Triplet cytotoxic chemotherapy with gemcitabine, 5-fluorouracil and cisplatin for advanced pancreatic cancer

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Abstract. In advanced or relapsed pancreatic cancer, mono- or duo-therapy has shown modest efficacy at best. The present study evaluated the efficacy of a triplet combination in relapsed or advanced pancreatic cancer. A total of 37 patients with adenocarcinoma of the pancreas in stage III/IV or with relapsed disease were treated with a gemcitabine, 5-fluorouracil and cisplatin (GFP) regimen every 3 weeks. Only 29 out of 37 patients were evaluable for response due to early treatment interruption in 8 patients. The overall response rate was 24.1% and the disease control rate was 68.9%. The progression-free survival (PFS) rate was 61.5, 30.9 and 17.6% at 3, 6 and 9 months, respectively, and the overall survival (OS) rate was 46.5 and 30.6% at 6 and 12 months, respectively. Grade 3/4 leukopenia, neutropenia and thrombocytopenia occurred in 18.4, 29.9 and 24.5% of 147 cycles, respectively. Old age and a poor performance status (PS) were associated with the early discontinuation of chemotherapy (P=0.038 and P=0.036, respectively). In patients <65 years old and with a PS of <2, the median PFS and OS times were 5.3 months and 10.3 months, respectively. Overall, although GFP resulted in acceptable response and survival rates, it does not appear to have marked superiority to gemcitabine-based single or duplet chemotherapy.

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Introduction

Advanced pancreatic cancer has a poor prognosis with a median survival time of 3-5 months, which has not been changed in the era of 5-fluorouracil (5-FU) chemotherapy (1). The emergence of the nucleoside analogue gemcitabine has improved the response rate and clinical benefits compared with 5-FU monotherapy. However, the median survival time of affected patients remains at ~6 months (2-4).

As there are few other agents active against pancreatic cancer, numerous efforts have sought to improve the efficacy of combination regimens for this dismal disease. In previous studies, the combination of gemcitabine+irinotecan or gemcitabine+docetaxel showed an overall response rate in the range of 10-20%, however, the overall survival (OS) time was not improved beyond 6 months (5-7). The combination of gemcitabine plus 5-FU with or without leucovorin showed an overall response rate in the range of 5-25.9%, however, the OS time was in the range of 6.7-10.3 months (8-10).

In one study, cisplatin therapy produced a response rate of 21%, with a median duration of response of 4 months (11). Use of a combination of gemcitabine and cisplatin produced a response rate of 11-26.4%, which was better than gemcitabine only, and the median survival time was 7.1-8.2 months (12-14). Gemcitabine acts synergistically with 5-FU and with cisplatin (15-20). 5-FU acts synergistically with cisplatin (21). This suggests that these three agents may exhibit a triple-synergic effect on advanced pancreatic cancer.

With the expectation of synergism based on these previous studies, the present study investigated the efficacy and toxicities of a combination chemotherapy using a gemcitabine, 5-FU and cisplatin (GFP) regimen for the treatment of patients with advanced pancreatic cancer.

Patients and methods

Eligibility. The inclusion criteria were as follows: Patients with unresectable, relapsed or metastatic adenocarcinoma

of the pancreas (American Joint Committee on Cancer stage III or IV) (22); at least one measurable lesion (defined as a mass with clearly demarcated dimensions on computed tomography, routine chest X-ray or physical examination); no prior chemotherapy or radiotherapy (lesions outside of the prior radiation port was acceptable); Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or better (23); age between 18 and 70 years; no concurrent uncontrolled medical illness; no other malignancies (with the exception of squamous cell carcinoma of the skin treated by surgery); total bilirubin ≤2 times the upper normal limits (UNL), transaminases ≤3 times the UNL and alkaline phosphatase ≤2.5 times the UNL; adequate bone marrow function (hemoglobin, ≥9 g/dl; granulocytes, ≥1,800/μl; and platelets, ≥100,000/μl); and no other serious organ failure. A complete history was taken and a physical examination was performed on all patients prior to treatment. A cancer antigen (CA)19-9 test, electrocardiography, chest X-ray and abdominal computed tomography (CT) scan were performed. Signed informed consent was obtained from all patients prior to chemotherapy. The present study was based on the data from an initial single center study conducted by Inje University Sanggye Paik Hospital (Seoul, Korea), which was approved by the ethics committee of Inje University Saggye Paik Hospital.

