the most commonly used cytotoxic agent, is relatively effective against pancreatic cancer.[3] In a randomized controlled comparative study between gemcitabine and 5-FU, the median survival in the gemcitabine arm (5.65 months) was longer than that in the 5-FU arm (4.41 months). Other clinical benefits, such as pain relief, were also superior following treatment with gemcitabine as compared to 5-FU. However, side effects were more frequent after treatment with gemcitabine compared to treatment with 5-FU. Hematologic toxicities higher than grade 3 occurred more

Received: January 27, 2005 / Accepted: August 8, 2005
Reprint requests to: M. Kudo

frequently in the gemcitabine arm than in the 5-FU arm (neutropenia: 25.9% in gemcitabine versus 4.9% in 5-FU; anemia: 9.7% in gemcitabine versus 0.0% in 5-FU; thrombocytopenia: 9.7% in gemcitabine versus 1.6% in 5-FU). The frequency of vomiting severity of grade 3 or worse in the gemcitabine arm (12.7%) was higher than in the 5-FU arm (4.8%).[3] In the phase I study, infusion of gemcitabine (875 mg/m^2 on days 1, 8, and 15 of every 4-week cycle) over 60 min produced a high frequency of bone marrow suppression and liver dysfunction.[4] In addition, the lower dose of gemcitabine (300 mg/m^2) over more than 1 h resulted in a high incidence of side effects.[4] These results suggest that gemcitabine infusion with a duration of longer than 60 min is toxic for patients.

Tempero et al.[5] reported that the concentration of the active metabolite of gemcitabine (gemcitabine triphosphate, dFdCTP) in mononuclear cells increased linearly with an increase in gemcitabine doses from 35 to 250 mg/m^2, and reached a plateau (20 μmol/l) at doses of more than 350 mg/m^2. Thus, the target gemcitabine concentration in plasma was achieved, and the rate of gemcitabine triphosphate accumulation (20 μmol/l) by mononuclear cells was optimized at dose rates of approximately 10 mg/m^2 per minute, although an infusion duration of longer than 60 min caused a higher incidence of adverse effects.[5] Thus, we speculated that the lowest infusion dose (250 mg/m^2) of gemcitabine for 30 min, attaining a near-maximal level of mononuclear dFdCTP, might produce similar effects with fewer adverse events compared with the standard dose.

This study was undertaken to determine both the efficacy and safety of gemcitabine administered as either a standard infusion dose (1000 mg/m^2) or as a low-dose infusion (250 mg/m^2) in 25 patients with locally advanced or distant metastasized advanced pancreatic cancer.

Subjects and methods

Patient Selection

This was a single-institution study involving consecutive patients with advanced pancreatic cancer. The study was open from April 2001 to May 2004, during which time 25 patients were recruited. The patients were followed up until June 2005 when data analysis was performed.

All patients were histologically or cytologically proven to have locally advanced or distant metastasized adenocarcinoma of the pancreas by endoscopic ultrasound-guided fine-needle aspiration ($n = 18$), cytology of pure pancreatic juice obtained by endoscopic retrograde pancreatography ($n = 5$), or biopsy of liver metastasis ($n = 2$). Eligibility criteria were age >20 years, Eastern Cooperative Oncology Group performance status (ECOG-PS)[6] of 0 to 2, life expectancy >12 weeks, and continuation of therapy for more than 1 month. Furthermore, eligible patients were required to have adequate organ function, defined as a WBC count >3500/mm^3, platelet count >125 000/mm^3, hematocrit >30%, hemoglobin >10 g/l, bilirubin less than 2.0 mg/dl, and aspartate aminotransferase (AST) <3.0 times the normal limit. The study was approved by the ethical committee of Kinki University School of Medicine. Written informed consent was obtained from all the patients before entering the study.

Study design

Using a two-envelope factorial design, patients were randomly assigned to receive intravenous infusion of gemcitabine at a dose of either 1000 mg/m^2 over 30 min (defined as the standard arm) on days 1, 8, and 15 of every 4-week cycle, or 250 mg/m^2 over 30 min every week.[7,8] All patients were pretreated with granisetron hydrochloride (3 mg). If nausea continued after the infusion, metoclopramide, ramosetron hydrochloride, or prochlorperazine was administered.

