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Original Article

An analysis of the chemotherapy efficacy on the survival of advanced gastric cancer patients

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Abstract: Objective: This research is to investigate the chemotherapy effiacy in advanced gastric cancer patients and prognostic factors so that to provide a basis for improving the diagnosis and treatment of advanced gastric cancer. Methods: A retrospective analysis was performed on the efficacy of chemotherapy with advanced gastric cancer (GC) diagnosed as well as survival data. The survival rate was estimated by Kaplan-Meier and compared by Log-rank test. Factors influencing the prognosis of patients were analyzed by Cox proportional hazard regression model. Results: The overall response rate (ORR) was 36.2% in 102 patients with advanced GC after chemotherapy. The incidences of grade III-IV hematological toxicity and grade III-IV nausea and vomiting in SOX group (14.9% and 0.0%) were lower than that in FOLFOX6 group (30.9% and 10.9%) (P<0.05). Our result showed that the survival rates among patients with different ECOG score, tumor status, histological grade, the number of organs involved in metastasis and chemotherapy efficacy were statistically significant (P<0.05). Multivariate cox regression analysis showed that ECOG score ≥2 points, poorly differentiated/undifferentiated histological grade and SD/PD of chemotherapy efficacy were prognostic risk factors. Conclusion: Adverse reactions are milder in the SOX group. And the long-term prognosis of patients with advanced GC is poor. Patients with ECOG score ≥2 points, poorly differentiated/undifferentiated histological grade, or SD/PD of chemotherapy efficacy are more likely to undergo bad prognosis.

Keywords: Advanced gastric cancer, chemotherapy, efficacy, survival analysis

Introduction

Gastric cancer (GC) was one of the most common malignant tumors in China. Anually, about 400,000 people were attacked by and 290,000 people died from it. And the incidence and mortality of GC ranked the second and third place among all tumors in China, respectively [1, 2]. Because of its insidious onset and no specific clinical manifestation, most GC cases often had developed to advanced stage when diagnosed [3]. Since advanced GC missed the best time for surgery, chemotherapy became the major method for its treatment. Therefore, it is extremely important to select a rational, effective and safe chemotherapy regimen [4]. However, current chemotherapy for GC was diversified clinically, so there is no unified chemotherapy regimen yet [5]. This study is intended to investigate some factors which may influence the prognosis of advanced GC patients via a retrospective analysis of the efficacy and safety of chemotherapy in 102 advanced GC patients admitted in our hospital. It would promote the diagnosis and treatment of advanced GC and provide a basis for improving patients' quality of life.

Materials and methods

Object of study

The object of study was advanced GC patients diagnosed in our hospital from January 2011 to July 2013. Inclusion criteria were as follows: a. Specimens taken from primary tumor sites were confirmed histopathologically GC; b. Patients with distant metastasis/postoperative recurrence; c. Measurable lesions whose efficacy was evaluable; d. Performance status (ECOG) ≤2 points; e. Detailed clinical efficacy and follow-up data were available. Exclusion criteria were as follows: a. Combined with primary tumor at other sites; b. Patients with dysfunction of major organs like the heart and kidney etc.. In total, 102 advanced GC patients were included in this study, including 70 male (68.6%) and 32 female (31.4%). Their age ranged from 30 to 81 years with mean age of 58 years, averaging (60.5±13.4) years. Pathological types

included 15 cases of signet-ring cell carcinoma, 23 cases of poorly differentiated adenocarcinoma, 37 cases of moderately differentiated adenocarcinoma, two cases of highly differentiated adenocarcinoma and 25 cases of undifferentiated adenocarcinoma. TNM staging included 39 cases with stage IIIb (38.2%) and 63 cases with stage IV (61.8%).