Treatment methods. For each patient, 800 mg/m^2 gemcitabine was intravenously infused in D_5W solution or 100 ml normal saline (N/S) at 10 mg/m^2/min on day 1 (D1) and day 8 (D8). 5-FU was continuously infused over 24 h at a dose of 800 mg/m^2/day in D_5W or N/S 1 l on D1 through D4. Cisplatin (60 mg/m^2) was infused for 3 h on D2, with a 24-h interval after the start of gemcitabine infusion. The treatment was repeated every 3 weeks.

Complete blood cell counts (CBCs) were checked between D8-15 and whenever necessary to check the nadir blood cell counts thereafter. CBCs, and serum calcium, creatinine, liver enzyme and electrolyte levels were checked prior to commencing each treatment cycle. The dose and treatment interval were adjusted based on the following criteria: The chemotherapy was continued when the D1 granulocyte and platelet count were ≥1,800/μl and ≥100,000/μl, respectively. If not, the chemotherapy was delayed for 1 week. If the chemotherapy was delayed for longer than 2 weeks prior to hematological recovery, the study was discontinued. In cases where a nadir granulocyte count of <500/μl or a platelet count of <25,000/μl was observed during the previous cycle, the dose of gemcitabine and cisplatin was reduced by 10% in the next cycle. The reduction was allowed only once unless the patient experienced serious infection and/or hemorrhage. On each successive D8, 100% of gemcitabine was administered in cases where granulocytes recovered to ≥1,000/μl and platelets recovered to ≥100,000/μl. When the D8 granulocyte count was 500-999/μl and/or the platelet count was 50,000-99,000/μl, the D8 dose of gemcitabine was reduced to half. Furthermore, if the granulocyte and/or platelet counts were <500/μl and <50,000/μl, respectively, the D8 dose of gemcitabine was administered 1 week later when the above criteria were met; otherwise, the D8 dose of gemcitabine was skipped. During the chemotherapy, granulocyte/macrophage-colony stimulating factor (G/M-CSF) use was allowed according to the clinician's

decision, while prophylactic use was not allowed. When the creatinine clearance was between 30-50 ml/min, the dose of cisplatin was reduced to half; cisplatin was discontinued if the creatinine clearance was <30 ml/min, and the study was discontinued.

For grade 3/4 stomatitis or diarrhea, 5-FU was reduced by 25%. If the grade 3/4 toxicity was observed again in the next cycle, the study was discontinued. When grade 3/4 neurotoxicity (intolerable paresthesia and/or marked motor function loss) occurred, cisplatin was discontinued and the patient was taken off the protocol.

Response and toxicity evaluation. A physical examination and chest X-ray was performed every cycle prior to commencing chemotherapy. An abdominal CT scan was repeated prior to every 2 cycles of chemotherapy or any time disease progression was suspected. Blood chemistry and CBCs were also checked every cycle prior to chemotherapy. If the level of CA19-9 was high prior to treatment, the tumor marker was checked every cycle prior to the next chemotherapy.

Response and toxicity were evaluated according to WHO criteria (24). Complete response (CR) was defined as disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical change related to tumor for at least 4 weeks. A partial response (PR) was defined as a reduction of ≥50% in the sum of the products of two perpendicular diameters of all measured lesions lasting ≥4 weeks. Stable disease (SD) was defined as <50% reduction and <25% increase in the sum of the products of all measurable lesions without appearance of new lesion. Progressive disease was defined as the appearance of any new lesion or definite increase in tumor size and a >25% increase in the sum of the products of all measured lesions.

Treatment was continued until tumor progression or unacceptable toxicity occurred. Toxicity was evaluated prior to each cycle of therapy. The duration of response or SD was measured from the beginning of treatment until the documentation of progression. The response assessment was performed every 2 cycles of chemotherapy.

Statistics. The primary objective of the study was to examine the response rate and toxicity. The secondary objectives were to examine progression-free survival (PFS) and OS. The response rate of the gemcitabine/cisplatin combination for advanced pancreatic cancer patients has been recorded at 10-30% (12-14). If 40% was used as an expected response rate, 20% as a minimal acceptable response rate and 10% as a drop-out rate, 33 patients were required as a minimum, according to the Fleming one-stage procedure (P_1-P_0=0.20, α=0.05, β=0.2) (25).