Dosages were calculated based on patient body-surface area (BSA), which was determined according to the actual height and weight measured at the beginning of each cycle. Weekly doses were modified based on absolute granulocyte counts (AGC), platelet counts, and the clinical assessment of nonhematological toxicities on scheduled treatment days. For example, when the AGC decreased to between 0.5×10^9/l and 0.99×10^9/l, or when the platelet count was between 50×10^9/l and 74×10^9/l, doses of gemcitabine were reduced to 50%, but the treatment itself was continued. However, no gemcitabine was given when the AGC was less than 0.5×10^9/l or when platelet counts were less than 50×10^9/l. In case of nonhematological toxicities indicative of grade 3 or 4 as defined by the World Health Organization (WHO), the gemcitabine dosage was reduced to 50% of the intended dose. In patients with WHO grade 4 granulocytopenia, thrombocytopenia, or nonhematologic toxic effects during a treatment course, the starting dose for the next cycle was reduced to 75% of the intended dose. Neutrophilic growth factors were administered for the treatment of prolonged myelosuppression (AGC $< 0.5 \times 10^9$/l for at least 5 days, neutropenic fever of any duration, or neutropenia with a documented infection).

Baseline efficacy and safety evaluation

Before treatment, the clinical and objective status of each patient was assessed by medical history, weight measurement, complete physical examination, and

disease-related symptoms such as pain intensity, analgesic requirement, performance status (PS using an ECOG scale), and serum CA19-9 determination. Other pretreatment evaluations included a baseline radiologic assessment by contrast-enhanced computed tomography (CE-CT) scan and contrast-enhanced ultrasonograpy (CE-US).[9,10] Blood chemistry was also investigated, and urinalysis, ECG, and chest X-ray were done.

Pain intensity was measured by visual analog scale (0–10). Pain scores were assessed using a standardized 11-point continuous visual analog pain scale, with 0 equaling no pain, 5 moderate pain, and 10 the worst pain ever.[11] ECOG PS was evaluated as 0 (fully active, able to carry on all predisease activities without restriction), 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work), 2 (ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours), 3 (capable of only limited self-care, confined to bed or chair more than 50% of waking hours), 4 (completely disabled; incapable of any self-care and totally confined to bed or chair), or 5 (dead).[6]

Evaluation of response

During treatment, all patients were observed with limited physical examinations, including weight measurement, evaluation of disease-related symptoms, analyses of responses to an analgesic use questionnaire (based on a graded scale for categorization of analgesics required), assessment of PS, urinalysis, and toxicity rating and radiological assessment. Analgesic use level, PS, weight, and clinical symptoms were recorded weekly at each clinical visit. Serum CA 19-9 was measured before each treatment cycle. Radiological assessment was undertaken every two cycles and whenever clinical assessment suggested disease progression.

CA19-9 response was defined as a decline of more than 50% from baseline CA19-9 levels at at least one subsequent time point.[12,13] Tumor measurements were assessed using images generated by CE-CT and CE-US.[10] Standard WHO tumor response criteria were used to determine objective tumor response.[14] Complete response (CR) was defined as the disappearance of all measurable and evaluable diseases for at least 4 weeks without appearance of any new lesion. Partial response (PR) indicated a reduction greater than or equal to 50% of the sum of the greatest perpendicular dimensions of all measurable lesions for at least 4 weeks without appearance of new lesions. Stable disease (SD) represented a decrease <50% in the sum of the greatest perpendicular dimensions of measurable lesions or an increase <25% of the sum of products of the greatest perpendicular dimensions of measurable disease for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase >25% of the sum of measurable lesions, the appearance of new lesions, or aggravation of any evaluable disease.

The survival period was measured from the time of initiation of the therapy until death or to the last follow-up exam. The study was discontinued in patients who showed unacceptable toxicities or evidence of progressive disease, or at the patient's or investigator's request. Time to treatment failure was defined as the time from the initiation of therapy to the first observation of PD or discontinuation due to worsening of PS and adverse effects.

