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ORIGINAL ARTICLE

Incidence of and risk factors for cardiotoxicity after fluorouracil-based chemotherapy in locally advanced or metastatic gastric cancer patients

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Abstract

Objectives Cardiotoxicity is an important side effect in patients receiving chemotherapy and the application of anthracycline drugs for gastric cancer treatment is uncommon. The purpose of this study was to determine the incidence rate of and risk factors for cardiotoxicity in gastric cancer patients treated with fluorouracil-based chemotherapy.

Materials and methods We retrospectively enrolled patients with locally advanced or metastatic gastric cancer from 2011 to 2016. Patients were treated with multiple cycles of fluorouracil-based chemotherapy at Peking University First Hospital. The incidence of cardiotoxicity and patients' clinical data were obtained from hospital clinical databases and manually reviewed.

Results A total of 129 patients were eligible for and were enrolled in this study. A median of 6 chemotherapy cycles were administered (range 1–18 cycles). Cardiotoxicity was observed in 38 of 129 patients (29.5%). Twelve patients (9.3%) exhibited toxicity greater than grade 2, and 2 (1.6%) patients died of cardiac toxicity. The only independent risk factor for serious cardiotoxicity identified by multivariable analysis was a history of cardiac disease (OR 4.108, 95% CI 2.778–6.074, $P < 0.001$).

Conclusions Chemotherapy-related cardiotoxicity may be underestimated in Chinese gastric cancer patients. Close monitoring for cardiotoxicity and enhanced cardiac management are recommended for patients who receive fluorouracil-based chemotherapy, especially for patients with high-risk factors for serious cardiotoxicity. New strategies, such as identifying the administration schedule of fluorouracil with minimal cardiotoxicity, and cardio-oncology, are necessary to prevent and treat chemotherapy-induced cardiotoxicity.

Keywords Cardiotoxicity · Cardio-oncology · Chemotherapy · Fluorouracil · Gastric cancer

Introduction

Gastric cancer is the fifth most common type of cancer and is the third leading cause of cancer-related death in both sexes worldwide [1]. The incidence of gastric cancer is higher in China than in other countries [1, 2]. Although early detection is more common in Asia than in other regions, most patients in China are diagnosed at an advanced stage and cannot undergo surgery at the time of diagnosis. Chemotherapy is the primary treatment for these patients.

Chemotherapy can alleviate symptoms and improve survival and quality of life compared to the best supportive care in patients with advanced and metastatic disease [3, 4]. However, conventional chemotherapies and targeted therapies are associated with increased risks of cardiotoxicity, such as arrhythmias, heart failure (HF), myocardial ischemia/infarction, hypertension, and thromboembolism [5]. Cardiotoxicity is life-threatening to patients and often alters the disease prognosis; thus, early detection and diagnosis are necessary [6]. A plethora of scientific research has been conducted on the causes of cardiotoxicity, including cytotoxic drugs and other biological agents [7–12]. Among them, the cardiotoxicity of anthracyclines and trastuzumab, two first-line agents used as breast cancer therapies, have been extensively studied. However, with the advent of new therapeutic

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drugs, application of anthracycline drugs for gastric cancer is uncommon. Thus, whether chemotherapy causes cardiotoxicity in patients with gastric cancer is an open and urgent question. To date, very few studies have examined the cardiac safety of chemotherapy in gastric cancer patients. The incidence rate of cardiotoxicity, risk factors for cardiotoxicity, and the influence of cardiotoxicity on chemotherapy remain to be explored. In this study, we retrospectively analyzed 129 patients diagnosed with locally advanced or metastatic gastric cancers who were monitored for cardiotoxicity through multiple cycles of fluorouracil-based chemotherapy. To our knowledge, this is the first report of risk factors for cardiotoxicity in advanced gastric cancer patients treated with non-anthracycline chemotherapy.