Chemotherapy regimens

(1) SOX regimen (Oxaliplatin + Tegafur, Gimeracil and Oteracil Potassium Capsules): Oxaliplatin (Jiangsu Hengrui Medicine Co., Ltd.) 130 mg/m^2, intravenous drip (d1); Tegafur, Gimeracil and Oteracil Potassium Capsules: For cases with body surface area <1.25 m^2, 40 mg bid; For cases with (1.25 m^2≤body surface area <1.5 m^2), 50 mg bid; For cases with body surface area ≥1.5 m^2, 60 mg bid (day 1-14) for 21 days as a cycle. (2) FOLFOX6 regimen (Oxaliplatin + Calcium Folinate + 5-Fluorouracil): Oxaliplatin (Jiangsu Hengrui Medicine Co., Ltd.) 85 mg·m^{-2}, intravenous drip for 2 hours (day 1); Calcium Folinate (Hainan STAR Pharmaceutical Co., Ltd.) 400 mg·m^{-2}, intravenous drip for 2 hours; Subsequent 5-fluorouracil (Tianjin Jinhui Pharmaceutical Co., Ltd.) 400 mg·m^{-2}, intravenous drip, followed by 600 mg·m^{-2} maintained drip for 22 hours (day 1-2); Repeat every 2 weeks for 28 days as a cycle. All patients received at least 2 cycles of chemotherapy (2-12 cycles; meadian: 6 cycles). During chemotherapy, symptomatic treatments like vomit stopping and liver protection were given for support.

Follow-up method

The follow-up data of patients was collected by methods like regular outpatient reexamination or telephone follow-up. Patients were followed up till death or up to December 31, 2014. The follow-up rate was 100%. The survival time ranged from the initiation of chemotherapy to death or the last follow-up, and was presented in month.

Research method

By looking up hospitalization records, auxiliary checklists, follow-up records and other records, clinical efficacy and follow-up data were collected for advanced GC patients included. A unified questionnaire was used to record relevant information, mainly including sex, gender, pathological type, staging, differentiation degree, associated examination results, chemotherapy regimens, time of the last follow-up and survival time etc.

Evaluation of therapeutic efficacy

(1) Evaluation of short-term therapeutic efficacy: Response Evaluation Criteria in Solid Tumors (RECIST) was used for evaluation. Results were listed as follows: a. Complete remission (CR) - Lesions completely disappeared for four weeks and above; b. Partial remission (PR) - The sum of the longest diameter of lesions decreased ≥30% for four weeks and above; c. Stable disease (SD) - The sum of the longest diameter of lesions increased <20% or decreased <30%; d. Progression disease (PD) - The sum of the longest diameter of lesions increased ≥20%; CR+PR meant that the treatment was effective and overall remission rate (ORR) = The number of effective ones/total cases ×100%. Adverse reactions were evaluated according to criteria for adverse reactions established by National Cancer Institute and were classified into grade 0-IV. (2) Evaluation of survival: Survival was performed by using progressionfree survival (PFS) and overall survival (OS).

Statistical analysis

Statistical analysis was conducted by using software SPSS19.0. Quantitative data was described by mean ± standard deviation and enumeration data by relative numbers like ratio and proportion. Statistical inference was performed by χ^2 test and Fisher's exact test. The survival rates of advanced GC patients receiving different chemotherapy regimens were evaluated by Kaplan-Meier method and compared by Log-rank test. Relevant factors influencing the prognosis of advanced GC patients were investigated by using Cox proportional hazard regression model ($\alpha_{Introduced}$=0.05, $\alpha_{Eliminated}$=0.10). The significance level was α=0.05. P<0.05 meant that there was statistically significant difference.

Results

Short-term therapeutic efficacy

The short-term chemotherapy efficacy in 102 patients with advanced GC including three cases of CR (2.9%), 34 cases of PR (33.3%), 47 cases of SD (46.1%), 18 cases of PD (17.7%) and 36.2% of ORR. In 47 patients receiving SOX regimen, there were two cases of CR, 16 cases

Table 1. Comparison of short-term chemotherapy efficacy among advanced GC patients with different characteristics (n=102)