Clinical benefit was evaluated by PS, pain intensity, analgesic consumption, and body weight. Pain improvement was defined as an improvement of >50% from baseline over at least 4 weeks, pain worsening was defined as worsening from baseline over at least 4 weeks, and pain stable was defined as unchanged results. PS improvement was defined as a decrease from baseline over at least 4 weeks, and PS worsening as an increase from baseline over at least 4 weeks, and PS stable as any other results. Analgesic consumption was measured weekly in morphine-equivalent milligrams. Analgesic consumption decrease was defined as a decrease of >50% from baseline over at least 4 weeks, analgesic consumption worsening as worsening from baseline over at least 4 weeks, and analgesic consumption stable as other results. Weight improvement was defined as a weight gain (excluding third-space fluid) of >7% from baseline over at least 4 weeks, weight worsening as weight loss (excluding third-space fluid) of <7% from baseline over at least 4 weeks, and weight stable as other results.

Evaluation of adverse effects

Safety evaluation was performed by weekly history and physical examinations, complete blood counts, chemistry profiles, and urinalyses. All signs, symptoms, or laboratory abnormalities were assessed using WHO criteria for toxicities.

Statistical analysis

The survival curves were calculated according to the Kaplan-Meier method. Statistical differences in survival time and time to treatment failure between the two treatment arms were calculated using the log-rank test. The χ-squared test for nonparametric data was performed to compare the clinical benefits and the number of adverse effects between the two examinations.

Table 1. Baseline characteristics

	Low dose (n = 11)	Standard dose (n = 10)
Age, years		
Median	66.2	67.9
Range	50–80	57–84
Sex		
Male	5/11	5/10
Female	6/11	5/10
ECOG PS		
0	10/11	8/10
1/2	1/10	2/10
Primary tumor site		
Head	8/11	5/10
Body	2/11	3/10
Tail	1/11	2/10
Extent of disease		
Locally advanced	4/11	3/10
Metastatic	7/11	7/10

ECOG PS: Eastern Cooperative Oncology Group performance status

Table 2. Response in both arms

	Low dose (n = 11)		Standard dose (n = 10)	
	No. of patients	%	No. of patients	%
Complete response	0/11	0	0/10	0
Partial response	2/11	18	2/10	20
Stable disease	5/11	45	3/10	30
Progressive disease	4/11	36	5/10	50

Results

Patient characteristics

Between April 2001 and May 2004, 25 patients initially enrolled in the trial were randomly assigned to the two arms. Of these, four were found to be ineligible within 1 month: two in the low-dose infusion regimen and two in the standard-dose infusion regimen. Reasons for discontinuation within 1 month were disseminated intravascular coagulation in two (one in the standard-dose arm, one in the low-dose arm) and occurrence of severe vomiting (grade 4) after the initial therapy (one in the standard-dose arm). One patient changed his decision to participate in the study (low-dose arm). Of the remaining 21 patients, 11 received the standard-dose and 10 the low-dose therapy (Table 1). All patients were assessed for safety. The two groups were well balanced for prognostic factors. The median age of patients was 67 years (range, 50 to 84 years), and ten patients (45%) were men. Patient characteristics at study entry are shown in Table 1. Fourteen patients had metastatic diseases, and seven patients had surgically unresectable locally advanced disease. Most patients had pain at the start of the study: six (55%) on the low-dose infusion regimen and seven (70%) on the standard-dose infusion regimen. Three (30%) on the low-dose regimen and four (36%) on the standard-dose regimen used morphine. An ECOG-PS of 0 was recorded in ten (91%) and eight (80%), and ECOG 1 to 2 was recorded in one (9%) and two (20%), patients randomized to the low-dose group and standard-dose group treatment, respectively. There were no significant differences in age, sex, performance status, or spread of diseases between the two groups.

Tumor response

All the patients who completed at least one cycle of therapy were evaluated for objective antitumor response (Table 2). The CR+PR rate accounted for 18% (2/11) in the low-dose arm and 20% (2/10) in the standard-dose arm. CA19-9 responders were 36% (4/11) in the low-dose arm and 30% (3/10) in the standard arm. Change in tumor size and CA19-9 levels did not differ significantly between the groups.