Materials and methods

Study population

All patients who underwent fluorouracil-based chemotherapy for locally advanced or metastatic gastric cancer at the Department of Medical Oncology of Peking University First Hospital between January 2011 and October 2016 were included in this study if they met the following criteria: (a) age > 18 years old; (b) gastric adenocarcinoma confirmed by histology or cytology; and (c) complete follow-up data from initial treatment until at least 60 days after the last treatment cycle. Patients were excluded if they: (a) underwent anthracycline-based chemotherapy at any time; (b) received a targeted drug; (c) were treated with concurrent chemoradiotherapy or (d) had heart metastasis or a tumor directly invading or compressing the heart. The clinical research protocol was approved by the Institutional Review Board (IRB) of Peking University First Hospital.

Evaluation of cardiotoxicity

We evaluated cardiotoxicity grades according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [13]. Cardiotoxicity was defined as new emergence of any of the following signs after chemotherapy: (1) cardiac-related symptoms including chest pain and palpitations; (2) acute myocardial infarction (AMI), HF, or emerging valvular diseases; (3) any emerging arrhythmia, such as atrial fibrillation (AF), sinus tachycardia, or atrioventricular block; or (4) pericardial and myocardial diseases. A serious cardiac event was defined as a grade ≥ 3 event.

All patients underwent 12-lead electrocardiography (ECG) during the screening and baseline periods, which was repeated on the day before each cycle. The attending physician decided whether transthoracic echocardiography (TTE), troponin, or B-type natriuretic peptide was needed. All patients underwent telemetry monitoring during chemotherapy. If cardiotoxicity occurred, the duration of telemetry monitoring was prolonged. All events were reviewed by an adjudication panel, and diagnosis and treatment of all AMI and HF events were conducted under the guidance of cardiologists.

The diagnostic criteria of AMI were based on the third universal definition of myocardial infarction [14], and the diagnostic criteria of HF were based on the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF [15].

Risk factors for serious cardiotoxicity

Clinical stages were evaluated using the TNM Classification of Malignant Tumors 7th Edition (Union for International Cancer Control). To evaluate risk factors for serious cardiotoxicity, we included the following clinical factors: gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), body mass index (BMI) (before diagnosis with gastric cancer), number of metastases, comorbid diseases, smoking history, history of cardiac disease, previous thoracic surgery, previous radiotherapy, previous chemotherapy, administration of fluorouracil, hematological toxicities, concurrent infections, and duration of chemotherapy. In addition, we evaluated laboratory results before treatment including serum lipids, plasma D-dimer, plasma fibrinogen (FIB), serum potassium, and serum magnesium.

Statistical analysis

The incidence rates of cardiotoxicity and serious cardiotoxicity were compared using Chi square or Fisher's exact tests according to the administration schedules. All statistical tests were two-sided, and for a value of $P < 0.05$ was considered significant. A logistic regression model was used for the univariable and multivariable analyses. Clinical features with P values less than 0.05 in the univariable analysis were included in a multivariable analysis. SPSS 22.0 statistical software (IBM SPSS Statistics, Armonk, NY, USA) was used for all statistical analyses.

Results

Patient characteristics

In this study, we manually reviewed 246 patients with locally advanced or metastatic gastric cancer who received fluorouracil-based chemotherapy at the Department of

Medical Oncology of Peking University First Hospital. We excluded 67 patients who underwent anthracycline-based chemotherapy, 36 patients who did not have complete follow-up data according to the inclusion criteria, 7 patients who received a targeted drug, and 4 patients who had received concurrent chemoradiotherapy. We also excluded two patients diagnosed with neuroendocrine carcinoma and 1 patient who had heart metastasis. Finally, a total of 129 patients who received a median of 6 cycles of chemotherapy (range 1–18 cycles) were evaluated. In this cohort, 55 (42.6%) patients had received chemotherapy previously. The demographics and general characteristics of patients in this study are summarized in Table 1. There were 28 female and 101 male patients. The median age was 63 years (range 28–80 years). A total of 123 (95.3%) patients had stage IV disease, 85 (65.9%) patients had an ECOG PS of 0 or 1, 81 (62.8%) patients had undergone abdominal surgery, and 2 (1.6%) patients had received radiotherapy previously. Only 49 (38%) patients had undergone TTE before chemotherapy.