Proportions and categorical data were compared using Fisher's exact test. Continuous data were compared using Student's t-test or the Mann-Whitney U test. PFS time was calculated from the date of the initial treatment to the date of disease progression or any cause of mortality. OS time was calculated from the date of the initial treatment until mortality. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test and Breslow test. All statistical analyses were performed using SAS version 9.1 (Cary, NC, USA). All analyses were two-sided and statistically significant differences were defined by a P-value of <0.05.

Table I. Patient characteristics.

Characteristic	Value
Median age (range), years	61 (40-70)
Gender, n (%)	
Male	27 (73.0)
Female	10 (27.0)
Performance status, n (%)	
0-1	26 (70.3)
2	11 (29.7)
Disease status, n (%)	
Unresectable/metastatic	5/27 (13.5/73.0)
Recurrent	5 (13.5)
Previous treatment, n (%)	
No previous treatment	28 (75.7)
Palliative surgery	4 (10.8)
Surgery ± adjuvant chemo- and/or radiotherapy	5 (13.5)
Primary sites, n (%)	
Head	16 (43.2)
Body and tail	21 (56.8)
Metastatic site, n (%)	
Liver	20 (54.1)
Distant lymph node	19 (51.4)
Peritoneum	14 (37.8)
Lung	6 (16.2)

Table II. Overall best response in the 29 evaluable patients.

Response	Value
Complete response, n (%)	0 (0.0)
Partial response, n (%)	7 (24.1)
Stable disease, n (%)	13 (44.8)
Progressive disease, n (%)	9 (31.0)
ORR, % (95% CI)	24.1 (12.2-42.1)
DCR, % (95% CI)	69.0 (50.8-82.7)

ORR, overall response rate; DCR, disease control rate; CI, confidence interval. [a]Early mortality in 5 patients prior to evaluation, early discontinuation in 3 patients due to adverse events and/or other diseases (cerebral infarct, lethargy and pneumonia).

Results

Patient characteristics. Between April 2002 and March 2009, 37 patients were enrolled into this study. The median age was 61 years old (range, 40-70 years old). The patient characteristics are shown in Table I. In total, 26 (70.3%) patients showed an ECOG PS grade of 0-1 and 11 patients (29.7%) showed a grade of 2. A total of 8 patients underwent a percutaneous transhepatic biliary drainage procedure due to obstructive jaundice prior to chemotherapy. After the completion of the study, 29 patients were evaluable and 8 patients dropped out early without the assessment of response.

Dose intensity of treatment drugs. A total of 153 cycles of treatment were administered, with a median of 3 cycles per patient (range, 1-12 cycles), and the dose intensity data was available in 147 cycles. D1 gemcitabine was administered at 97.8% during the 147 cycles of chemotherapy, D8 gemcitabine was administered at 75.0%, cisplatin was administered at 96.9% and 5-FU was administered at 97.6%. Among the 8 patients who could not be evaluated, a total of 10 cycles were administered, with a median of 1 cycle per patient (range, 1-2 cycles). During the 10 cycles, D8 gemcitabine was omitted in 3 cycles and reduced to the half dose in 2 cycles.

Treatment response and outcomes. Among the 29 patients evaluable for the response, 7 (24.1%) patients exhibited a PR and 13 (44.8%) patients experienced SD (Table II). The overall response rate was 24.1% [95% confidence interval (CI), 12.2-42.1) and the disease control rate was 69.0% (95% CI, 50.8-82.7). The median PFS and OS times of the evaluable patients were 4.1 months (95% CI, 3.0-5.2) and 6.6 months (95% CI, 4.9-8.2), respectively. The median PFS and OS times of all enrolled patients were 3.9 months (95% CI, 2.4-5.4) and 5.8 months (95% CI, 4.8-6.8), respectively (Fig. 1A and B). The PFS rate of all enrolled patients was 61.5±8.5, 30.9±9.0 and 17.6±7.7% at 3, 6 and 9 months, respectively. A total of 10 patients underwent second-line therapy after progression. The most frequently used regimen was an oral 5-FU derivative-based regimen in 9 patients. The OS rate was 46.5±8.4 and 30.6±8.0% at 6 and 12 months, respectively. The response rate and OS time were not associated with any clinical factors, including age (<65 vs. ≥65 years) and PS (<2 vs. ≥2) (both P=1.000).