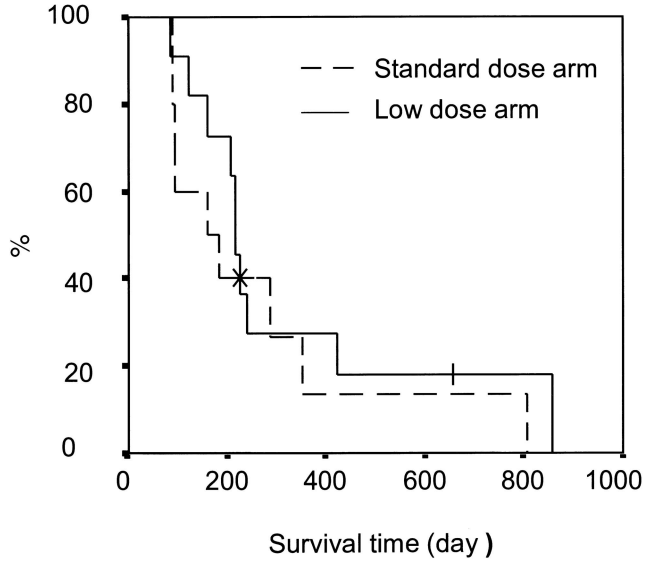

Fig. 1. Comparison of survival time between the low-dose arm and the standard-dose arm. The Kaplan-Meier estimates of the overall survival duration in the low-dose ($n = 11$) and standard-dose ($n = 10$) therapy groups

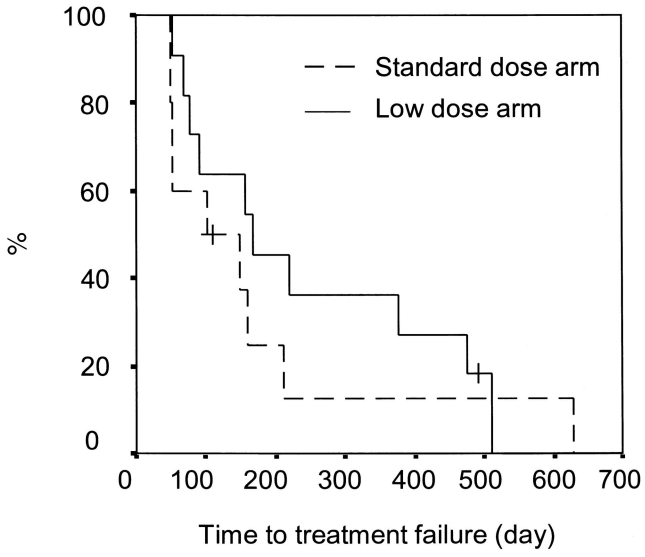

Fig. 2. Comparison of time to treatment failure between the low-dose arm and the standard-dose arm. The Kaplan-Meier estimates of overall survival by disease extent or discontinuation in the low-dose ($n = 11$) and standard-dose ($n = 10$) therapy groups

Survival period

The median survival time for all patients was 5.2 months [95% confidence interval (CI), 2 to 24.6 months] in the standard arm and 7.2 months (95% CI, 2.9 to 21.5 months) in the group receiving low-dose therapy. The Kaplan-Meier estimates of survival are shown in Fig. 1. Survival did not differ significantly between the two groups ($P = 0.47$).

Time to treatment failure

In the standard-dose arm, the median time to treatment failure for all patients was 3.4 months (1.5 months to 18 months) and 5.6 months (1.5 months to 17.6 months) in the low-dose therapy group (Fig. 2). Time to treatment failure did not differ significantly between the two groups ($P = 0.46$).

