RESEARCH COMMUNICATION

Long Term Survivors with Metastatic Pancreatic Cancer Treated with Gemcitabine Alone or Plus Cisplatin: a Retrospective Analysis of an Anatolian Society of Medical Oncology Multicenter Study

Ali Inal[1]*, Aydın Ciltas[2], Ramazan Yıldız[3], Veli Berk[4], F Tugba Kos[5], Faysal Dane[6], Ilkay Tugba Unek[7], Dilsen Colak[8], Nuriye Yıldırım Ozdemir[5], Suleyman Buyukberber[2], Mahmut Gumus[3], Metin Ozkan[4], Abdurrahman Isıkdogan[1]

Abstract

Background: The majority of patients with pancreatic cancer present with advanced disease. Systemic chemotherapy has limited impact on overall survival (OS) so that eligible patients should be selected carefully. The aim of this study was to analyze prognostic factors for survival in Turkish advanced pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and receiving gemcitabine (Gem) alone or gemcitabine plus cisplatin (GemCis). Methods: This retrospective evaluation was performed for patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and who received gemcitabine between December 2005 and August 2011. Twenty-seven potential prognostic variables were chosen for univariate and multivariate analyses to identify prognostic factors associated with survival. Results: Among the 27 variables in univariate analysis, three were identified to have prognostic significance: sex (p = 0.04), peritoneal dissemination (p =0.02) and serum creatinine level (p=0.05). Multivariate analysis by Cox proportional hazard model showed only peritoneal dissemination to be an independent prognostic factor for survival. Conclusion: In conclusion, peritoneal metastasis was identified as an important prognostic factor in metastatic pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and receiving Gem or GemCis. The findings should facilitate pretreatment prediction of survival and can be used for selecting patients for treatment.

Keywords: Pancreas - cancer - gemcitabin - prognosis - long term survivors

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Introduction

Pancreatic cancer is the fourth most common among cancer-related deaths in the United States. Surgical opportunity the only potentially curative treatment, but only less than 20% of these patients present with surgically resectable disease. In spite of surgery with a curative treatment, the rate of overall 5-year survival rate remains at approximately 20% and most will generally occur metastatic disease within the first year of surgery therapy. Without effective treatment the median survival for patients with metastatic pancreatic adenocarcinoma is 3 to 6 months. The rate of overall 5-year survival among advanced pancreatic cancer is generally under 5% (Ryan et al., 1998; Cooperman et al., 2001; Jemal et al., 2009; Royal et al., 2011).

For advanced and metastatic pancreatic cancer, systemic chemotherapy with single-agent Gem is currently recommended as a standard of first-line chemotherapy (Burris et al., 1999; Heinemann et al., 2007; National Comprehensive Cancer Network. 2012).

Systemic chemotherapy for patients with pancreatic cancer has limited impact on OS due to not only a low response rates, but also because of severe side effects (Colucci et al., 2002; Viret et al., 2004; Heinemann et al., 2006). Patients eligible for chemotherapy should be selected carefully. A very different prognostic factors in several trials have been identified for survival in patients with advanced pancreatic cancer (Ueno et al., 2000; Ikeda, 2001; Engelken, 2003; Papadoniou et al., 2008; Shimoda et al., 2010), while in the literature there was just one small study (20 patients) with pancreatic cancer patients

*[1]Department of Medical Oncology, Dicle University, Diyarbakir, [2]Gazi University, Ankara, [4]Erciyes University, Kayseri, [5]Ankara Numune Education and Research Hospital, Ankara, [7]Department of Medical Oncology, Dokuz Eylül University, İzmir, [3]Dr. Lütfi Kirdar Kartal Education and Research Hospital, [6]Division of Medical Oncology, Marmara University School of Medicine, Istanbul, [8]Yıldırım Beyazıt Education and Research Hospital, Ankara, Turkey *For correspondence: dr.ainal@gmail.com, dr.ali33@mynet.com*

who survived more than one year from the diagnosis of recurrent and/or metastatic disease (Goulart et al., 2009).

Goulart BH et al. (2009) suggest that bilirubin and CA 19-9 levels were predictive of longer survival in a subgroup of patients with metastatic pancreatic cancer has prolonged survival after treatment with Gem.

We performed a a multicenter retrospective analysis of prognostic factors in the pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and Gem or GemCis.

Materials and Methods

Patient Population

We retrospectively evaluated for pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and receiving Gem or GemCis between December 2005 and August 2011.

They met the following inclusion criteria; 1) they were 18 years or older in age; 2) they had histologic or cytologic diagnosis recurrent and/or metastatic adenocarcinoma; 3) no previous chemotherapy or radiotherapy; 4) a survival more than one year from the diagnosis of metastatic or recurrent disease; 5) they had to have measurable disease.

