RESEARCH ARTICLE

Prognostic Factors in First-Line Chemotherapy Treated Metastatic Gastric Cancer Patients: A Retrospective Study

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Abstract

Background: The majority of patients with gastric cancer in developing countries present with advanced disease. Systemic chemotherapy therefore has limited impact on overall survival. Patients eligible for chemotherapy should be selected carefully. The aim of this study was to analyze prognostic factors for survival in advanced gastric cancer patients undergoing first-line palliative chemotherapy. Methods: We retrospectively reviewed 107 locally advanced or metastatic gastric cancer patients who were treated with docetaxel and cisplatin plus fluorouracil (DCF) as first-line treatment between June 2007 and August 2011. Twenty-eight potential prognostic variables were chosen for univariate and multivariate analyses. Results: Among the 28 variables of univariate analysis, nine variables were identified to have prognostic significance: performance status, histology, location of primary tumor, lung metastasis, peritoneum metastasis, ascites, hemoglobin, albumin, weight loss and bone metastasis. Multivariate analysis by Cox proportional hazard model, including nine prognostic significance factors evident in univariate analysis, revealed weight loss, histology, peritoneum metastasis, ascites and serum hemoglobin level to be independent variables. Conclusion: Performance status, weight loss, histology, peritoneum metastasis, ascites and serum hemoglobin level were identified as important prognostic factors in advanced gastric cancer patients. These findings may facilitate pretreatment prediction of survival and can be used for selecting patients for treatment.

Keywords: Gastric cancer - first-line chemotherapy - prognostic factors

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Introduction

Despite the reduced incidence, gastric cancer is the second most common among cancer-related deaths in the word. In two-third of patients with gastric cancer are diagnosed with metastatic disease (Kamangar et al., 2006; Jemal et al., 2011). Without effective treatment, the median survival for metastatic disease is 3 to 5, however it may be extended 8-12 months with the platinum and taxane-containing regimens (Van Cutsem et al., 2006; Roth et al., 2007). Randomized trials have shown that systemic chemotherapy resulted in a significant survival benefits when compared with best supportive care (Murad et al., 1993; Pyrhonen et al., 1995; Glimelius et al., 1997). The meta-analysis by Wagner et al. suggests that the combination chemotherapy response rates over monotherapy alone in patients with advanced gastric cancer (Wagner et al., 2006). In the Tax 325 study, two regimens were compared; 75 mg/m^2 docetaxel and cisplatin on day 1 and 750 mg/m^2 5-Fluorouracil continuous infusion per day on days 1-5, every 3 weeks (DCF) versus cisplatin 100 mg/m^2 on day 1 and 1000 mg/m^2 5-Fluorouracil continuous infusion per day on days 1–5, every 4 weeks (CF). The DCF arm response rates (37 vs 25%) and overall survival (OS) higher than CF arm, while the toxicities of grade 3 to 4 was higher in the DCF arm (Van Cutsem et al., 2006).

Very different prognostic factors in several studies have been identified for survival in patients with advanced gastric cancer (Tsujitani et al., 2001; Chau et al., 2004; Yoshida et al., 2004; Kim et al., 2008; Roshanaei et al., 2011; Maroufizadeh., 2012). Systemic chemotherapy for patients with gastric cancer has limited impact on OS due to not only a low response rates, but also severe side effects. Determining the prognostic factors of survival for metastatic gastric cancer patients with first-line chemotherapy treated patients can help physicians in the decision-making process for individual patients.

We performed a retrospective analysis of prognostic factors in the metastatic gastric cancer patients treated with first-line DCF chemotherapy.

Materials and Methods

Patient Population

We retrospectively reviewed 107 locally advanced or

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metastatic gastric cancer patients who were treated DCF as first-line treatment between June 2007 and August 2011.

All had advanced gastric cancer. Patients who had received prior treatment were excluded.

Treatment and Assessment

The DCF protocol included 50-75 mg/m^2 docetaxel and cisplatin on day 1 and 500-750 mg/m^2/day 5-FU infusion for 5 days, repeated every 3 weeks. Imaging studies were documented by computed tomography at baseline and every three cycles for patients.

The responses to chemotherapy were measured according to Response Evaluation Criteria in Solid Tumors (RECIST).