Other parameters of efficacy

The analgesic category was improved in 3 (30%) of 10 patients in the standard arm and in 2 (18%) of 11 patients in the low-dose arm. A summary of changes in ECOG-PS in the standard arm showed that PS was stable in 5 (50%) of 10 patients and worse in 5 (50%). In the low-dose arm, ECOG-PS showed improvement in one, stable in seven, and worse in three (27%) patients. The PS became worse in the two patients with PS of 1 to 2 in the standard arm, while it improved in the patient with PS of 1 to 2 in the low-dose arm. In the standard-dose arm, pain was improved in three (30%) of ten patients. In the low-dose arm, pain was improved in 2 (18%) of 11 patients. In the standard arm, one (10%) of ten patients had weight improvement, five patients (50%) maintained stable weight, and the weight of four patients (40%) worsened. In the low-dose arm, reduction of weight loss was observed in 4 (36%) of 11 patients, 5 patients (45%) maintained stable weight, and 2 patients (18%) lost more weight. None of these differences was statistically significant.

Table 3. Toxicities in both arms

Toxicity	Low dose	Standard dose
Anemia	0	3
Neutropenia	1	3
Thrombocytopenia	0	3
General fatigue	3	5
Nausea/vomiting	1	2
Diarrhea	1	4
Total	5	20

χ-squared test, $P = 0.0012$

Adverse effects

Grade 3 and 4 adverse effects for each patient are summarized in Table 3. Twenty episodes of WHO grade 3 and 4 toxicities were observed in the standard-dose arm, whereas six episodes were noted in the low-dose therapy group. The incidence of toxic effects noted in

the standard-dose therapy group was significantly higher than in the low-dose therapy group ($P < 0.005$). Incidences of WHO grade 3 or 4 neutropenia (30% versus 9%), thrombocytopenia (30% versus 0%), and anemia (30% versus 0%) in the standard therapy arm were consistently higher, compared with those in the low-dose therapy arm. The difference in hematological toxicities between the groups was prominent ($P = <0.001$). Incidences of WHO grade 3 or 4 vomiting were 20% in the standard-dose arm and 9% in the low-dose arm. Five (50%) and four (36%) patients required antiemetics other than granisetron hydrochloride in the standard-dose arm and low-dose arm, respectively.

Dose omissions and reductions

Among the ten patients in the standard-dose therapy group, the dose was titrated downward in two patients (20%), and the second dose was skipped in two patients (20%). The dose reduction and omission in the standard arm were due to neutropenia. In contrast to the standard-dose arm, the patients in the low-dose arm received dose reductions due to onset of nausea and vomiting, but neither anemia nor neutropenia necessitated dose reduction. Discontinuation in the standard arm was necessary (not considering progressive disease) owing to worsening PS ($n = 2$), neutropenia ($n = 1$), or vomiting ($n = 1$). Among the 11 patients in the low-dose arm, dose discontinuation due to side effects was not necessary. All patients in the low-dose arm continued to receive gemcitabine without discontinuation until disease progression.

Discussion

Gemcitabine is an effective drug in the treatment of patients with metastatic pancreatic carcinoma.[3,15–17] It is clinically more beneficial in more patients than other chemotherapeutic agents such as 5-FU,[3,5,15–21] but its efficacy is still insufficient even when combined with other agents.[18,22] The standard dosage of gemcitabine in Japan against pancreatic adenocarcinomas has been 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks. However, this dose induces bone marrow suppression and worsens performance status so frequently that some patients, particularly elderly patients,[23] forgo treatment. Therefore, an optimal gemcitabine dosage and treatment schedule should be determined in order to prolong quality of life. Because the concentration of the active metabolite of gemcitabine (gemcitabine triphosphate, dFdCTP) in mononuclear cells was optimized at doses of more than 250 mg/m^2, we hypothesized that the lowest dose (250 mg/m^2) needed to reach the near-maximal level of dFdCTP might produce similar effects with fewer adverse events. Hence, we investigated the effect of low-dose gemcitabine on pancreatic adenocarcinomas in comparison with the standard dose.

