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ORIGINAL ARTICLE

Prognostic factors in patients with advanced pancreatic cancer treated with gemcitabine alone or gemcitabine plus cisplatin: retrospective analysis of a multicenter study

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Summary

Purpose: *The majority of patients with pancreatic cancer present with advanced disease. Systemic chemotherapy for patients with pancreatic cancer has limited impact on overall survival (OS). Patients eligible for chemotherapy should be selected carefully. The aim of this study was to analyse prognostic factors for OS in advanced pancreatic cancer patients treated with first-line palliative chemotherapy with gemcitabine alone or gemcitabine plus cisplatin.*

Methods: *We retrospectively reviewed 343 locally advanced or metastatic pancreatic cancer patients who were treated with gemcitabine or gemcitabine plus cisplatin as first-line chemotherapy between December 2000 and June 2011.*

Fifteen potential prognostic variables were chosen for analysis. Univariate and multivariate analyses were conducted to identify prognostic factors associated with OS. Univariate and multivariate statistical methods were used to determine prognostic factors.

Results: *Among the 15 variables of univariate analysis, 6 were identified to have prognostic significance: stage ($p<0.001$), cholestasis ($p=0.02$), weight loss, prior pancreatectomy, serum CEA level ($p<0.001$) and serum CA19-9 level ($p<0.001$). In addition, age, chemotherapy and liver metastasis were of borderline significance ($p=0.06$).*

Multivariate analysis (Cox proportional hazard model) included the 6 significant prognostic factors of univariate analysis and showed that stage was independent prognostic factor for OS, as were weight loss, and serum CEA level.

Conclusion: *Stage, weight loss, and serum CEA level were identified as important prognostic factors for OS in advanced pancreatic cancer patients. These findings may also facilitate pretreatment prediction of OS and can be used for selecting patients for treatment.*

Key words: cancer, gemcitabine, pancreas, prognosis

Introduction

Pancreatic cancer is the 4th most common cause of cancer-related deaths in the United States. Without effective treatment, the median OS for metastatic disease is 3-6 months. The overall 5-year survival rate in unresectable pancreatic cancer is generally under 5% [1-4].

Systemic chemotherapy with single-agent gemcitabine is currently recommended as a standard first-line chemotherapy for the treatment of advanced pancreatic cancer [3,5].

Several randomized Phase II and III trials in pa-

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tients with advanced pancreatic adenocarcinoma suggest that the combination of gemcitabine and cisplatin (Gem/Cis) response rates were higher than gemcitabine alone, however the trials were not enough powered to indicate a statistically significant prolongation of survival [6-9].

Systemic chemotherapy for patients with pancreatic cancer has limited impact on OS due to not only low response rates, but also because of severe side effects, thus patients eligible for chemotherapy should be selected carefully.

Very different prognostic factors have been identified in several studies for OS in patients with advanced pancreatic cancer [10-16].

We performed a multicenter retrospective analysis of prognostic factors in patients receiving gemcitabine-based chemotherapy for locally advanced or metastatic pancreatic cancer.

Methods

Patient population

We retrospectively reviewed 343 locally advanced or metastatic pancreatic cancer patients who were treated with gemcitabine or gemcitabine plus cisplatin as first-line chemotherapy between December 2000 and June 2011.

Patients who had received prior treatment were excluded.

Treatment and assessment of response

Gemcitabine was administered at 1000 mg/m^2 i.v. over 30 min on days 1 and 8 of each 21-day cycle and its dose was kept the same when combined with cisplatin. Cisplatin was administered at 70 mg/m^2 on day 1 of each 21-day cycle. Imaging studies were carried out by computed tomography at baseline and every 3 cycles.

Response to chemotherapy was measured according to Response Evaluation Criteria in Solid Tumors (RECIST).

Factors analysed

Fifteen 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 pancreatectomy (present or absent), ECOG performance status (0-1, 2-3), location of primary tumor (head or body-tail), stage (locally advanced or metastatic disease), grade (well, poor or moderate), chemotherapy (Gem or Gem/Cis), presence of diabetes mellitus at diagnosis, presence of cholestasis at diagnosis, hypertension, weight loss, liver metastasis, serum carcinoembryonic antigen (CEA) level (<10 or ≥10 ng/ml) and serum carbohydrate antigen 19-9 (CA19-9) level (<1000 or ≥1000 U/ml).

Statistical analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows). Differences of the clinical characteristics between the two groups were analysed by chi-square test and Student's t-test. OS was calculated with the log-rank test. The Kaplan-Meier method was used to construct survival curves. The Cox proportional hazards regression model was used to determine statistical significant variables related to OS. Differences were assumed to be significant with a p-value<0.05.

Results

Patient characteristics

From September 2005 through March 2011, 343 untreated patients with locally advanced or metastatic pancreatic cancer were enrolled onto study. One hundred and thirty-two patients were treated with single-agent gemcitabine. Two hundred and eleven patients were treated with Gem/Cis. The median patient age was 60 years (range 29-84) with 231 (67.3%) males and 112 females (32.7%). Two hundred and seven patients (61%) were diagnosed with metastatic disease and 136 (39%) with locally advanced disease. Sixty-nine patients (20.1%) received second-line chemotherapy. The median OS was 9.0 months (range 1-65). The patient baseline characteristics are listed in Table 1.