Ninety-one (70.5%) patients received a bolus and continuous intravenous infusion of 5-fluorouracil (5-FU) (400 mg/m^2 bolus day 1 and 1200 mg/m^2 continuous infusion over 24 h on days 1 and 2 of each cycle), 24 (18.6%) patients received capecitabine (1000 mg/m^2 twice daily on days 1–14 of each cycle), and 14 (10.9%) patients received S-1 (40–60 mg twice daily on days 1–14 of each cycle) orally. Combined chemotherapeutic drugs included taxanes and platinum (oxaliplatin or cisplatin).

Among all patients in our study, only 5 (3.9%) were referred for pre-chemotherapy cardiovascular evaluation at the Department of Cardiology at Peking University First Hospital; after chemotherapy, of the 38 patients with cardiac toxicity, 9 were referred to cardiologists.

Table 1 Characteristics of patients with gastric cancer

Clinical feature	Value[a]
Age	
≤65	73 (56.6)
>65	56 (43.4)
Gender	
Male	101 (78.3)
Female	28 (21.7)
Tumor location	
Esophagogastric junction	27 (20.9)
Gastric	102 (79.1)
ECOG PS	
0–1	85 (65.9)
2–3	44 (34.1)
Stage	
III	6 (4.7)
IV	123 (95.3)
Metastasis	
≤2	81 (62.8)
>2	48 (37.2)
BMI (kg/m^2)	
≥28	15 (11.6)
<28	114 (88.4)
Previous abdominal surgery	
Yes	81 (62.8)
No	48 (37.2)
Previous radiotherapy	
Yes	2 (1.6)
No	127 (98.4)
Previous chemotherapy	
Yes	55 (42.6)
No	74 (57.4)
Fluorouracil	
5-FU	91 (70.5)
Capecitabine	24 (18.6)
S1	14 (10.9)
Duration of chemotherapy (months)	
≤3	49 (38.0)
>3	80 (62.0)

ECOG PS Eastern Cooperative Oncology Group Performance Status, *BMI* body mass index

[a]Number of cases and percentage

Incidence of cardiotoxicity

Overall, we identified 38 (29.5%) patients with 40 cardiac adverse events (Table 2) during systemic chemotherapy; of which, 12 (9.3%) cases were serious events, including 3 cases of AMI, 3 cases of HF, 4 case of AF and 2 case of chest pain. Other cardiac events included 3 cases of QT interval prolongation, 6 cases of sinus arrhythmia, 9 cases of ventricular arrhythmia, 2 cases of atrioventricular block, 2 cases of palpitations, and 6 cases of ST and T wave abnormalities. Two patients had HF combined with ventricular premature beats. In the entire cohort, 2 patients (1.6%) died of cardiac events, 9 patients (7.0%) discontinued chemotherapy due to cardiotoxicity, and 1 patient (0.8%) was administered a replacement chemotherapy regimen at the physician's request. According to the CTCAE version 5.0, 26 (20.2%) patients showed grade 1–2 toxicity, and 12 (9.3%) patients showed grade 3–5 toxicity.

Incidence of cardiotoxicity according to administration schedules

The incidence rates of cardiotoxicity and serious cardiotoxicity according to administration schedules are shown in

Table 2 Cardiac events in the overall study population

Events	Grade ≥ 3	Number of events
AMI	3	3
Chest pain	2	2
HF	3	3
Sinus arrhythmia	0	6
AF	4	4
Palpitations	0	2
Ventricular premature beat	0	9
Atrioventricular block (*I*°)	0	2
QT interval prolongation	0	3
Abnormal ST and T waves	0	6
Total	12	40

AMI acute myocardial infarction, *HF* heart failure, *AF* atrial fibrillation

Table 3. No significant difference was observed in the incidence of all cardiotoxicity or serious cardiotoxicity among the three different administration schedules.

