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Gemcitabine Alone versus combination of Gemcitabine and Cisplatin for the Treatment of Patients with Locally Advanced and/or Metastatic Pancreatic Carcinoma: A Retrospective Analysis of multicenter study

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The majority of patients with pancreatic cancer is of advanced disease. Several randomized Phase II and III trials suggest that the combination of gemcitabine and cisplatin (GemCis) response rates were higher than Gemcitabine (Gem) alone, however the trials were not enough powered to indicate a statistically significant prolongation of survival in patients with advanced pancreatic adenocarcinoma. The aim of this retrospective multicenter study is to evaluated the efficiency of Gem alone versus GemCis in patients with locally advanced and/or metastatic pancreatic adenocarcinoma .

A total of 406 patients, from fourteen centers were evaluated retrospectively. All patients received Gem or GemCis as first-line treatment between September 2005 to March 2011. Primary end of this study were to evaluate the toxicity, clinical response rate, progression-free survival (PFS) and overall survival (OS) between the arms.

There were 156 patients (M: 98, F: 58) in Gem arm and 250 patients (M: 175, F: 75) in the combination arm. Gemcitabin arm patients older than the combination arm (median 63 vs 57.5, p=0.001). In patients with the combination arm had a higher dose reduction (25.2% vs 11.3%, p=0.001) and dose delay (34% vs 16.8%, p=0.001). Among patients with the combination and Gemcitabin arm gender, diabetes mellitus, performance status, cholestasis, grade, stage did not have a statistically difference (p>0.05).

Clinical response rate to the combination arm was higher than the Gem arm (69.0% vs 49.7%, p=0.001). PFS was more favorable in the GemCis arm than Gem alone, but the difference did not attain statistical significance (8.9 vs 6.0, p=0.08). OS was not significantly superior in the GemCis arm (12.0 vs 10.2, p>0.05).

Grade III-IV hematologic and nonhematologic toxicity were higher in the combination arm.

PFS was more favorable in the GemCis arm than Gem alone, but the difference did not attain statistical significance. OS was not significantly superior in the GemCis arm.

Key words: advanced pancreatic cancer, first-line chemotherapy, gemcitabine, cisplatin

Pancreatic cancer is the fourth most common among cancer-related deaths in the United States [1]. Without effective treatment, the median survival for locally advanced disease is 8 to 12 months and only 3 to 6 months for metastatic disease. The overall 5-year survival rate among pancreatic cancer patients is under 5% [2,3].

Advanced pancreatic adenocarcinoma is often refractory to standard chemotherapy. Most of the randomized trials

with single chemotherapeutic agents or combinations had low impact on survival. Systemic chemotherapy with single-agent Gem is currently recommended as a standard of first-line chemotherapy for treatment of locally advanced and metastatic pancreatic cancer [3,4].

It has been shown that the combination of gemcitabine and cisplatin is supported in preclinical studies, because Gem increases cisplatin-induced DNA damage [5,6]. Several randomized Phase II and III trials suggest that GemCis response rates were higher Gem alone, however the trials were not enough powered to indicate a statistically significant prolongation of survival in patients with advanced pancreatic adenocarcinoma [7-12].

We performed a a multicenter retrospective analysis of the treatment outcomes of Gem versus GemCis in patients with locally advanced or metastatic pancreatic cancer.

Patients and methods

Patient Population. We retrospectively evaluated 406 locally advanced or metastatic pancreatic cancer patients who were administered Gem or GemCis as first-line treatment between September 2005 to March 2011.

They met the following inclusion criteria; 1) they were 18 years or older in age; 2) they had histologic or cytologic diagnosis of locally advanced and/or metastatic pancreatic carcinoma; 3) no previous chemotherapy or radiotherapy; 4) they had to have measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST).

Treatment and Assessment. Gem was administrated at 1000 mg/m2 IV over 30 min on Days 1 and 8 of each 21-day cycle. Cisplatin was added at 70 mg/m2 on day 1 every 21-day cycle to the Gem schedule . This study used WHO toxicity criteria and in this study we recorded grade III~IV toxicity. Imaging studies were documented by computed tomography at baseline and every three cycles for patients.

