Prognostic Factors of Unresectable Pancreatic Cancer Treated with Nafamostat Mesilate Combined with Gemcitabine Chemotherapy

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Abstract. *Background: The aim of this study was to investigate prognostic factors of survival for patients with unresectable pancreatic cancer treated with nafamostat mesilate combined with gemcitabine chemotherapy. Patients and Methods: The study included 41 patients who were diagnosed with unresectable pancreatic cancer and eligible for our clinical study of nafamostat mesilate, combined with gemcitabine chemotherapy for unresectable pancreatic cancer between February 2007 and November 2010 at Jikei University Hospital. We retrospectively investigated the relation between patients' characteristics and overall survival using univariate and multivariate analyses. Results: In univariate analysis, absence of jaundice (p=0.0365), presence of ascites with or without histological diagnosis of carcinomatosis (p=0.0042), lymphocyte count ≥2,000/μl (p=0.0088), serum C-reactive protein ≥1 mg/dl (p=0.014), serum carcinoembryonic antigen ≥5 ng/ml (p=0.0064) and serum CA19-9 ≥500 U/ml (p=0.0164) were significant predictors of poor overall survival. In multivariate analysis, absence of jaundice (p=0.0057), presence of ascites with or without histological diagnosis of carcinomatosis (p=0.0326), lymphocyte ≥2,000/μl (p<0.0001) and CA19-9 ≥500 U/ml (p=0.0198) were independent predictors. Conclusion: Jaundice, ascites, high lymphocyte count and high serum CA19-9 levels are independent prognostic predictors for poor overall survival of patients with unresectable pancreatic cancer treated with nafamostat mesilate combined with gemcitabine chemotherapy.*

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Pancreatic cancer is one of the most fatal types of human cancers of the digestive system, with an overall 5-year survival rate of only 1-4%, because of rapid tumor growth and high potential for distant metastasis. In addition, despite developments in diagnostic techniques and modalities, the majority of patients with pancreatic cancer are diagnosed at an advanced stage and therefore, only 14% of patients are amenable to resection (1). Gemcitabine is currently the standard treatment for unresectable pancreatic cancer (2), but the therapeutic benefit of gemcitabine is limited (3). Therefore, new therapeutic approachs and assessment of prognostic predictors are important for the management of patients with unresectable pancreatic cancer.

Recent studies have demonstrated that NF-κB plays an important role in the regulation of cell apoptosis, inflammation, and oncogenesis (4-7). Inhibition of NF-κB is considered a new treatment strategy for cancer (8-11). In addition, constitutive activation of NF-κB has been reported to play a key role in the aggressive behavior of pancreatic cancer (12-15). We have reported that nafamostat mesilate, a serine-protease inhibitor of NF-κB (16, 17), widely used for the treatment of pancreatitis (18), disseminated intravascular coagulation (19, and anticoagulation in hemodialysis (20) in Japan, inhibits NF-κB activation by suppressing IκBα phosphorylation and induces apoptosis of pancreatic cancer cells both *in vitro* and *in vivo* (21, 22). High efficacy of nafamostat mesilate combined with gemcitabine for pancreatic cancer has been demonstrated in animal experiments (23) and applied to phase I (24) and II clinical trials (25).

The aim of this study was to investigate prognostic factors of survival of patients with unresectable pancreatic cancer treated with nafamostat mesilate combined with gemcitabine chemotherapy.

Patients and Methods

Between February 2007 and November 2010, 43 patients diagnosed with unresectable locally-advanced or metastatic pancreatic cancer

were enrolled in our clinical study (24, 25) of nafamostat mesilate combined with gemcitabine chemothrerapy for unresectable pancreatic cancer, performed in the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Out of these, two patients were excluded, one patient due to nafamostat mesilate allergy and another patient for whom a port-catheter could not be inserted due to tumor invasion of the celiac artery, leaving the remaining 41 patients for this study.

Complete blood count and chemistry profiles were routinely measured before systemic chemotherapy of our clinical study. The complete blood count included hemoglobin, white blood cells (WBC), lymphocytes and platelets. The serum biochemistry data included serum total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), total bilirubin (T-Bil), C-reactive protein (CRP) and tumor markers including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). The patients were classified into two groups for each parameter as follows: hemoglobin <12 or ≥12 g/dl, WBC <10,000 or ≥10,000 /μl, lymphocyte count <2,000 or ≥2,000/μl, serum albumin <3.5 or ≥3.5 g/dl, CRP <1.0 or ≥1.0 mg/dl, CEA <5 or ≥5 ng/ml, and CA19-9 <500 or ≥500 U/ml, respectively.