Safety. During the 153 cycles of chemotherapy, toxicity was observed in 147 cycles (Table III). Grade 3/4 leukopenia, neutropenia and thrombocytopenia were documented in 18.4, 29.9 and 24.5% of 147 cycles, respectively. Grade 3/4 oral mucositis was observed in 4.1% of patients and grade 3 nausea/vomiting and diarrhea in 2.0 and 1.4% of 147 cycles, respectively. The incidence of grade 3/4 neutropenia (the total number of grade 3/4 neutropenia/total received cycles of each patient) and grade 3/4 thrombocytopenia (the total number of grade 3/4 thrombocytopenia/total received cycles of each patient) were associated with PS at diagnosis. The poor PS (PS of 2) was associated with a higher incidence of grade 3/4 neutropenia (P=0.009) and grade 3/4 thrombocytopenia (P=0.006) compared with a PS of 0/1. Although the elderly (≥65 years) more frequently exhibited a poor PS [PS of 2; 4 out of 9 (44.4%) patients], this was not statistically significant (P=0.571). Also, the incidence of neutropenia and thrombocytopenia was not associated with age (P=0.468 and P=0.906, respectively).

In the 8 patients whose response could not be assessed due to early treatment interruption prior to first response evaluation, 5 of the patients succumbed prior to the first response evaluation (3 to sepsis, 1 to pneumonia and 1 to demyelinating disease), and 3 patients were taken off the study due to adverse events or other diseases (lethargy, cerebral infarct and pneumonia).

Table III. Toxicity profiles observed in 147 cycles.

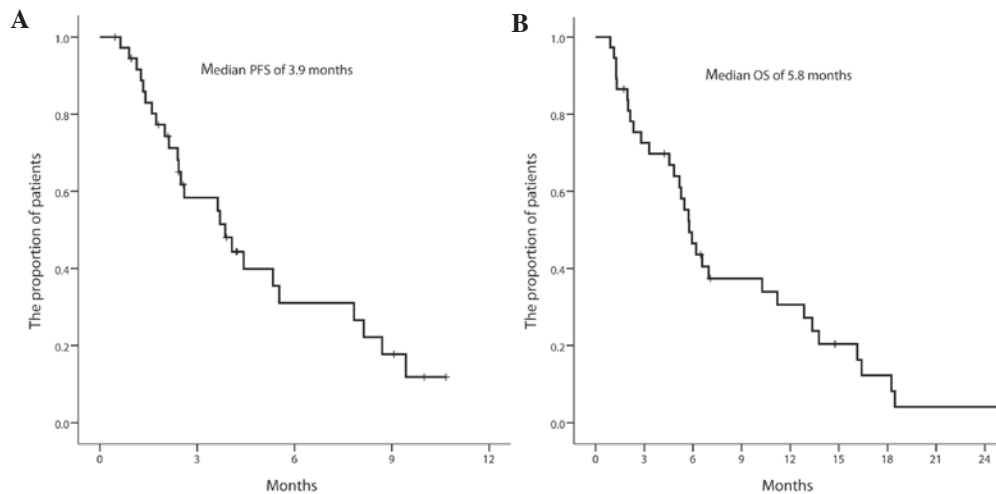| Toxicity	Observed cycles, n (%)		Observed patients, n (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematological				
Anemia	13 (8.8)	-	7 (18.9)	
Leukopenia	22 (15.0)	5 (3.4)	12 (32.4)	5 (13.5)
Neutropenia	26 (17.7)	18 (12.2)	9 (24.3)	14 (37.8)
Thrombocytopenia	20 (13.6)	16 (10.9)	8 (21.6)	12 (32.4)
Non-hematological				
Nausea/vomiting	3 (2.0)	-	3 (8.1)	
Mucositis	4 (2.7)	2 (1.4)	3 (8.1)	2 (5.4)
Diarrhea	2 (1.4)	-	1 (2.7)	
Neuropathy	-	-		

Figure 1. (A) Progression-free survival (PFS) in all enrolled patients. (B) Overall survival (OS) in all enrolled patients.

Clinical characteristics associated with early discontinuation. Early discontinuation (≤3 cycles of chemotherapy without evident disease progression) occurred in 10 patients. Among those 10 patients, 8 dropped out early prior to first response assessment and 2 patients showed SD at first assessment and withdrew their consent for participation. The median age of the 10 patients who dropped out of the study was 64.5 years (range, 56-69 years), while the median age of the other 27 patients was 60.0 years (range, 40-70 years). The incidence of early discontinuation was associated with old age (P=0.036; Fig. 2A) and a poor PS (P=0.038; Fig. 2B). A poor PS was observed in 6 (60.0%) of the 10 early discontinuation patients compared with 5 (18.5%) of the other 27 patients. However, the early discontinuation was not associated with other clinical characteristics, such as gender (P=0.229), percutaneous transhepatic biliary drainage insertion (0.404), stage (P=0.229), relapse (P=0.284), primary lesions (P=0.700) and metastatic site (liver, P=0.700; peritoneum, P=0.214; lung, P=0.303; and distant lymph node, P=0.128). Also, the incidence of grade 3/4 neutropenia and thrombocytopenia was not associated with early discontinuation

(P=0.537 and P=0.201, respectively). The non-hematological toxicities could not be analyzed due to a low incidence in this study.