The responses to chemotherapy were measured according to RECIST [11]. A complete response (CR) was defined as disappearance of all target lesions, no new lesions and normalization of the tumor markers for at least 4 weeks. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of the measurable lesions. Progression was defined as at least a 20% increase in the sum of longest diameter of the measurable lesions. Stable disease (SD) was defined as small changes.

Factors analysed. Eight clinical variables were chosen on the basis of previously published clinical trials. The variables were divided into categories: age (≤65 or >65 years), gender (male or female), ECOG performance status (0-1, 2-3), stage (locally advanced or metastatic disease), grade (well, poor or moderate), chemotherapy (Gem or GemCis), presence of diabetes mellitus at diagnosis, presence of cholestasis at diagnosis.

Statistical Analysis. All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for windows). The differences of the clinical characteristics between the two groups were analyzed by a chi-square test. OS and PFS were calculated with the log-rank test. The Kaplan–Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistical significant variables related to OS and PFS. Differences were assumed to be significant when P value of less than 0.05.

Results

Patient Characteristics. Between September 2005 to March 2011, 406 untreated patients with locally advanced (40.3%), and metastatic pancreatic cancers (59.7%) were enrolled in this study from 14 different centers. The patients' baseline characteristics are listed in Table 1. There were 156 patients (M: 98, F: 58) in Gem arm and 250 patients (M: 175, F: 75) in the combination arm. Gem arm patients older than the combination arm (median 63 vs 57, p=0.001). In patients with the combination arm had a higher dose reduction (25.2% vs 11.3%, p=0.001) and dose delay (34.0% vs 16.8%, p=0.001). Among patients with the combination and Gem arm gender, diabetes mellitus, performance status, cholestasis, grade, stage did not have a statistically difference (p>0.05).

Safety Results. The toxicities of grade 3 to 4 during treatment are shown in table-2.

Neutropenia was the most common significant hematologic toxicity and nausea- vomiting was the most common nonhematologic toxicity in the both arm. Grade III-IV hematologic

Table 1. The general characteristics of the patients

Characteristic	Gem	GemCis	p
Enrolled patients.	156	250	
Sex			
Male	98	175	P>0.05
Female	58	75	
Median age,years	63	57	p=0.001
Performance status (%)			
0	17.6	20.7	
1-2	74.8	73	P>0.05
3	7.6	6.3	
The number of cycles (median)	4	5	P>0.05
Dose reduction (%)	11.3	25.2	p=0.001
Dose delay (%)	16.8	34	p=0.001
Stage (%)			
Locally advanced	36.5	44	P>0.05
Metastatic	63.5	56	
Primary tumor(%)			
Head	71	69.8	
Body	15.2	14.7	P>0.05
Tail	13.8	15.5	
Diabetes Mellitus (%)	33.5	30	P>0.05
Cholestasis(%)	27.6	32.1	P>0.05

Table 2. Toxicity profile of grade 3 to 4

Characteristic	Gem (%)	GemCis (%)	p
Hematologic toxicity :			
Neutropenia	8.8	23.3	P=0.001
Febrile neutropenia	6.0	15.5	P=0.042
Thrombocytopenia	4.8	12.9	P=0.01
Anemia	7.2	14.2	P=0.049
Nonhematologic toxicity :			
Nausea	8.2	17.3	P=0.02
Vomiting	4.9	13.3	P=0.01
Diarrhea	3.9	9.6	P=0.05
Abnormal liver function	2.4	2.6	P>0.05
Renal toxicity	1	2,6	P>0.05

Table 3. Treatment efficacy of the patients

Characteristic	Gem (%)	GemCis (%)	p
Response			
Complete response	4.5	8.9	
Partial response	16.8	25.8	0.001
Stable disease	28.4	34.3	
Progressive disease	50.3	31.0	
Clinical response	49.7	69.0	0.001

Table 4. Univariate analysis for OS

Parameter	*Log-rank test value*	*Degrees of freedom*	p value
Gender	4.23	1	0.04
Age	0.50	1	0.47
Stage	26.3	1	0.001
Performance status	7.23	2	0.27
Grade	2.73	2	0.25
Chemotherapy	0.67	1	0.41
Diabetes Mellitus	2.20	1	0.13
Cholestasis	4.46	1	0.35

and nonhematologic toxicity were higher in the combination arm.