Factors Analyzed

Twenty-eight clinical variables [age, gender, prior gastrectomy, performance status, location of primary tumor, stage, grade, histology, diabetes mellitus, hypertension, weight loss, dose reduction, second-line chemotherapy, liver metastasis, lung metastasis, bone metastasis, peritoneum metastasis, ascites, hemoglobin (Hb), WBC count, platelet (PLT) count, serum albumin (alb), serum calcium, serum alkaline phosphatase (ALP), serum lactic dehydrogenase (LDH), serum total bilirubin, serum carcinoembryonic antigen (CEA) level and serum carbohydrate antigen 19-9 (CA19-9) level] were chosen on the basis of previously published clinical trials.

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 (OS) was calculated with the log-rank test. The Kaplan–Meier method was used survival curves. The Cox proportional hazards regression model was used to determine statistical significant variables related to survival. Differences were assumed to be significant when the P value was less than 0.05.

Results

Patient Characteristics

Between June 2007 to August 2011, 107 untreated patients with locally advanced and metastatic gastric cancer were enrolled in this study. The median age of patients was 52 years (range 23-76) with 69 males and 38 females. Ninety-two patients (86%) were diagnosed as having metastatic gastric cancer and 15 patients (14%) had locally advanced gastric cancer. 28 patients (26.2%) received second-line chemotherapy. The median OS was 9.0 months. The patient's baseline characteristics are listed in Table 1.

Prognostic Factor Analysis

The results of univariate analysis are summarized in Table 2. Among the twenty-eight variables of univariate analysis, eight variables were identified to have prognostic significance: Performance status (P=0.003), histology (P=0.02), location of primary tumor (P=0.003), lung metastasis (P =0.02), peritoneum metastasis (P<0.001), ascites (P<0.001), hemoglobin (P=0.03), albumin (P=0.03). In addition, weight loss and bone metastasis showed borderline significance (p=0.06).

Multivariate analysis included the nine prognostic significance factors observed to besignificant on univariate analysis. The results of multivariate analysis are shown in Table 3. Multivariate analysis by Cox proportional hazard model showed that performance status was considered independent prognostic factors for survival, as were weight loss, histology, peritoneum metastasis, ascites and serum hemoglobin level.

Table 1. General Characteristics of the Patients

Characteristic		No. of patients (%)
Sex:	Male	69 (64.50)
	Female	38 (35.53)
Age, median (range)		52 (23-76)
Age:	<65	90 (84.1)
	≥65	17 (15.9)
Performance status:	0-1	77 (72.0)
	2-3	28 (26.2)
	Unknown	2 (1.9)
Stage:	Locally advanced	15 (14.0)
	Metastatic	92 (86.0
Histology:	Adenocarcinoma	72 (68.3)
	Mucinous adenocarcinoma	31 (29.0)
	Signet ring cell carcinoma	4 (3.7)
Grade:	Well	6 (5.6)
	Moderate	12 (11.2)
	Poor	17 (15.9)
	No data	77 (72.0)
Location of primary tumor:		
	Gastroesophageal junction	15 (14.0)
	Fundus	3 (2.8)
	Body	21 (19.6)
	Antrum	35 (32.7)
	Total	8 (7.5)
	Unknown	25 (23.4)
Dose reduction		27 (25.2)
Second-line chemotherapy		28 (26.2)
Diabetes Mellitus		6 (6.5)
Weight loss		58 (56.3)
Hypertansiyon		9 (8.4)
Metastatic sites:	Liver	47 (43.9)
	Lung	8 (7.5)
	Bone	7 (6.5)
	Peritoneum	39 (36.4)
Ascites		28 (26.2)
Prior gastrectomy		48 (44.9)
Baseline laboratory parameters, median:		
	Hemoglobin, g/l	10.6
	WBC	8500
	PLT	347
	Albumin, g/dl	3
	Alkaline phosphatase, U/l	90
	LDH, U/l	238
	Total Bilirubin, mg/dl	0.5
	Calcium, mg/dl	8.4
	CEA, ng/mL	5

Table 2. Univariate Analysis of Survival Time by Categorical Variable (Degrees of freedom=1)