Treatment and Assessment

Gemcitabine was administrated at 1000 mg/m^2 IV over 30 min on Days 1 and 8 of each 21-day cycle. Cisplatin was added at 70 mg/m^2 on day 1 every 21-day cycle to the gemcitabine schedule. Tumor response was documented by computed tomography imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) at baseline and every three cycles for patients.

Factors Analyzed

Twenty-seven clinical variables were chosen on the basis of previously published clinical trials. The variables were divided into two categories: age (<65 or ≥65 years), gender (male or female), prior pancreactomy (present or absent), performance status (0-1, 2-3), location of primary tumor (head or body-tail), grade (well, poor or moderate), first-line chemotherapy (Gem or GemCis), second-line chemotherapy (present or absent), the presence of diabetes mellitus at diagnosis, the presence of cholestasis at diagnosis, weight loss ≥ 10%, liver metastasis, peritoneal dissemination, baseline laboratory parameters (<median or ≥ median) at the time of firstline chemotherapy administration.

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 chi-square test and student t test. Overall survival was calculated with the log-rank test. The Kaplan–Meier method was for used survival curves. Differences were assumed to be significant when the p value was less than 0.05.

Results

Patient Characteristics

Between September 2005 and March 2011, 40 untreated patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease were enrolled in this study.

Sixteen patients were treated with single-agent Gem. Twenty-four patients were treated with GemCis. The median age of patients was 61.5 years (range 29–76) with 27 males and 13 females. 14 patients (35.0%) received second-line chemotherapy. The median OS was 15.0 months (Figure 1). The patients' baseline characteristics are listed in Table 1.

Prognostic Factor Analysis

The results of univariate analysis are summarized in

Table 1. The General Characteristics of the Patients

Characteristic		No. of patients (%)
Sex	Male	27 (67.5)
	Female	13 (32.5)
Age, median (range)		61 (29-76)
Age	<65	28 (70.0)
	≥65	12 (30.0)
Performance status	0-1	26 (65.0)
	2-3	8 (20.0)
	Unknown	6 (15.0)
Grade	Well	4 (10.0)
	Poor or moderate	4 (10.0)
	No data	32 (80.0)
Location of primary tumor	Head	23 (57.5)
	Body–tail	8 (20.0)
	Unknown	9 (22.5)
First-line Chemotherapy	Gem	16 (40.0)
	GemCis	24 (60.0)
Diabetes Mellitus		14 (35.0)
Cholestasis		10 (25.0)
Weight loss		15 (37.5)
Metastatic sites	Liver	27 (67.5)
	Peritoneum	5 (12.5)
Second-line chemotherapy		14 (35.0)
OS, median (range)		15 (13-41)
Baseline laboratory parameters,(median)		
Hemoglobin, g/l		12.5
WBC		8650
Albumin, g/dl		3.8
Glukoz, mg/dl		115
ALP, U/l		241
AST, U/l		31
ALT,U/l		36
LDH, U/l		240
GGT, U/l		118
BUN, mg/dl		14
Kreatin, mg/dl		0.7
Total Bilirubin, mg/dl		0.7
Calcium, mg/dl		9.2
CEA, ng/mL		10
CA19-9, ng/mL		980

*WBC, White blood cell; AST, aspartate transaminase; ALT, alanine transaminase; ALP, Alkaline, Phosphatase; GGT, γ - glutamyl trans peptidase; BUN, Blood Urea Nitrogen; LDH, Lactic dehydrogenase; CEA, Carcinoembryonic antigen; CA 19-9, Carbohydrate antigen

Table 2. Univariate Analysis of Survival Time by Categorical Variable

Variable	Log-rank test value	p
Sex	3.9	0.04
Age	0.9	0,32
Location of primary tumor	1.3	0.25
Grade	0.1	0.73
Performance status	0.4	0.5
Cholestasis	0.3	0.53
Weight loss	0.6	0.42
Diabetes Mellitus	0.01	0.99
Hypertansiyon	0.3	0.85
Peritoneal dissemination	5	0.02
Liver metastasis	0.2	0.61
Chemotherapy	1.3	0.24
Baseline laboratory parameters,(median)		
CEA	1.1	0.29
CA19-9	0.2	0.59
BUN	2.5	0.1
Creatinine	3.7	0.05
Albumin	2.2	0.13
Glukoz	1.4	0.23
ALP	0.3	0.55
AST	0.1	0.7
ALT	0.1	0.7
LDH	1.1	0.28
GGT	0.2	0.63
Total Bilirubin	0.08	0.92
Calcium	0.2	0.87
Hemoglobin	0.4	0.51
WBC	1.5	0.21

*Degree of freedom = 1

Table 3. Multivariate Analysis of Prognostic Factors

Parameter	OR	%95 CI	p value
Sex	0.9	0.25-3.18	0.88
Peritoneal dissemination	3.37	1.17-9.66	0.02
Creatinine	2.06	0.79-5.37	0.13

Table 2. Among the 27 variables of univariate analysis, three variables were identified to have prognostic significance: Sex (P = 0.04), peritoneal dissemination (P =0.02) and serum creatinine level (P=0.05).