Efficacy. Treatment efficacy was shown in Tables 3. The clinical response was 69.0% for patients assigned to GemCis arm compared with 49.7% for patients assigned to Gem arm (p=0.001).

PFS was more favorable in the GemCis arm than Gem alone, but the difference did not attain statistical significance (8.9 vs 6.0, p=0.08))(Fig. 1). OS was not significantly superior in the GemCis arm (12.0 vs 10.2, p>0.05))(Fig. 2).

Prognostic Factor Analysis. The results of univariate analysis for Overall survival are summarized in Table 4. Among the 8 variables of univariate analysis, 2 were identified to have prognostic significance: stage (p<0.001) and gender (p=0.04). Multivariate analysis included the 2 factors with prognostic significance that emerged in univariate analysis. The results of multivariate analysis are shown in Table 5. Multivariate analysis

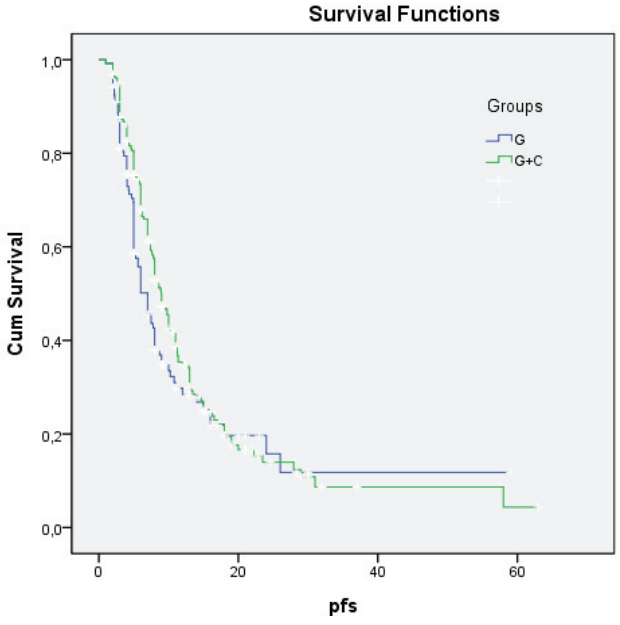

Figure 1. Kaplan-Meier estimates of PFS curve (p=0.08) (G: gemcitabine, GC: gemcitabine+cisplatin).

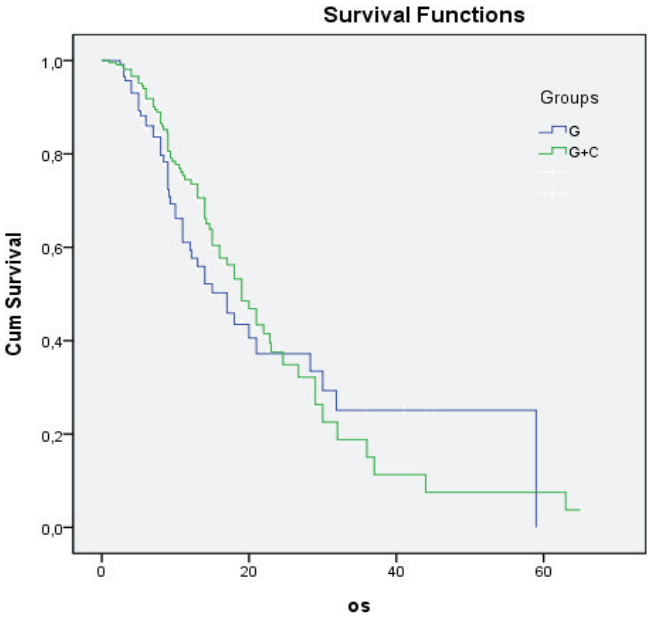

Figure 2. Kaplan-Meier estimates of OS curve (p>0.05) (G: gemcitabine GC: gemcitabine+cisplatin).

by Cox proportional hazard model showed that stage was an independent prognostic factor for OS.