We investigated the relation between patients' characteristics and overall survival after the first chemotherapy of our clinical study by univariate and multivariate analyses. The factors included age, gender, symptoms (jaundice, abdominal pain, back pain, weight loss and fatigue), diabetes mellitus, biliary drainage, tumor location (head *vs*. body or tail), distant metastasis (liver, lung and ascites with or without histological diagnosis of carcinomatosis), hemoglobin, WBC, lymphocyte count, serum albumin, CRP, CEA, and CA 19-9.

This study was approved by the Ethics Committee of the Jikei University School of Medicine.

Statistical analysis. The data are expressed as medians. Univariate analysis was performed using non-paired *t*-test and Chi-square test. Analysis of overall survival was performed using the log-rank test. Multivariate analysis was performed using stepwise Cox proportional hazards regression model. All *p*-values were considered statistically significant when the associated probability was less than 0.05.

Results

Patients' characteristics. Table I lists the patients' characteristics enrolled in this study. The median age of the 41 patients was 64 (range 38-79) years, out of whom 11 (27%) were female. Symptoms consisted mainly of jaundice in 32%, abdominal pain in 22% and back pain in 20%. Twenty-six patients (63%) had cancer of the pancreatic head, and 28 patients (68%) had distant metastasis, the majority of the liver (49%). The median survival time of the patients was 13.2 (range1.3-30.6) months.

Univariate and multivariate analysis of overall survival. Table II lists the relationship between the patients' characteristics and overall survival. In univariate analysis, overall survival was significantly worse in the absence of jaundice (p=0.0365, Figure 1A); presence of ascites, with or with out histological diagnosis of carcinomatosis (p=0.0042, Figure 1B); lymphocyte count ≥2,000/μl (p=0.0088, Figure 1C); serum CRP ≥1 mg/dl (p=0.014); serum CEA ≥5 ng/ml (p=0.0064, Figure 1D); and serum CA19-9 ≥500 U/ml (p=0.0164, Figure 1E).

Table I. *Patients' characteristics*.

Factor	Median, n	Range, %
Median age (years)	64	38-79
Gender		
Male	30	73%
Female	11	27%
Presenting symptoms		
Jaundice	13	32%
Abdominal pain	9	22%
Back pain	8	20%
Weight loss	12	30%
Fatigue	4	10%
Diabetes mellitus		
Yes	19	46%
No	22	54%
Biliary drainage		
Yes	19	46%
No	22	54%
Tumor location		
Head	26	63%
Body or tail	15	37%
Distant metastasis		
Yes	28	68%
No	13	32%
Liver metastasis		
Yes	20	49%
No	21	51%
Lung metastasis		
Yes	2	4.9%
No	39	95.1%
Ascites or carcinomatosis		
Yes	5	12%
No	36	88%
Median complete blood count		
Hemoglobin (g/dl)	12.7	9.7-14.6
WBC (/μl)	6700	3700-25,600
Lymphocyte (/μl)	1,400	600-4,000
Platelet ($\times 10^4$/μl)	23.7	11.7-45.4
Median blood chemistry profile		
Total protein (g/dl)	6.9	5.2-7.9
Albumin (g/dl)	3.9	2.3-4.4
AST (U/l)	21	9-118
ALT (U/l)	23	7-306
ALP (U/l)	319	44-1,752
γ -GTP (U/l)	66	15-744
Total bilirubin (mg/dl)	0.9	0.4-2.7
CRP (mg/dl)	0.46	0.04-7.83
Median tumor marker		
CEA (ng/ml)	6.8	0.9-583.4
CA19-9 (U/ml)	563	1-23,400

WBC: White blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; γ-GTP: γ-glutamyl transpeptidase; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Table II. *Univariate analysis of overall survival.*