Prognostic factors analysis

The results of univariate analysis are summarized in Table 2. Among the 15 variables of univariate analysis, 6 were found to have prognostic significance: stage (p<0.001), cholestasis (p=0.02), weight loss (p=0.005), prior pancreatectomy (p<0.001), serum CEA level (p<0.001) and serum CA19-9 level (p<0.001). Age, chemotherapy and liver metastasis showed borderline significance (p=0.06).

Multivariate analysis included the 6 factors with prognostic significance that emerged in univariate analysis. The results of multivariate analysis are shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that stage, weight loss and serum CEA levels were independent prognostic factors for OS.

Discussion

Systemic chemotherapy for patients with pancreatic cancer has limited impact on OS due to not only low response rates, but also because of severe side effects. Patients eligible for chemotherapy should be selected carefully. This retrospective multicenter study analysed prognostic factors for OS in advanced pancreatic cancer patients who were undergoing first-line palliative chemotherapy with gemcitabine alone or gemcitabine plus cisplatin.

Table 1. Patient, disease and chemotherapy characteristics

Characteristics	*No. of patients (%)*
Sex	
Male	231 (67.3)
Female	112 (32.7)
Age, years median (range)	60 (29-84)
Age, years	
<65	237 (69.1)
≥65	106 (30.9)
ECOG performance status	
0-1	202 (58.9)
2-3	84 (24.5)
Unknown	57 (16.6)
Stage	
Locally advanced	136 (39)
Metastatic	207 (61)
Grade	
Well	28 (8.2)
Poor or moderate	85 (24.7)
No data	230 (67.1)
Location of primary tumor	
Head	219 (63.8)
Body-tail	104 (30.3)
Unknown	20 (5.8)
Chemotherapy	
Gemcitabine	132 (38.5)
Gemcitabine/cisplatin	211 (61.5)
Other characteristics	
Diabetes mellitus	105 (30.7)
Cholestasis	92 (30.4)
Weight loss	151 (46)
Hypertension	74 (25.9)
Liver metastasis	166 (50.8)
Prior pancreatectomy	160 (46.8)
CEA (ng/ml)	
<10	198 (69.2)
≥10	88 (30.8)
CA19-9 (U/ml)	
<1000	226 (66.7)
≥1000	113 (33.3)

Table 2. Univariate analysis of overall survival by categorical variable

Variable	*Log-rank test value*	*Degrees of freedom*	*p-value*
Sex	2.3	1	0.12
Age	3.3	1	0.06
Location of primary tumor	0.08	1	0.76
Grade	3.1	1	0.20
Stage	30.4	1	<0.001
ECOG performance status	1.6	1	0.19
Cholestasis	5.2	1	0.02
Weight loss	7.9	1	0.005
Diabetes mellitus	2.1	1	0.13
Hypertension	0.32	1	0.85
Prior pancreatectomy	20.7	1	<0.001
Liver metastasis	37.4	1	0.06
Chemotherapy	3.3	1	0.06
CEA	18.1	1	<0.001
CA19-9	22.8	1	<0.001

Table 3. Multivariate analysis of prognostic factors

Factors	*OR*	*95% CI*	*p-value*
Stage	2.41	1.64-3.56	<0.001
Weight loss	1.69	1.19-2.42	0.001
CEA	1.63	1.12-2.38	0.01
Cholestasis	1.09	0.71-1.16	0.68
Prior pancreatectomy	0.73	0.47-1.14	0.17
CA19-9	1.39	0.95-2.04	0.08

OR: odds ratio, 95% CI: 95% confidence interval

In univariate analysis, 6 of 15 potential factors were identified as significant prognosticators for OS. However, only 3 independent significant prognostic factors were found in multivariate analysis: stage, weight loss and serum CEA levels.

Many authors reported that weight loss was an independent prognostic factor of OS [10,13,15], while Marechal et al. [17] found no significant impact on OS. Similarly, weight loss was found as independent prognostic factor for OS in our study. Weight loss may be indicative of increased disease aggressiveness and disease burden.

Age was not significantly associated with improved survival in numerous clinical studies [10,11,17-20]. In our study also age was not found as independent prognostic factor for OS.

Similarly, like in the Heinemann et al. study [7], disease stage was independent prognostic factor of OS.

Tumor markers, especially CA19-9 and CEA, were used to assess treatment efficacy in pancreatic cancer patients. Elevated levels of serum CEA and CA 19-9 may be an indicator of tumor aggressiveness compared to low levels. Many authors [11,13,15,19,21] have published that the baseline serum CA 19-9 level in patients with advanced pancreatic adenocarcinoma is independently correlated with OS, while this did not apply for serum CEA level. In 2 clinical trials [10,15], serum baseline CEA level was found as independent prognostic factor for OS in advanced pancreatic cancer patients. In the present study, not only serum baseline CA 19-9 level, but also CEA level were independent prognostic factors for OS.

In conclusion, stage, weight loss, and serum CEA levels were identified as independent prognostic factors in advanced pancreatic cancer patients who were administered first-line palliative chemotherapy with gemcitabine alone or gemcitabine plus cisplatin. Prospective and larger clinical trials are needed in this topic to elucidate the true role of these and other prognostic factors in pancreatic cancer.

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