In the univariate analysis, stage (p<0.001) and age (p=0.01) were considered independent prognostic factors for PFS (Table 6). Stage was considered independent adverse prognostic factor on multivariate analysis (Table 7).

Table 5. Cox regression analysis for Overall survival

Parameter	OR	%95 CI	p value
Stage	0.48	0.35-0.64	0.001
Gender	1.36	0.99-1.85	>0.05

Table 6. Univariate analysis for Progression-free survival

Parameter	Log-rank test value	Degrees of freedom	p value
Age	5.77	1	0.01
Stage	16.0	1	0.001
Gender	1.59	1	0.20
Performance status	5.35	2	0.69
Grade	2.69	2	0.26
Chemotherapy	2.95	1	0.86
Diabetes Mellitus	0.02	1	0.96
Cholestasis	4.57	1	0.33

Table 7. Cox regression analysis for Progression-free survival

Parameter	OR	%95 CI	p value
Stage	2.48	1.66-3.72	0.001
Age	1.48	0.98-2.25	>0.05

Discussion

The aim of this retrospective multicenter study was to evaluated the efficiency of Gem alone versus GemCis in patients with advanced pancreatic adenocarcinoma. Clinical response rate to the combination arm was higher than Gem arm (69.0% vs 49.7%, p=0.001). PFS was more favorable in the GemCis arm than Gem alone (8.9 vs 6.0, p=0.08). OS was not significantly superior in the GemCis arm (12.0 vs 10.2, p>0.05). Grade III-IV hematologic and nonhematologic toxicity were higher in the combination arm.

To improve therapeutic efficacy, numerous clinical studies randomized trials have investigated gemcitabine plus platinum analog combination regimens in patients with advanced pancreatic adenocarcinoma [8-11,13,14]. Some clinical studies suggest that the combination of Gem and Cis may improve objective response rates (ORR), PFS, and OS [11,15,-17]. Previous studies had shown that Gem induced a clinical response of 42% to 48% [8,11,18], while the GemCis consistently increased CR to a range of 55% to 70% [8,11,15-17]. These findings were similarly found in our study was a clinical response of 69% in the GemCis arm, whereas Gem arm was 49.7%(p=0.001).

Two clinical studies suggested that GemCis chemotherapy was associated with a prolongation of PFS, but only one trial [11] showed a significantly longer of PFS (5 vs 2 months; P = 0.048). In our study, PFS was more favorable in the GemCis arm than Gem alone, but the trend did not reach statistical significance (8.9 vs 6.0 months, p=0.08). Moreover, PFS was more longer than in other studies. This result can be explained by rate of patients with locally advanced pancreatic cancer was higher than in other studies. In addition to combination arm patients had a higher dose reduction, dose delay and were younger than Gem arm.

In the Heinemann et al. study [8], Grade 3–4 toxicities for Gem versus GemCis were observed in less than 15% of patients. Only nausea and vomiting were significantly more frequent in the GemCis arm (22.2% v 5.9%). In our retrospective study, the toxicities of grade 3 to 4 were higher in than Heinemann study. Higher toxicity rates in our study with both treatment groups compared to the Heinemann et al. study may be due to the different doses of chemotherapy and the modality of chemotherapy administration.

In the recent analysis Heinemann [7] suggested that not only stage of disease, but also performance status were independent prognostic factors for PFS and OS. This analysis was indicated that patients with good performance status (ECOG PS = 0) achieved the biggest benefit from gemcitabine– platinum combination therapy. In our study, stage was independent prognostic factors for OS and PFS, while performance status had no significant effect. It may be concluded that the choice of a treatment should be based according to prognostic factors.

In conclusion, PFS and clinical response were more favorable in the GemCis arm than Gem alone, but the difference of PFS did not attain statistical significance. OS was not significantly superior in the GemCis arm. Patients with the combination arm had a higher dose reduction, dose delay and a poor tolerability. Thus may be preferred to receive single-agent Gem in patients with advanced pancreatic adenocarcinoma.

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