Factor	N	Overall survival	
		Median (years)	*p*-Value
Age (years)			
<60	11	0.73	0.7598
≥60	30	0.60	
Gender			
Male	30	0.64	0.5414
Female	11	0.61	
Jaundice			
Yes	13	1.21	0.0365
No	28	0.59	
Abdominal pain			
Yes	9	0.59	0.844
No	32	0.73	
Back pain			
Yes	8	0.44	0.7756
No	33	0.64	
Weight loss			
Yes	12	0.64	0.7701
No	29	0.61	
Fatigue			
Yes	4	0.59	0.9186
No	37	0.64	
Diabetes mellitus			
Yes	19	0.96	0.9705
No	22	0.53	
Biliary drainage			
Yes	19	0.61	0.6942
No	22	0.64	
Tumor location			
Head	26	0.60	0.2668
Body or tail	15	0.69	
Distant metastasis			
Yes	28	0.52	0.2828
No	13	1.10	
Liver metastasis			
Yes	20	0.44	0.0764
No	21	1.10	
Lung metastasis			
Yes	2	1.15	0.4801
No	39	0.61	
Ascites or carcinomatosis			
Yes	5	0.42	0.0042
No	36	0.62	
Hemoglobin (g/dl)			
<12	12	0.58	0.4779
≥12	29	0.61	
WBC (/μl)			
<10,000	36	0.71	0.2768
≥10,000	5	0.46	
Lymphocyte count(/μl)			
<2,000	32	0.67	0.0088
≥2,000	9	0.42	
Albumin (g/dl)			
<3.5	7	0.61	0.4268
≥3.5	34	0.62	
CRP (mg/dl)			
<1.0	25	0.60	0.014
≥1.0	16	0.62	
CEA (ng/ml)			
<5	13	1.10	0.0064
≥5	28	0.60	
CA19-9 (U/ml)			
<500	18	1.15	0.0164
≥500	23	0.59	

WBC: White blood cell; CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

In multivariate analysis, the significant factors in univariate analysis were included. Independent and significant predictors of overall survival consisted of absence of jaundice (p=0.0057); presence of ascites, with or without histological diagnosis of carcinomatosis (p=0.0326); lymphocyte count ≥2,000/μl (p<0.0001); and serum CA19-9 ≥500 U/ml (p=0.0198) (Table III).

Discussion

The prognosis of patients with pancreatic cancer is poor and most patients have unresectable pancreatic cancer at the time of initial diagnosis. Therefore, their management is a common and important clinical problem. Several reports have discussed the predictors of overall survival for patients with unresectable pancreatic cancer. Park *et al*. reported that three factors, serum CA19-9>670 U/ml, American Joint Committee on Cancer stage, and treatment modality, proved to be independently significant by multivariate analysis (26). Papadoniou *et al*. reported 10 factors pertinent to survival in multivariate analysis: tumor location, metastasis, performance status, jaundice, weight loss, CRP, CEA, palliative surgery and chemotherapy (27). Weber *et al*. reported that the presence of distant metastases was the only independent prognostic factor for survival (28). Yi *et al*. reported that multivariate analysis revealed poor prognostic factors for overall survival of patients treated with first-line gemcitabine-based chemotherapy consisting of the presence of liver metastases, ascites or peritoneal carcinomatosis, serum CRP >1.2 mg/dl, and serum albumin <3.5 g/dl (29). In the present study, absence of jaundice, presence of ascites, lymphocyte count ≥2,000/μl and serum CA19-9 ≥500 U/ml were independent significant predictors of survival by multivariate analysis in patients with unresectable pancreatic cancer treated with nafamostat