Factors	Cases (n (%))	Short-term efficacy▼ (n (%))		ORR$^{\Delta}$ (%)	χ^2	*P*
		CR	PR			
Total	102 (100.00)	3 (2.9)	34 (33.3)	37 (36.2)		
Age (years)						
<60	61 (59.2)	2 (3.3)	22 (36.0)	24 (39.3)	0.619	0.432
≥60	41 (40.8)	1 (2.4)	12 (29.3)	13 (31.7)		
Sex						
Male	70 (68.6)	1 (1.4)	23 (32.9)	24 (34.2)	0.382	0.537
Female	32 (31.4)	2 (6.3)	11 (34.4)	13 (40.6)		
ECOG score (point)						
0	24 (23.5)	2 (8.3)	9 (37.5)	11 (45.8)	1.858	0.395
1	37 (36.3)	1 (2.7)	13 (35.1)	14 (37.8)		
2	41 (41.2)	0 (0.0)	12 (29.3)	12 (29.3)		
Site of GC						
Cardia	27 (26.5)	0 (0.0)	13 (48.1)	13 (48.1)	2.240	0.135
Stomach	75 (73.5)	3 (4.0)	21 (28.0)	24 (32.0)		
Tumor state						
Distant metastasis	30 (29.1)	0 (0.0)	10 (33.3)	10 (33.3)	0.769	0.380
Local recurrence	73 (70.9)	3 (4.1)	24 (32.9)	27 (37.0)		
Histological stage						
Highly/moderatelydifferentiated	39 (38.2)	3 (7.7)	15 (38.5)	18 (46.2)	2.666	0.103
Poorly differentiated/undifferentiated	63 (61.8)	0 (0.0)	19 (30.2)	19 (30.2)		
TNM staging						
Stage IIIb	39 (38.2)	2 (62.5)	16 (33.9)	18 (46.2)	2.666	0.103
Stage IV	63 (61.8)	1 (46.8)	18 (23.4)	19 (30.2)		
Number of organs involved						
1	33 (32.3)	2 (6.1)	14 (42.4)	16 (48.5)	3.146	0.076
≥2	69 (67.7)	1 (1.4)	20 (29.0)	21 (30.4)		
Chemotherapy regimen						
SOX	47 (46.1)	2 (4.3)	16 (34.0)	18 (38.3)	0.154	0.694
FOLFOX6	55 (53.9)	1 (1.8)	18 (32.7)	19 (34.5)		

Note: ▼CR, complete remission; PR, partial remission; $^{\Delta}$CR+PR meant that the treatment was effective; $^{*}P<0.05$.

of PR and 38.3% of ORR. In 55 patients receiving FOLFOX6 regimen, there were one case of CR, 18 cases of PR and 34.5% of ORR. ORRs in both groups had no statistically significant difference (χ^2=0.154, P>0.05). Short-term ORRs of patients from different age groups and of different sex, ECOG score, site of GC, tumor state, histological grade, TNM staging and number of organs involved had no statistically significant difference (P>0.05) (**Table 1**).

Adverse reactions

Adverse reactions in 102 advanced GC patients receiving chemotherapy was dominated by hematological toxicity. The incidence of grade III-IV hematological toxicity was 23.5% (24/102) and was dominated by anemia and neutropenia. As for grade III-IV hematological toxicity and grade III-IV nausea and vomiting, the incidence in SOX group (14.9% and 0.0%) was significantly lower than that in FOLFOX6 group (30.9% and 10.9%) (P<0.05) (**Table 2**).

Survival condition

As of the cutoff date of follow-up, 102 patients with advanced GC experienced disease progression and 90 patients (88.2%) died from disease. In all patients, median PFS was 6.5

Table 2. Comparison of adverse reactions after chemotherapy in advanced GC patiens (n=102)

Regimen	Hematological toxicity (n (%))		Nausea and vomitting (n (%))		Peripheral nerve toxicity (n (%))		Oral mucositis (n (%))	
	I-II	III-IV	I-II	III-IV	I-II	III-IV	I-II	III-IV
SOX	12 (31.9)	7 (14.9)	7 (14.9)	0 (0.0)	6 (12.7)	3 (6.4)	5 (10.6)	1 (2.1)
FOLFOX6	18 (32.7)	17 (30.9)*	9 (16.4)	6 (10.9)*	4 (7.3)	0 (0.0)	7 (12.7)	0 (0.0)

Note: *Compared with SOX group, $P<0.05$.