Risk factors for serious cardiotoxicity

The associations between serious cardiac events and various clinical characteristics were evaluated to identify risk factors for events. In univariable analyses, age, history of cardiac disease, smoking history, ECOG PS, anemia (hemoglobin < 90 g/L), ≥ grade 3 neutropenia, and respiratory infections were significantly associated with the incidence of serious cardiac adverse events in all patients (Table 4). In contrast, gender, BMI, history of hypertension, history of diabetes mellitus (DM), hyperlipemia, stroke, previous thoracic surgery, previous radiotherapy, previous chemotherapy, baseline plasma D-dimer, baseline plasma fibrinogen > 4 g/L, hypokalemia, hypomagnesemia, use of interleukin 11, number of metastases, administration of fluorouracil, and duration of chemotherapy were not significantly associated with serious cardiac events.

The only independent risk factor for the occurrence of serious cardiac events was a history of cardiac disease (OR 4.108, 95% CI 2.778–6.074, $P < 0.001$).

Discussion

Cardiotoxicity is one of the most common adverse events associated with systemic chemotherapy, and the resultant cardiotoxicity associated with oncological treatment often limits its benefits [16]. Because of the short survival time of patients with advanced gastric cancer, we only examined acute cardiotoxicity. In this study, we retrospectively examined the incidence of cardiac adverse events and assessed risk factors for serious cardiotoxicity in patients with locally advanced or metastatic gastric cancer who received fluorouracil-based chemotherapy.

In our study, the cardiotoxicity incidence rate was 29.5%; approximately 9.3% of patients' cardiotoxic events affected subsequent treatments. The incidence rate of cardiotoxicity was obviously higher in our study than in other studies. We suggest that one of the reasons for this discrepancy is the difference in the ECOG PS. The reported frequency of cardiotoxicity in phase III studies of chemotherapy varies between 0.7 and 9.6% [17–19]. More than 90% of the patients enrolled in these phase III studies had scores of 0 or 1 point on the ECOG PS. However, in our study, only 65% of patients had an ECOG PS score of 0–1. The ECOG PS has been reported to be related to the occurrence of cardiotoxicity [20]. Our univariable analysis also confirmed that the ECOG PS score was a risk factor for the occurrence of cardiotoxicity. Recently, a multicenter prospective observational study [21] showed that the incidence rates of cardiotoxicity for patients with gastrointestinal cancers treated with fluorouracil-based chemotherapy was 30.6%; this result is similar to the result of our study. The second reason may be

Table 3 Incidence of cardiotoxicity for different administration schedules

Administration schedule	Number of patients	Cardiac events	χ^2	*P*	Serious cardiac events	χ^2	*P*
Group A							
Continuous 5-FU	91	29	0.064	0.800	7		0.237*
Capecitabine	24	7			4		
Group B							
Continuous 5-FU	91	29		0.223*	7		1.000*
S1	14	2			1		
Group C							
Capecitabine	24	7		0.438*	4		0.633*
S1	14	2			1		

*Fisher's exact test

Table 4 Univariable analysis of risk factors for serious cardiotoxicity in patients with locally advanced or metastatic gastric cancer

