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Gemcitabine Therapy in Patients with Advanced Pancreatic Cancer

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Background: *Advanced, unresectable pancreatic cancer is an extremely aggressive disease. The 5-year survival rate for pancreatic cancer is only less than 5%. Current therapeutic options for patients with locally advanced or metastatic disease are limited. This analysis is a retrospective evaluation of the efficacy and toxicity of gemcitabine regimen as first-line chemotherapy in patients with advanced pancreatic cancer.*

Methods: *Seventeen chemotherapy-naïve patients with advanced or recurred pancreatic cancer were consecutively treated. Gemcitabine was diluted in normal saline and administered intravenously over 1 hour. Gemcitabine 1,000 mg/m^2 was administered once weekly for 3 out of every 4 weeks.*

Results: *The median age of patients was 55 years (range 44~82 years). Based on RECIST criteria, there were 5 cases of stable disease (45%) and 6 cases of progressive disease (55%) among the 11 assessable patients. The median survival time was 189 days (range, 84 to 409 days), the 1 year survival rate was 18% in all 17 patients. Grade 3~4 toxic side effect was leucopenia only (29%) and was easily managed without infection.*

Conclusion: *Gemcitabine is well tolerated, but has no objective response in advanced pancreatic cancer.*

Key Words : *Pancreatic Cancer; Gemcitabine*

INTRODUCTION

According to a report of the Korea National Statistical Office, there were 5.7 per 100,000 estimated deaths from pancreatic cancer in Korea, making it the fifth leading cause of cancer-related mortality in the year 2000.

The only effective treatment for this disease is complete surgical resection.

Unfortunately, 5% to 25% of patients present with tumors possible for resection. Most patients with advanced, unresectable pancreatic cancer have a short-term survival of 3 to 6 months and those patients suffer from visceral pain, nausea, vomiting, weight loss and weakness as the disease progresses[1, 2]. Even though current therapeutic options for patients with locally advanced or metastatic disease are limited, single-agent gemcitabine is recommended to be the first-line treatment in those patients in terms of quality of life or modest survival advantage[3, 4].

We evaluate the response, toxicity and survival of gemcitabine therapy in patients with advanced pancreatic cancer.

MATERIALS AND METHODS

Patients

This retrospective analysis examined the outcome of

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17 consecutive patients treated with gemcitabine. Patients had a diagnosis of pancreatic cancer that was locally advanced, metastatic or recurred after surgical resection. Patients were treated between April 2000 and January 2002. Among the patients, none had received previous chemotherapy or radiation.

Chemotherapy

Gemcitabine hydrochloride (Gemzar®) was diluted in normal saline and administered intravenously over 1 hour. Gemcitabine 1,000 mg/m² was administered once weekly for 3 out of every 4 weeks. If blood counts had not recovered to an absolute neutrophil count $\geq$ 1,000/μL and platelet count $\geq$ 50,000/μL on the day of therapy, chemotherapy was omitted. WHO toxicity criteria were used in this study. The dose of gemcitabine was reduced by 25% for all other grade 3 toxicities (except alopecia) and omitted for any grade 4 toxicity.

Pretreatment, follow-up studies and response evaluation

Tumor measurements were performed by abdominal CT scan that documented measurable disease before treatment. Clinical examinations, complete blood counts (CBC), biochemical tests, CA19-9 and chest X-rays were carried out before each cycle of therapy. CBC biochemical tests were checked on days 7 and 14 after each cycle. Patients who received at least three cycles of treatment were assessable for response unless they had definitive evidence of progression after the first cycle. Patients who had received at least one cycle of treatment were assessable for toxicity. Responses were graded according to RECIST criteria[5]. Complete remission (CR) was defined as the disappearance of all known lesions, no new lesions and normalization of tumor markers for at least 4 weeks. Partial remission (PR) was indicated by a decrease of 30% or greater in the sum of the longest diameters of the target lesions from baseline, non-progressive disease in the nontarget lesion, and no new lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters of the target lesions or the appearance of new lesions. Stable disease (SD) was defined as insufficient decrease in size of tumor to qualify for PR or insufficient increase in size sufficient enough to qualify for PD.

Statistical Methods

Survival curves were constructed by using Kaplan-Meier methods.

RESULTS

The patients characteristics and baseline biochemical parameters are listed in Table 1 and 2. The median age was 55 years (range, 44~82). All patients had measurable disease: 4 patients had liver metastases and 13 patients had pancreatic mass. All patients received at least one cycle of chemotherapy and were therefore assessable for toxicity and 11 received at least three cycles of therapy and were assessable for response. 9.6% of the gemcitabine injections were given at a reduced dose due to leukopenia and 21.6% of the gemcitabine injections were omitted because of symptomatic progressive disease and leukopenia.