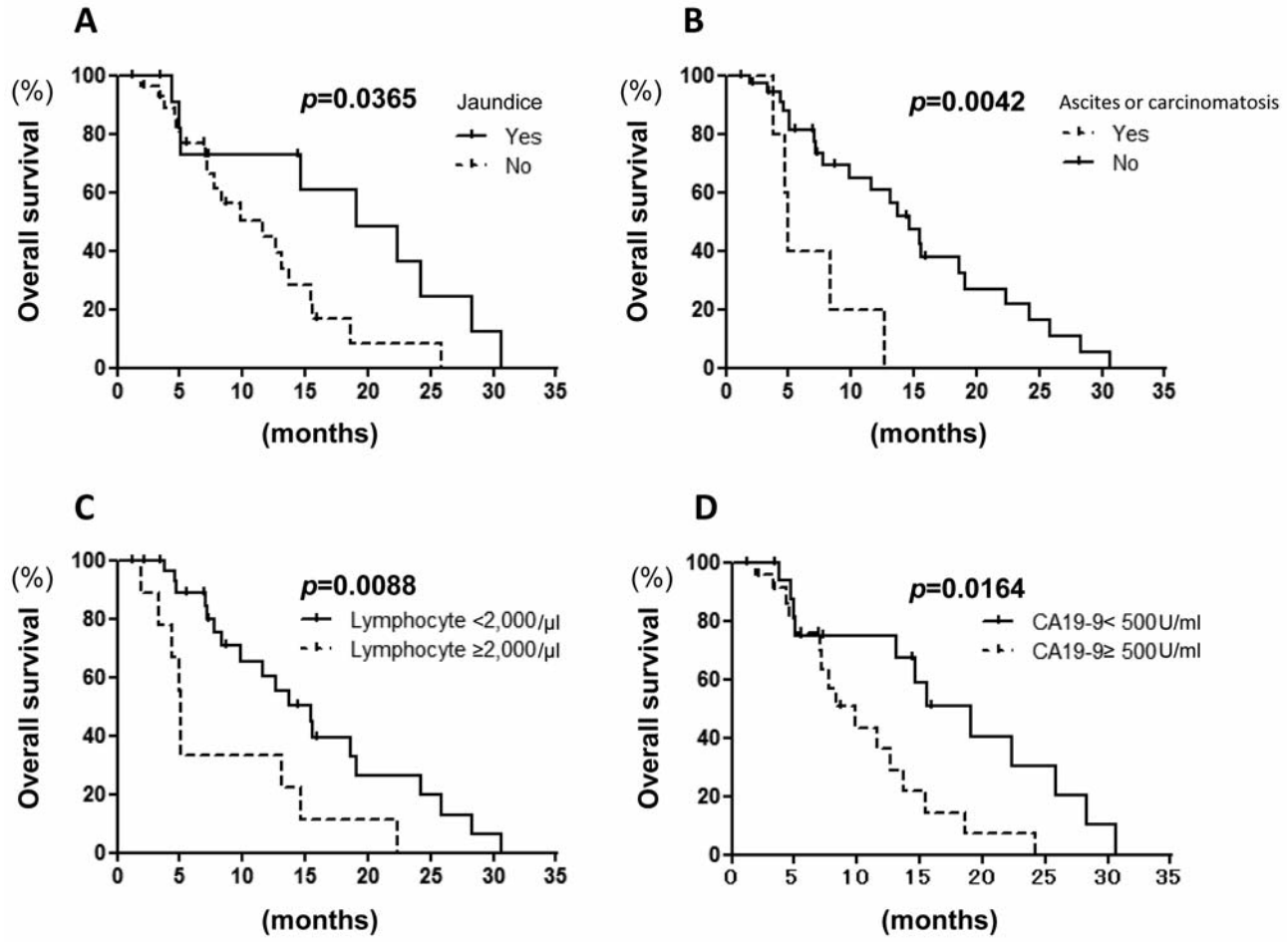

Figure 1. *Kaplan-Meier curves of overall survival in patients with and without jaundice (A), in patients with and without ascites or carcinomatosis (B), in patients with peripheral blood lymphocyte count less than and ≥2,000/μl (C) and in patients with serum CA19-9 less than and ≥500 U/ml (D).*

mesilate combined with gemcitabine chemotherapy. This study may contribute to the decision regarding the therapeutic strategy for patients with unresectable pancreatic cancer.

Generally, patients with distant metastases have poor prognosis. However, the present study showed that the presence of distant metastases was not a predictive factor of poor survival (p=0.2828). Because our basic research demonstrated that nafamostat mesilate inhibited adhesion, invasion and angiogenesis of pancreatic cancer (30), it is suggested that such clinical trials are effective for metastatic pancreatic cancer. To date, FOLFIRINOX has significantly improved median overall survival, as compared with gemcitabine-alone in patients with metastatic pancreatic cancer, with a median survival time of 11.1 months (31). Although our clinical trial was not randomized, the median survival time of the patients was 13.2 months.

Several investigators have reported that a decrease in the number of lymphocytes correlated with a poor prognosis in patients with pancreatic cancer by reducing tumor immunity (32-34). On the contrary, in this study, a reduced lymphocyte count did not correlate with a poor prognosis. Because NF-κB regulates the expression of many cytokines and immunoreceptors affecting tumor immunity (35), it is

Table III. *Multivariate analysis of overall survival.*

Factor	Odds ratio (95% CI)	*p*-Value
Jaundice (Yes)	0.169 (0.480-0.597)	0.0057
Ascites or carcinomatosis (Yes)	3.638 (1.113-11.893)	0.0326
Lymphocyte count (≥2,000/μl)	24.016 (5.003-115.278)	<0.0001
CRP (≥1.0 mg/dl)	1.447 (0.448-4.75)	0.5372
CEA (≥5 ng/ml)	1.348 (0.336-5.409)	0.6735
CA19-9 (≥500 U/ml)	5.669 (1.316-24.410)	0.0198

CRP: C-reactive protein; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; CI: confidence interval.

suggested that the anti-tumor through effect tumor immunity was not very important in this clinical trial of the NF-κB inhibitor, nafamostat mesilate.

In conclusion, the present study demonstrated that absence of jaundice, presence of ascites, a high lymphocyte count and high serum CA19-9 levels, were independent prognostic predictors of poor overall survival of patients with unresectable pancreatic cancer treated with nafamostat mesilate combined with gemcitabine chemotherapy.

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