Variable	Log-rank test value	p
Age	0.4	0.5
Sex	0.001	0.9
Stage	1.6	0.2
Grade	4.3	0.2
Performance status	8.7	0.03
Histology	7.2	0.02
Location of primary tumor	3.4	0.003
Dose reduction	0.2	0.6
Second-line chemotherapy	3.1	0.08
Weight loss	3.4	0.06
Diabetes Mellitus	0.1	0.7
Hypertansiyon	0.02	0.9
Prior gastrectomy	0.5	0.4
Liver metastasis	0.1	0.8
Lung metastasis	5.0	0.02
Bone metastasis	3.3	0.06
Peritoneum metastasis	17.7	<0.001
Ascites	13.4	<0.001
Hemoglobin	4.4	0.03
Alb	4.7	0.03
WBC	2.0	0.1
PLT	0.4	0.4
Alkaline phosphatase	2.2	0.1
LDH	0.1	0.6
Total Bilirubin	0.2	0.6
Calcium	0.02	0.8
CEA	0.1	0.7
CA19-9	0.5	0.8

Table 3. Multivariate Analysis of Prognostic Factors

Parameter	OR	%95 CI	p value
Performance status	0.06	0.15-0.24	<0.001
Weight loss	3.06	1.27-7.36	0.012
Histology	0.21	0.07-0.60	0.004
Peritoneum metastasis	0.33	0.09-1.23	0.06
Ascites	0.13	0.03-0.49	0.03
Hemoglobin	4.66	1.61-13.4	0.004

Discussion

Systemic chemotherapy for patients with gastric cancer has limited impact on OS due to not only a low response rates, but also severe side effects. Patients eligible for chemotherapy should be selected carefully. This retrospective study analyzed prognostic factors for survival in advanced gastric cancer patients who were undergoing first-line palliative DCF chemotherapy.

On univariate analysis, nine of twenty-eight potential factors were identified as significant prognostic factors for survival. However, only six independent significant prognostic factors were found on multivariate analysis: performance status, weight loss, histology, peritoneum metastasis, ascites and serum hemoglobin level.

A poor performance status is usually accepted a negative prognostic factor for all cancer patients (Chau et al., 2004; Mitry et al., 2004; Hoang et al., 2005; Krishnan et al., 2006; Lee et al., 2007). The importance of this marker was also confirmed in advanced gastric cancer patients (Yoshida et al., 2004; Lee et al., 2007; Kim et al., 2008). Similarly performance status found that the prognostic importance for survival in our study.

The weight loss is usually associated with gastro-esophageal malignancy. Increased weight loss may represent a more aggressive tumour biological behaviour and increased tumour burden. Weight loss was found to be an independent prognostic factor of survival (Andreyev et al., 1998; Sougioultzis et al., 2010), while Kanagavel et al. (2010) no observed significant effect for overall survival. In our study, weight loss is found to be independent risk factor for survival.

The prognostic significance of peritoneal metastases and ascites with advanced gastric cancer was investigated in few clinical studies. It has been shown significantly associated with in some clinical studies (Kim et al., 2008; Chau et al., 2004; Sadeghi et al., 200), whereas Kanagavel et al.(2010) had no significant effect for overall survival. In our retrospective study, peritoneum metastasis and ascites were found to be an independent prognostic factor for survival.

Anemia is common among advanced gastric cancer patients. Anemia may be caused by many factors. These include a result of bleeding, chemotherapy-induced myelosuppression, marrow infiltration by tumor, hemolysis, nutritional deficiency or cytokine-mediated anemia of chronic disease. The previously by many authors (Chau et al., 2004; Park et al., 2006; Kim et al., 2008; Kanagavel et al., 2010) had showed that the low hemoglobin level in patients with advanced gastric cancer is correlated independently with poor prognosis, while in some studies (Lee et al., 2007; Kim et al., 2008), the low hemoglobin level had no significant effect for overall survival. In our analysis, anemia was found to be an independent prognostic factor on survival in patients receiving first-line therapy.

The histological patterns of gastric cancer also vary from country to country. These may depend on the prevalent socioeconomic conditions, genetic and environmental factors. The prognostic significance of histological subtype with advanced gastric cancer patients was investigated in few clinical trials (Kanagavel et al., 2010). Kanagavel et al. had no prognostic importance for survival. Unlike earlier studies, our study found that histological subtype is an independent risk factor for survival.

The present study has some limitations which need to be taken into account. Firstly, its retrospective study. Secondly, we did not evaluate molecular characteristics of the tumor. Thirdly, there was the small number of patients.

In conclusion, age, weight loss, liver metastasis, serum CEA level and serum CA19-9 level were identified as important prognostic factors in advanced gastric cancer patients who were undergoing first-line palliative gemcitabine alone or gemcitabine plus cisplatin. These findings may also facilitate pretreatment prediction of survival and can be used for selecting patients for treatment. However, before final conculsion can be drawn, larger prospective and clinical trials need to be conducted for confirmation.

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