Table 1. Patient Characteristics

No. of Patients	No. 17	%
Sex		
Male	10	59
Female	7	41
Performance status		
ECOG		
1~2	11	65
3~4	6	35
Metastatic sites		
Liver	4	23.5
Lymph nodes	4	23.5
Peritoneal	3	18
Diagnosis		
Pathologic	12	70.5
Clinical	5	29.5
CA19-9		
Increased	14	82
Not increased	3	18

Table 2. Baseline biochemical parameters of patients

Parameter	Median	Range
Leukocyte count, $\times 10^9$/L	5.99	2.79~21.4
Hemoglobin, g/dL	11.3	8.3~13.6
Platelet, $\times 10^9$/L	235	85~989
Total bilirubin, mg/dL	0.8	0.5~8.4
AST, U/L	32	12~127
ALT, U/L	24	8~217
Creatinine, mg/dL	0.78	0.46~1.88

Treatment, response and survival

Treatment administration is summarized in Table 3. A total of 51 cycles were administered. The median number of cycles per patient was three (range, 1～6).

Among 11 assessable patients, there was no CR and no PR. There were 5 cases of SD (45%) and six cases of PD (55%). The median survival time was 189 days (range, 84 to 409 days), the 1 year survival rate was 18% in all patients (Figure 1).

Table 3. Treatment administration

No. of cycles	
Total	51
Median	3
Range	1～6
Relative dose intensity, %	90

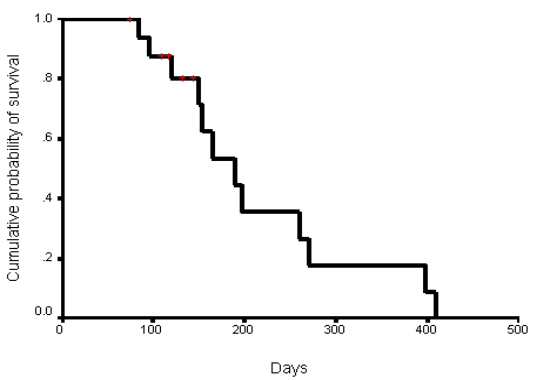

Figure 1. Overall survival of all patients

Toxicities

The hematologic and nonhematologic toxicities were evaluated for all patients and shown in Table 4. Grade 3～4 toxic side effect was only leucopenia (29%) and was easily managed without infection. Less severe grade 1～2 nonhematologic toxic side effect occurred more frequently.

Table 4. Frequency of toxicity in 17 patients

Toxicity (WHO)	Grade (% patients)				
	0	1	2	3	4
Nausea/Vomiting	70	24	6	–	–
Stomatitis	94	–	6	–	–
Diarrhea	82	–	18	–	–
Leucopenia	70	–	12	17	12
Thrombocytopenia	94	6	–	–	–
Fever	94	–	6	–	–

DISCUSSION

This study demonstrated results of the low toxicity and the good compliance of gemcitabine treatment in patients with advanced pancreatic cancer. Even though grade 3 and 4 myelosuppression was shown in some patients (29%), systemic toxicity from gemcitabine was mild with a low incidence of nausea or vomiting.

However, no patients achieved objective response, only 5 patients out of the eleven assessable patients experienced stable disease and 6 had disease progression.

There were several phase II and III trials for an analysis of single gemcitabine in previously untreated patients with advanced pancreatic cancer and these studies reported partial response rate in the range of 5.4% to 12%[3, 6-10].

Given the variability in tumor response rates that can occur from difficulty in distinguishing tumor from inflammation or fibrosis, it is not surprising that our small-sized study showed a partial response rate of 0%.

Meanwhile, the median survival time and 1-year survival in this study were 6.2 months and 18%, respectively, which were similar outcomes compared with previous trials[4, 6, 7, 10]. Median survival time for patients treated with single-agent gemcitabine has ranged form 5.6 to 6.3 months[4, 6, 7, 10]. In a randomized trial[4], the 1-year survival was observed in 18% for the gemcitabine -treated patients and 2% for the 5-FU-treated patients. The authors also noted that clinical benefit response was experienced by 23.8% of gemcitiabine-treated patients compared with 4.8% of 5-FU-treated patients. Unfortunately, we could not evaluate clinical benefit parameters, such as pain, performance status and weight, because of retrospective analysis.

In conclusion, our study provides support for the low toxicity of gemcitabine in the treatment of patients with advanced pancreatic cancer.

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