Clinical features	Total patients	Serious cardiac events	OR (95% CI)	*P*
Gender			1.429 (0.294–6.932)	0.658
Female	28	2		
Male	101	10		
Age			7.717 (1.617–36.830)	0.01
≤65	73	2		
>65	56	10		
ECOG PS			12.206 (2.540–58.655)	0.002
2–3	44	10		
0–1	85	2		
BMI (kg/m^2)			1.495 (0.179–12.480)	0.71
< 28	114	11		
≥28	15	1		
Hyperlipemia			1.719 (0.426–6.944)	0.447
Yes	22	3		
No	107	9		
DM			1.262 (0.253–6.298)	0.776
Yes	18	2		
No	111	10		
History of cardiac disease			12.625 (3.403–46.836)	<0.0001
Yes	24	8		
No	105	4		
Hypertension			2.343 (0.707–7.769)	0.164
Yes	41	6		
No	88	6		
Stroke			1.239 (0.142–10.841)	0.847
Yes	9	1		
No	120	11		
Previous thoracic surgery			2.400 (0.455–12.667)	0.302
Yes	11	2		
No	118	10		
Previous radiotherapy			10.545 (0.616–180.483)	0.104
Yes	2	1		
No	127	1		
Previous chemotherapy			1.045 (0.313–3.485)	0.943
Yes	55	5		
No	74	7		
Smoking history			5.086 (1.068–24.225)	0.041
Yes	65	11		
No	64	1		
Baseline D-dimer (mg/L)			1.657 (0.495–5.552)	0.413
≥0.24	56	7		
<0.24	63	5		
Baseline FIB (g/L)			2.897 (0.866–9.692)	0.084
>4	35	6		
≤4	90	6		
Hypokalemia			0.863 (0.259–2.875)	0.81
Yes	58	5		
No	71	7		
Hypomagnesemia			2.244 (0.988–5.093)	0.053
Yes	33	5		

Table 4 (continued)

Clinical features	Total patients	Serious cardiac events	OR (95% CI)	*P*
No	96	7		
Anemia (g/L)			8.636 (2.385–31.271)	0.001
< 90	30	8		
≥ 90	99	4		
Administration schedules			0.550 (0.163–1.856)	0.335
Continuous 5-FU	91	7		
Capecitabine/S-1	38	5		
≥ 3 grade neutropenia			6.667 (1.863–23.857)	0.004
Yes	35	8		
No	94	4		
Use of interleukin 11			2.725 (0.508–14.612)	0.242
Yes	10	2		
No	119	10		
Infection (all sites)			5.152 (1.506–17.623)	0.009
Yes	32	7		
No	97	5		
Infection (respiratory)			12.250 (3.359–44.669)	< 0.0001
Yes	19	7		
No	110	5		
Duration of chemotherapy (months)			1.185 (0.354–3.962)	0.783
≤ 3	49	5		
> 3	80	7		
Metastasis			2.595 (0.775–8.693)	0.122
> 2	48	7		
≤ 2	81	5		

ECOG PS Eastern Cooperative Oncology Group Performance Status, *BMI* body mass index, *DM* diabetes mellitus, *FIB* fibrinogen

that other studies have different definitions of cardiotoxicity. Kwakman JJ et al. did not consider tachycardia and palpitations to be cardiotoxic events because of the non-specificity of the symptoms for a cardiac cause [19]; in that retrospective analysis, the incidence rates of all grade and grade ≥ 3 cardiac events were 5.9% and 2.3%, respectively, in patients with metastatic colorectal cancer. However, we suggest that, according to the CTCAE version 5.0, as long as new cardiac events related to chemotherapy are identified, they should be considered as cardiotoxic events. The third reason may be the difference in sample size. A review of the cardiotoxicity of chemotherapy showed that studies with a smaller sample size have a higher incidence of toxicity [22].