As old age and a poor PS were correlated with early discontinuation, the patients were separated into two groups: A high-risk group (n=16; age ≥65 or PS ≥2) and a low-risk group (n=21; age <65 and PS <2). According to these criteria, the median PFS time was 2.4 months (95% CI, 2.0-2.8) in the high-risk group and 5.3 months (95% CI, 2.9-7.7) in the low-risk group (P=0.071; P=0.021 in Breslow test) (Fig. 3A). The median OS time was 2.8 months (95% CI, 0.5-5.1) in the high-risk group and 10.3 months (95% CI, 4.1-16.4) in the low-risk group (P=0.047; Fig. 3B).

Discussion

The triplet GFP chemotherapy showed an acceptable disease control rate (24.1% for PR and 44.8% for SD) and a modest efficacy for median PFS and OS times (3.9 and 5.8 months, respectively). The 6-month PFS rate was 30.9% and the 1-year survival rate was 30.6%.
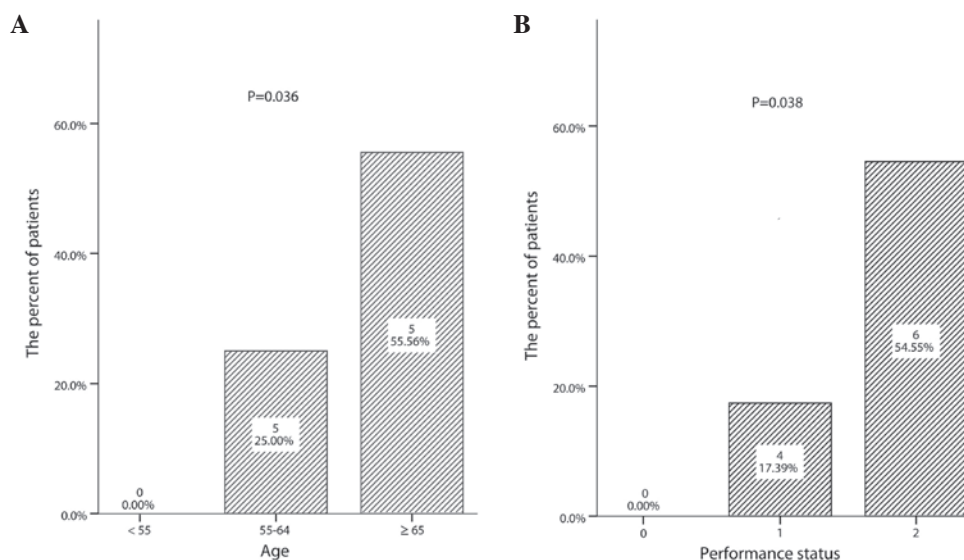
Figure 2. (A) Early discontinuation (≤3 cycles of chemotherapy without marked disease progression) according to age group. (B) Early discontinuation (≤3 cycles of chemotherapy without marked disease progression) according to performance status.
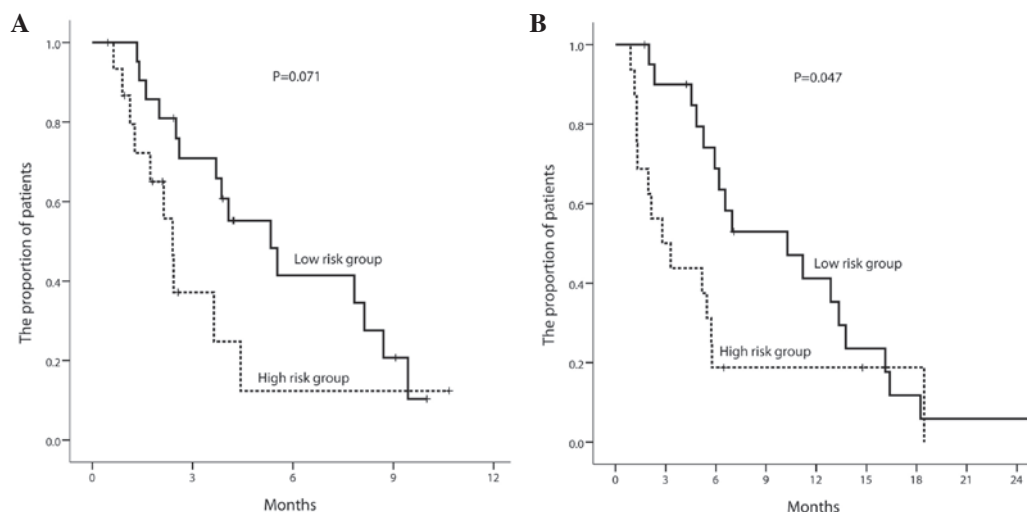