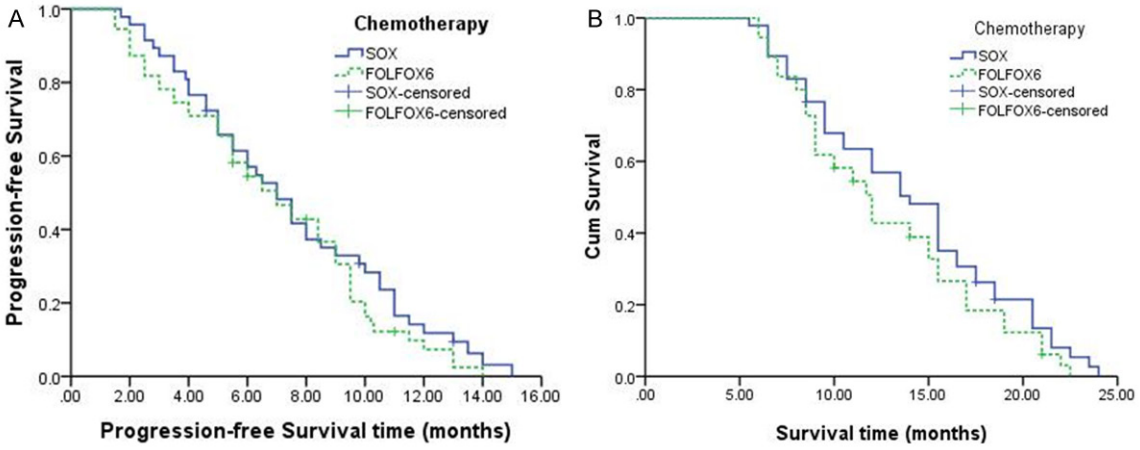

Figure 1. PFS profile (A) and OS profile (B) of 102 patients with advanced GC.

months (95% *CI*: 5.4-7.6) and median OS 12.8 months (95% *CI*: 10.1-15.5). In SOX group, median PFS was 7.0 months and median OS 14.0 months. In FOLFOX6 group, median PFS was 6.5 months and median OS 11.7 months. Both comparisons showed no statistically significant difference (χ^2=1.018 and 1.773, $P>0.05$) (**Figure 1**).

Univariate analysis on the prognosis of advanced GC patients receiving chemotherapy

Univariate analysis by Log-rank test showed that the survival condition of patients of different ECOG score (point), tumor state, histological stage, number of organs involved and chemotherapy efficacy had statistically significant difference ($P<0.05$). Besides, the survival condition of patients of different age, sex, site of GC and TNM staging receiving chemotherapy had no statistically significant difference ($P>0.05$) (**Figure 2**).

Multivariate analysis on the prognosis of advanced GC patients receiving chemotherapy

Factors which were proved to have statistical significance in terms of the effect on OS in advanced GC patients in univariate analysis were included in a Cox multiple stepwise regression model. Results showed that three factors, including ECOG score ≥2, histological stage (poorly differentiated + undifferentiated) and short-term efficacy of chemotherapy (SD+PD), were independent risk factors for the prognosis of patients ($P<0.05$) (**Table 3**).

Discussion

Although the total incidence of GC tended to decrease in recent years, its incidence and mortality ranked at the top among the most common malignant tumors in the world [6-8]. As a high-prevalence area of GC, China was characterized by low early diagnosis rate of patients with GC, low resection rate, low five-year survival rate and other features [9].