Differences in cardiotoxicity have been observed for different administration schedules. Several studies [23–25] have shown that continuous 5-FU infusion is a risk factor for cardiotoxicity compared to bolus infusion schedules. According to Jensen et al. [24] and a meta-analysis by Van Cutsem et al. [26], the incidence of cardiotoxicity due to capecitabine is similar to that of 5-FU administered using the Mayo regimen. Therefore, we speculate that the cardiotoxicity of capecitabine is less than that of continuous 5-FU infusion. However, recently, a multicenter prospective observational study showed that the incidence rates of cardiotoxicity in the capecitabine group was significantly higher than that in the 5-FU group [21]. α-Fluoro-β-alanine (FBAL), as a metabolite of 5-FU and capecitabine, is further catabolized into fluoroacetate. Fluoroacetate is known to be highly cardiotoxic [27]. Because S-1 contains gimeracil, which inhibits the degradation of 5-FU via dihydropyrimidine dehydrogenase (DPD) inhibition, the serum levels of FBAL and fluoroacetate significantly decrease during treatment with S-1 [28]. Therefore, S-1 may have less cardiotoxicity. However, in our study, no difference in cardiotoxicity was found among the three drugs. It is possible that the sample size was too small to detect a difference, or other drugs in the combination chemotherapy regimen affected the results. Identifying the drug with the least cardiac toxicity among these drugs can reduce the incidence of cardiac toxicity and increase patient tolerance of chemotherapy.

Prevention of chemotherapy-induced cardiotoxicity in high-risk patients is critical for their prognoses, as failure to prevent this complication not only increases the risk of cardiovascular morbidity and mortality, but may also limit

patients' ability to receive adequate treatments. Therefore, it is important to identify risk factors for cardiac toxicity. Several reports have found different risk factors for cardiotoxicity [29, 30]. However, no reports have examined the risk factors for cardiotoxicity in patients with advanced gastric cancer. We assessed the risk factors for cardiotoxicity reported in previous studies that included various cancers and chemotherapeutic regimens [30–33]. The univariable analysis indicated that age, ECOG PS ≥ 2, smoking history, history of cardiac disease, anemia (hemoglobin < 90 g/L), ≥ grade 3 neutropenia, and respiratory infections were risk factors for serious cardiotoxicity in advanced gastric cancer patients treated with fluorouracil-based chemotherapy. The multivariate analysis indicated a history of cardiac disease as the only independent risk factor for serious cardiotoxicity. Thus, for patients with risk factors for cardiotoxicity, cardiac management should be strengthened during chemotherapy. First, complete cardiac-related tests should be performed before chemotherapy by cardiologists or at cardio-oncology clinics to assess the cardiac risk of chemotherapy. Second, it is important to improve each patient's performance status and resolve anemia before chemotherapy to improve cardiac tolerance to chemotherapy. Third, the dose of chemotherapy should be reduced according to guidelines for chemotherapy regimens, in which bone marrow suppression is considered a dose restrictive toxicity, and primary prophylactic administration of granulocyte colony-stimulating factor should be strongly considered for the management of these patients.

The management of cardiac complications in cancer patients is often very difficult and complicated. For example, AF is particularly prone to relapse, and treatment of AF in cancer patients is challenging, particularly due to the use of antithrombotic therapies for stroke prevention in patients whose primary lesions are not removed [34–36]. In our study, three of four patients with AF relapsed, and the chemotherapeutic regimen of all four patients was affected. The complexities of treating cancer patients with cardiac complications have led to the development of new subspecialties, such as cardio-oncology, which is a multidisciplinary field focusing on the management and prevention of cardiovascular complications in cancer patients and survivors [37]. These specialists may provide optimal care to patients to reduce cardiotoxicity and improve their prognosis [38]. Therefore, development of such cardio-oncology programs is needed. However, in our study, few patients were referred to cardiologists, whether before or after chemotherapy.

Conclusion

We observed incidence rates of cardiotoxicity and serious cardiotoxicity of 29.5% and 9.3%, respectively, in patients with locally advanced or metastatic gastric cancers treated with fluorouracil-based chemotherapy. Chemotherapy-related cardiotoxicity may be underestimated in Chinese patients with gastric cancer. Close monitoring for cardiotoxicity should be performed for patients who receive fluorouracil-based chemotherapy, especially patients with high-risk factors for cardiotoxicity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest regarding this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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