In the present study, intravenous infusion of the standard dose of gemcitabine resulted in a median survival of 5.2 months, median time to treatment failure of 3.4 months, tumor response of 18%, decrease in CA19-9 of 30%, pain relief of 30%, analgesic category decrease of 30%, and weight gain of 10%. The intravenous infusion of the low dose of gemcitabine resulted in a median survival of 7.2 months, median time to treatment failure of 5.6 months, tumor response of 20%, decrease in CA19-9 of 36%, pain relief of 18%, analgesic category decrease of 30%, and weight gain of 36%. These parameters were comparable in both arms. Of note, PS worsened in the two patients with PS 1 to 2 in the standard arm, while it improved in the patient with PS 1 to 2 in the low-dose arm. These results suggest that the low-dose regimen of gemcitabine may be more suitable for patients with relatively worse PS, although the number of cases of PS of 1 to 2 in the present study was small.

Because we did not include a control group without gemcitabine, the actual improvement in survival, tumor size, and clinical benefit induced by gemcitabine compared with best supportive care without chemotherapy is questionable. Benchmarks of clinical outcomes with gemcitabine treatment in pancreatic adenocarcinoma patients may best be drawn from results of the pivotal trial conducted by Burris et al.[3] This study demonstrated that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms and confers a modest survival advantage over treatment with 5-FU (600 mg/m^2 once weekly). The median survival time, pain relief, decrease in analgesic category, and weight gain in both arms of our study are equivalent to those in the gemcitabine arm of the report by Burris et al.[3] and appear superior to those in the 5-FU arm. Therefore, the low dose of gemcitabine seems sufficient to increase survival time and improve disease-related symptoms.

Apart from the documented efficacy of gemcitabine, the side effects of gemcitabine must also be considered. Our careful comparison of gemcitabine safety between both infusion arms suggests that the standard-dose infusion therapy schedule is more toxic, with 50% of patients experiencing grade 3 or 4 neutropenia, 20% experiencing grade 3 or 4 anemia, 30% experiencing grade 3 or 4 thrombocytopenia, and 20% experiencing grade 3 or 4 vomiting, which were the main reasons for discontinuation of gemcitabine administration. In the low-dose arm, the incidence of neutropenia, thrombocytopenia, anemia, or vomiting was less than 10%, so chemotherapy was not omitted or discontinued in the low-dose group. Thus, since the low-dose treatment regimen can be used continuously, it may prolong the time to treatment failure (5.6 months vs 3.4 months).

Tempero et al.[5] conducted a randomized clinical trial with gemcitabine by using either a standard 30-min infusion or the fixed dose rate (FDR) infusion (10 mg/m^2 per minute) for 150 min in patients with pancreatic adenocarcinoma. The protocol of FDR infusion originated from the concept that the rate of gemcitabine triphosphate accumulation in mononuclear cells is optimized at a dose rate approximating 10 mg/m^2 per minute. The FDR infusion resulted in an 8.0 month median survival time and a high incidence rate of grade 3 or 4 myelosuppression (neutropenia, 48.8%; anemia, 23.3%; and thrombocytopenia, 37%). Our results using the low-dose infusion at 10 mg/m^2 per minute for 30 min produced a similar median survival (7.2 months) and low incidence rate of adverse events, suggesting that the flow rate of 10 mg/m^2 per minute may be sufficient to suppress tumors, whereas the longer treatment duration may result in a higher incidence of adverse effects.

Although gemcitabine is superior to other chemotherapeutic drugs such as 5-FU at tumor suppression, most elderly pancreatic carcinoma patients are unable to continue on the standard regimen of gemcitabine (1000 mg/m^2 three times a month) for more than 1 month.[25] We found that the low dose improved PS from 1 to 2 to 0 in two patients, indicating that the low-dose infusion of gemcitabine may be suitable for elderly patients or patients with relatively poor PS.

In conclusion, the low-dose gemcitabine therapy is as effective against tumors and causes fewer adverse effects than the standard-dose therapy, suggesting that the low-dose regimen is more promising because it can be continued longer, resulting in improved quality of life. Large-scale multicenter studies are warranted in the future to verify our conclusion.

Acknowledgments. This study was supported by grants from the Japan Society for the Promotion of Science.