Currently, systemic chemotherapy is the major approach for treating patients with advanced tumor. However, there has been no established standard regimen clinically [10]. ECF regimen (dominated by anthracycline) and DCF regimen (dominated by docetaxel) were recommended by NCCN (National Comprehensive Cancer Network) guideline. But their clinical applica-

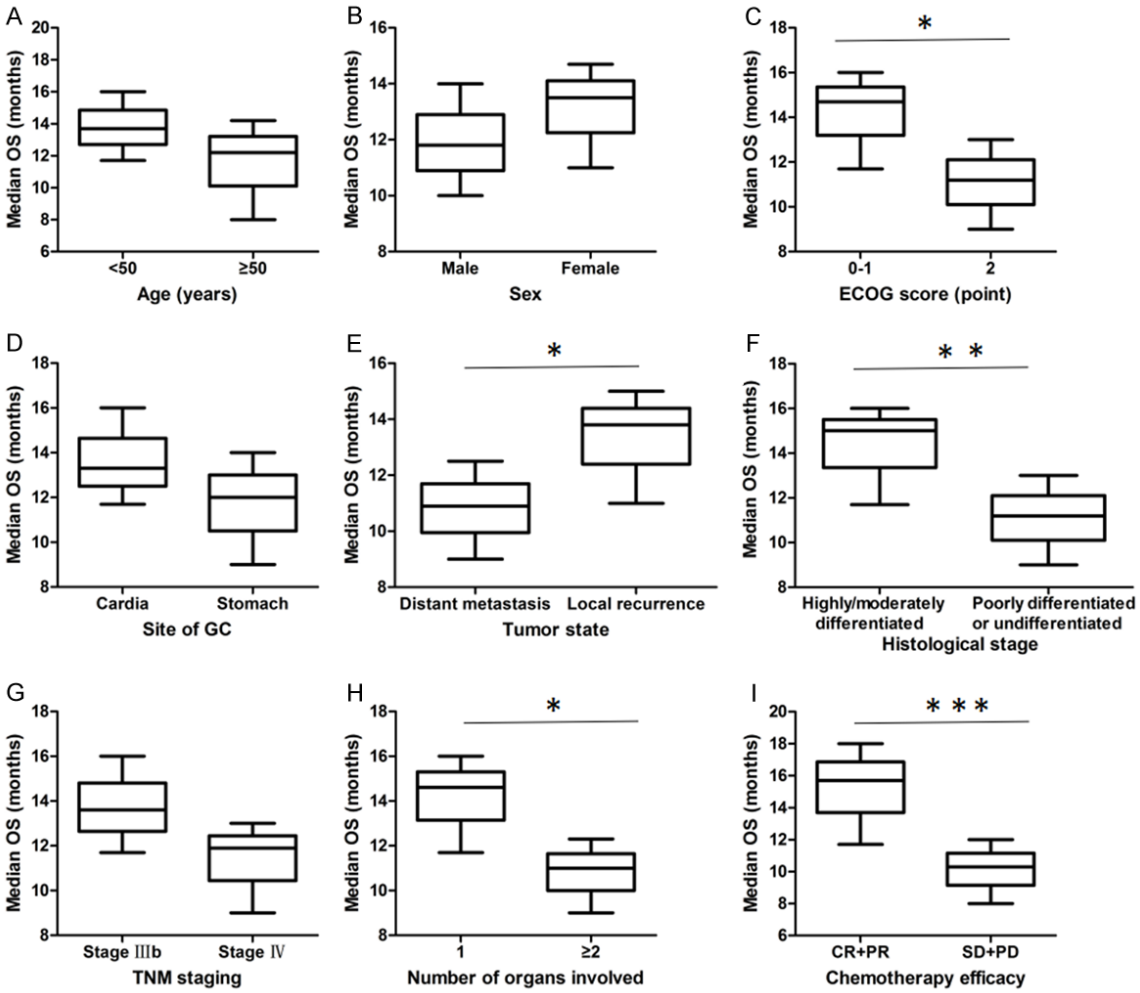

Figure 2. Univariate analysis on the prognosis of advanced GC patients with different characteristics receiving chemotherapy (n=102). A. Comparison between patients of age <50 and age ≥50, P>0.05; B. Comparison between males and females, P>0.05; C. Comparison between patients with ECOG score 0-1 and ECOG score, *P<0.05; D. Comparison between patients with GC in cardia and stomach, P<0.05; E. Comparison between patients with tumor states of distant metastasis and local recurrence, *P<0.05; F. Comparison between patients with Highly/moderately differentiated histological stage and poorly differentiated/undifferentiated stage, **P<0.01; G. Comparison between patients with TNM staging IIIb and IV, P>0.05; H. Comparison between patients with one and ≥2 of organs involved, *P<0.05; I. Comparison between patients with condition of CR+PR and SD+PD, ***P<0.001.

tion was limited due to high incidence of grade III-IV adverse reactions [11].