Multivariate analysis included the three prognostic significance factors in univariate analysis. The results of multivariate analysis was shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that peritoneal dissemination was considered independent prognostic factors for survival.

Discussion

Without effective treatment the median survival for patients with metastatic pancreatic adenocarcinoma is 3 to 6 months. Systemic chemotherapy for patients with pancreatic cancer has limited impact on OS owing to not only a low response rates, but also because of severe side effects. Patients eligible for chemotherapy should be selected carefully. This retrospective clinical trial sample represents only about 9.8% of 406 patients who were administered Gem or GemCis as first-line treatment at this institution. This retrospective multicenter study

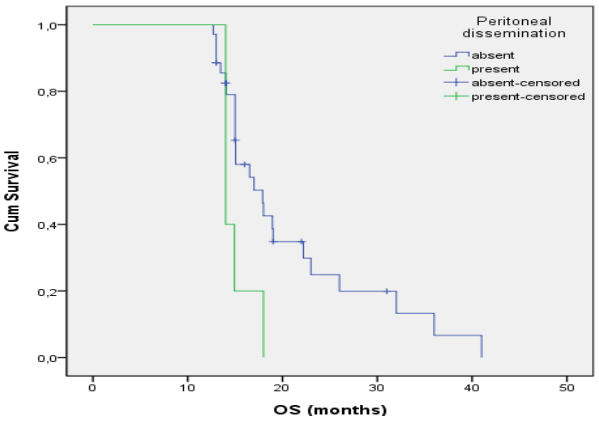

Figure 2. Survival of Patients According to Peritoneal Dissemination

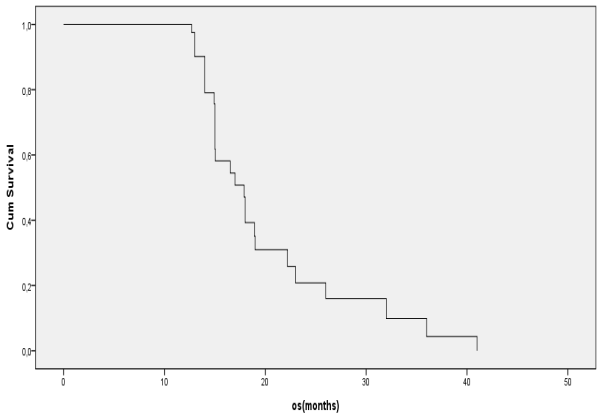

Figure 1. Overall Survivall in All Patients. OS: Median 15 Months (13-41)

analyzed prognostic factors for survival in pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and receiving Gem or GemCis.

On univariate analysis, three of twenty-seven potential factors were identified as significant prognostic factors for survival. However, only one independent significant prognostic factor was found on multivariate analysis: peritoneal dissemination.

To identify the prognostic factors of metastatic pancreatic cancer before first-line chemotherapy, numerous clinical studies have been done (Ueno et al., 2000; Ikeda 2001; Engelken, 2003; Papadoniou et al., 2008; Shimoda et al., 2010). However, very few studies were carried out for the prognostic value of peritoneal metastase in metastatic pancreatic cancer (Maréchal et al., 2007; Nakachi et al., 2007; Yi et al., 2011). In two clinical trials (Nakachi et al., 2007; Yi et al., 2011), peritoneal metastase was found as an independent risk factor for survival with advanced pancreatic cancer patients, while in the literature there was just one study (Goulart et al., 2009) with pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease. In this study the prognostic value of peritoneal metastase was not evaluated. In our retrospective study, we found that presence of peritoneal metastases associated with the negative prognostic importance for survival.

Pancreatic adenocarcinoma spreads easily into the peritoneal cavity, As a result of this, massive ascites

and deterioration of general condition are occurred. The negative prognostic importance of peritoneal metastases for survival may be explained with first-line chemotherapy failure.

Goulart et al. (2009) was found that Only bilirubin and CA 19-9 levels were predictive of longer survival in metastatic pancreatic adenocarcinoma treated with Gem. In the present study, neither serum baseline bilirubin nor CA 19-9 levels were not independent prognostic factors for overall survival.

The present study has got some limitations. The one of the limitations is retrospective nature, the other is small sample.

In conclusion, peritoneal metastasis was identified as important prognostic factors in metastatic pancreatic cancer patients who survived more than one year from the diagnosis of recurrent and/or metastatic disease and receiving Gem or GemCis. These findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for treatment. Therefore, prospective and larger clinical trials are needed.

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