References

1. Egawa S, Takeda K, Fukuyama N, Motoi F, Sunamura M, Matuno M. Pancreatic carcinoma in Japan. The national pancreatic cancer registry 2003;46:683–96.
2. Ministry of Health, Labour and Welfare Statistics and Information. 2001 vital statistics of Japan. http://wwwdbtk.mhlw.go.jp/toukei/youran/data13/1-35.htm (in Japanese).
3. Burris HA III, Moore MJ, Andersen J, Green MR, Rothen ML, Modiano MR, et al. Improvement in survival and clinical benefit with gemcitabine as first-line therapy for patients with advance pancreas cancer. J Clin Oncol 1997;15:2403–13.
4. Pollera CF, Ceribelli A, Crecco M, Oliva C, Calabresi F. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m^2) and high-dose (875 mg/m^2) levels. Invest New Drugs 1997;15:115–21.
5. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 2003;21:3402–8.
6. Oken, MM, Creech RH, Tormey DC, Horton J, Davis TE, Mcfadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
7. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2′,2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. Cancer Chemother Pharmacol 1991; 27:258–62.
8. Abbruzzese JL, Grunewald R, Weeks EA, Gravel O, Adams T, Nowak B, et al. A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. J Clin Oncol 1991;9:491–8.
9. Kudo M. Contrast harmonic imaging in the diagnosis and treatment of hepatic tumors. Tokyo: Springer; 2003.
10. Kitano M, Kudo M, Sakamoto H, Fukuta N, Nakaoka R, Kawasaki T. Dynamic imaging of pancreatic disease by contrast-enhanced coded phase inversion harmonic ultrasonograpy. Gut 2004;53:854–9.
11. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26.
12. Heinemann V, Schermuly MM, Stieber P, Schulz L, Jungst D, Wilkowski R. CA19-9 a predictor of response in pancreatic cancer treated with gemcitabine and cisplatin. Anticancer Res 1999;19: 2433–5.
13. Gogas H, Lofts FJ, Evans TR, Daryanani S, Mansi JL. Are serial measurements of CA19-9 useful in predicting response to chemotherapy in patients with inoperable adenocarcinoma of the pancreas? Br J Cancer 1998;77:325–8.
14. Miller AB, Hoogstraten B, Staguet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–14.
15. Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA III, et al. A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. Ann Oncol 1996;7: 347–53.
16. Casper ES, Green MR, Kelsen DP. Phase II trial of gemcitabine in patients with adenocarcinoma of the pancreas. Invest New Drugs 1996;12:29–34.
17. Daniel G, Haller MD. Chemotherapy for advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2003;56:16–23.
18. Berlin JD, Atalano P, Thomas JP, Kugler JW, Haller DG, Benson AB III. Phase III study of gemcitabine in combination with fluororacil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 2002;20:3270–5.
19. Storniolo AM, Enas NH, Brown CA, Voi M, Rothenberg ML, Schilsky R. An investigational new drug treatment program for patients with gemcitabine: results for over 3000 patients with pancreatic carcinoma. Cancer 1999;85:1261–8.
20. Rocha Lima CMS. A randomized phase 3 study comparing efficacy and safety of gemcitabine (GEM) and irinotecan (I), to GEM alone in patients with locally advanced or metastatic pancreatic cancer who have not received prior systemic therapy. Proc Am Soc Clin Oncol 2003;22:251.
21. Philip PA, Zalupski MM, Vaitkevicius VK, Arlauskas P, Chaplen R, Heilbrun LK, et al. Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. Cancer 2001;91:569–77.
22. Ulrich H, Kornek GV, Raderer Ml. A phase III trial of biweekly high dose gemcitabine for patients with metastatic pancreatic adenocarcinoma. Cancer 2000; 88:2505–11.
23. Takeuchi N, Maejima S, Hasebe O, Mastuda Y, Hanazaki K, Kaijima S, et al. Clinical problem in gemcitabine treatment for unresectable pancreatic cancer in the elderly: a multicentric retrospective study of 53 cases. Jpn J Cancer Chemother 2004;31:1987–91.
24. Hanada K, Hino F, Amano H, Ooe H, Hirota Y, Sasao S, et al. Gemcitabine in elderly patients with unresectable pancreas cancer. Jpn J Cancer Chemother 2002;29:2521–5.