Results of this study showed that the ORR of short-term chemotherapy efficacy in advanced GC patients was 36.2%, among which the ORR of patients receiving SOX (Oxaliplatin + Tegafur Gimeracil Oteracil Potassium Capsules) was 38.3% and that of patients receiving FOLFOX6 (Oxaliplatin + Calcium Folinate + 5-Fluorouracil) was 34.5% (*P*>0.05). These results were consistent with those of associated studies at home and abroad [12, 13]. As the third generation of platinum-based chemotherapeutics, Oxaliplatin displayed a trans-conformation [14]. With the central pt atom encircled by the 1,2-diamino ring of oxalic acid, it bound with the DNA covalent bond mainly by producing alkide, thus inhibiting DNA synthesis and replication and causing cell death [15]. Compared with cisplatin, oxaliplatin had higher effective rate, less adverse reactions and better tolerance for the treatment of GC.

Besides, it was also found that advanced GC patients receiving chemotherapy had milder adverse reactions, which was dominated by hematological toxicity (the incidence of grade

Table 3. Results of Cox proportional hazard regression analysis on the prognosis of advanced GC patients receiving chemotherapy (n=102)

Independent variable	Coefficient of regression	Standard error	Wald χ^2	P	*RR* (95% *CI*)
ECOG score	0.721	0.348	13.236	<0.001*	2.05 (1.04~4.07)
Histological stage	0.618	0.263	6.124	<0.018*	1.85 (1.11~3.11)
Short-term efficacy of chemotherapy	0.864	0.325	12.259	<0.001*	2.37 (1.25~4.49)

Note: *P<0.05.

III-IV was 23.5%), mainly anemia and neutropenia. However, the incidence of grade III-IV hematological toxicity and grade III-IV nausea and vomiting in SOX group (14.9% and 0.0%) was significantly lower than that in FOLFOX4 group (30.9% and 10.9%) (P<0.05). Tegafur Gimeracil Oteracil Potassium Capsule was the third generation of fluorouracil derivatives and mainly composed of tegafur, gimeracil and oteracil potassium [16]. Moreover, oteracil potassium had a specific inhibitory effect on orotate ribosyltransferase in intestinal mucosal cells [17]. Thus, it could block the phosphorylation of fluorouracil and alleviate gastrointestinal reaction [18].

In addition, it was also found in this study that the median PFS (6.5 months) and median OS (12.8 months) were both short in 102 advanced GC patients receiving chemotherapy with no statistically significant difference between SOX group and FOLFOX6 group (P>0.05), which was consistent with results of previous studies [12, 13, 19, 20]. It suggested that early diagnosis was the key to cure GC and improve patients' survival. Besides, an analysis was performed on factors influencing the prognosis of advanced GC patients. Results showed that the death rate of patients scored 2 for the ECOG performance status was 2.05 times more than that of patients scored 0-1, the death rate patients with poorly differentiated/undifferentiated histological grade was 1.85 times more than that of patients with highly/moderately differentiated histological grade, and the death rate of patients with poor chemotherapy efficacy (PD+SD) was 2.37 times more than that of patients with good efficacy (CR+PR). These results were consistent with studies conducted by Huang Jin et al. [21].

In conclusion, SOX regimen and FOLFOX6 regimen both have short-term efficacy and equivalent effects for the treatment of advanced GC patients. Major adverse reactions are hematological toxicity, while those in SOX group are milder. However the long-term prognosis of chemotherapy in advanced GC patients is poor overall, so early diagnosis is the key to the treatment of GC. Patients with ECOG score ≥2, poorly differentiated/undifferentiated histological grade and poor chemotherapy efficacy have increased prognostic risk and require special attention.

Disclosure of conflict of interest

None.

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