Figure 3. (A) Progression-free survival according to risk group for early discontinuation (≤3 cycles of chemotherapy without marked disease progression). (B) Overall survival according to risk group for early discontinuation (≤3 cycles of chemotherapy without marked disease progression).

In a recent phase III study, the folinic acid, 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) regimen resulted in a 6-month PFS rate of 52.8% and a 1-year OS rate of 48.4% in advanced pancreatic cancer patients (26). However, gemcitabine monotherapy remains the reference regimen for advanced pancreatic cancer (2,27), as the combination of gemcitabine with other cytotoxic drugs has not shown significant benefit, except in three studies (28-30). In phase II trials of triplet cyto-toxic chemotherapy [i.e., gemcitabine/docetaxel/capecitabine, gemcitabine/oxaliplatin/5-FU, gemcitabine/5-FU/cisplatin (GFP) or mitomycin/docetaxel/irinotecan], the previously reported overall response rate was between 0 and 33.3% and the median OS time was between 6.1 and 14.5 months (31-35). Although the response rate in the present study was accept-able, the 5.9-month median OS time may appear to be inferior to those of the reported phase II triplet trials. However, if the time-point survival rate is compared with those of previ-ously reported triplet trials, the 30.9% 1-year OS rate in the

present study is comparable with the results of the previous phase II GFP trials with 1-year OS rates of 26-34% (34,35). As 10 patients in the present study experienced early discontinua-tion, which is a major cause of shortened median survival time, this discrepancy between time-point survival rate and median survival time may indicate that the major drawback of this triplet GFP regimen is the difficulty of long-term maintenance rather than the efficacy of treatment. Also, this discrepancy may explain why the median OS time of the GFP regimen in the present study appears to be inferior to that of previous duplet regimens, such as the combination of gemcitabine with cisplatin (7.1-8.3 months) (12-14,29,36), gemcitabine with oxaliplatin (9.2 months) (37), and gemcitabine with fluoropy-rimidine (6.7-10.3 months) (9,10,28,38).

To find the appropriate group for triplet GFP chemotherapy, selection of the low-risk and high-risk group for early discontin-uation was performed according to age and PS. After grouping all the enrolled patients into the two risk groups, the low-risk

group showed an acceptable 5.3-month median PFS time and a 10.3-month median OS time, which were comparable with previously reported duplet or triplet regimens. Although the performance scales are somewhat subjective, there is a possibility that the PS at the initiation of chemotherapy may be a predictor of poor tolerance in hematological toxicity to triplet GFP chemotherapy. Also, elderly patients (≥65) adhered poorly to the triplet GFP chemotherapy. However, the exact reason is uncertain in the present study, as non-hematological toxicities could not be analyzed due to the low incidence in this study.

This triplet regimen showed substantial hematological toxicities. Grade 3/4 neutropenia and thrombocytopenia occurred in more than a half of the patients, who required subsequent dose reduction. This frequent grade 3/4 hematological toxicity may inevitably deteriorate the general medical condition of vulnerable patients with a poor PS, and this probably caused early discontinuation prior to even attaining any clinical benefits. As the study showed that the a poor PS was associated with more frequent hematological toxicities, careful monitoring of the CBC and prophylactic G-CSF use may be suggested during chemotherapy.

In conclusion, the GFP regimen has comparable activity to gemcitabine-based single or duplet chemotherapy in disease control, and modest efficacy in survival. This triplet GFP chemotherapy caused substantial hematological toxicity and a high rate of early discontinuation in the patients with an old age and poor PS. However, even when considering the result found in the younger patients with a good PS, these results do not appear to have marked superiority to gemcitabine-based single or duplet chemotherapy.

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