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Prognostic value of chemotherapy-induced neutropenia in advanced gastric cancer patients undergoing first-line chemotherapy with DCF: a retrospective study.

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Abstract

Objective: In this study, we investigated the correlation between the degree and timing of chemotherapy-induced neutropenia (CIN) caused by the DCF (docetaxel-platinum-fluorouracil) regimen as first-line chemotherapy and the survival of patients with advanced gastric cancer.

Methods: We retrospectively analysed 110 patients diagnosed with advanced gastric cancer between 2007 and 2012 at our hospital who received 2 to 6 cycles of the DCF regimen as first-line chemotherapy. According to the CTCAE 4, CIN is categorized as G0, G1/2, G3, or G4. We stratified all patients into the following two groups based on the onset (timing) of CIN: early onset and late onset.

Results: A total of 110 patients were included in this study. Among these patients, 15 (13.6%) did not exhibit CIN (grade 0), 54 (49.1%) experienced mild CIN (grade 1-2), 22 (20.0%) developed moderate CIN (grade 3), and 19 (17.3%) suffered from severe CIN (grade 4) during the first line of chemotherapy. The median progression-free survival (PFS) of the 110 patients was 6.0 months (95% CI: 5.5~6.6 months), and the median overall survival (OS) of the 110 patients was 12.7 months (95% CI: 11.2~14.2 months). According to a multivariate analysis, the hazard ratio of death was 0.59 (95% CI: 0.49-0.72, P=0.005) for patients with G1/2 CIN, 0.71 (95% CI: 0.52-0.90, P=0.001) for patients with G3 CIN, and 0.74 (95% CI: 0.46-0.93, P=0.023) for patients with G4 CIN compared with patients who did not suffer from neutropenia (G0).

Conclusion: Patients who experienced G1/2 CIN had a more favourable treatment response and prognosis, whereas the absence of CIN predicted poor efficacy and survival, which may occur because the dose was ineffective. In addition, patients with G4 CIN did not exhibit better efficacy and prognosis, and the clinical outcomes were better for early-onset neutropenia than for late-onset neutropenia.

Keywords: Gastric cancer, Chemotherapy-induced neutropenia, DCF regimen, Progression-free survival.

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Introduction

Gastric cancer is the world's second most common cause of cancer-related death, and most patients are diagnosed with advanced gastric carcinoma and are no longer eligible for surgery [1]. These patients were most commonly treated with palliative systemic chemotherapy [2], but the relative toxicities of chemotherapy regimens remain a problem despite evidence of the advantage of chemotherapy. Specifically, patients may experience varying levels of toxicities during chemotherapy, and chemotherapy-induced neutropenia is one of the main dose-limiting toxicities associated with many cytotoxic drugs [3]. Specifically, this type of neutropenia has been favourably associated with survival in several types of cancer [4-6], including breast cancer [3], advanced non-small-cell lung cancer [5], and metastatic colorectal cancer [7]. These articles suggested that chemotherapy-induced neutropenia was closely related a better treatment response and improved survival. We herein describe a retrospective analysis of 110 consecutive patients with advanced gastric cancer receiving DCF as first-line chemotherapy. Our goal was to investigate the association between chemotherapy-induced neutropenia and treatment response or prognosis in patients with advanced gastric cancer. We hypothesized that chemotherapy-induced neutropenia (CIN) may serve as a surrogate marker of better clinical outcomes in advanced gastric cancer [8].

Materials and Methods

Patients

We searched the database at our hospital for records of advanced gastric cancer from January 2007 to December 2012. A total of 110 consecutive patients with histologically confirmed advanced gastric cancer who completed 2-6 cycles of DCF triplet chemotherapy (docetaxel-platinum-fluorouracil) at the PLA general hospital (Beijing, China) were ultimately identified and included. The inclusion criteria were defined as

follows: age less than 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, inoperable gastric cancer, the presence of histologically proven unresectable gastric cancer, sufficient bone marrow function (leukocyte count 4.0 × 10^9/L, neutrophil count 2.0 × 10^9/L, platelet count 100 × 10^9/L, haemoglobin 9.0 g/DL), normal liver and renal functions, no history of prior chemotherapy for advanced disease, and no history of chemotherapy before the commencement of DCF treatment [3]. The exclusion criteria included the following: accepted surgery, history of other cancers, essential data unavailable, or underwent other chemotherapy prior to the DCF regimen. The clinicopathological features and demographic characteristics of the patients and the results of the neutropenia tests were extracted from the medical records. The patients were followed up by telephone until May 2014 to obtain survival information. Written informed consent was obtained from all patients, and the study was approved by the Ethics Committee of Chinese People's Liberation Army General Hospital; all aspects of the study comply with the Declaration of Helsinki. The ethics Committee of Chinese People's Liberation Army General Hospital specifically ensured that data were analysed anonymously.

Treatment delivery

All patients underwent a chemotherapeutic protocol prescribed by the PLA general hospital consisting of 75 mg/m^2 docetaxel (day 1), 75 mg/m^2 cisplatin (day 1), and 750 mg/m^2 fluorouracil (days 1-5) administered in 3-week intervals. Treatment was discontinued upon disease progression, severe toxicity or after completing 6 cycles of therapy. The prophylactic use of antibiotics or granulocyte colony-stimulating factor (G-CSF) was not permitted, except in the event of grade 4 neutropenia or febrile neutropenia. In case of grade 3 neutropenia, the docetaxel or cisplatin dose was reduced by 20%. Treatment was delayed in all cases of grade 4 or febrile neutropenia until cytotoxic manifestations were resolved. The relative dose intensity (RDI) was determined by calculating the ratio of the actual dose intensity to the ideal value if all planned doses were given on schedule.

Response assessment

Each patient was physically examined using chest, abdominal and pelvic CT scans or echography after every two cycles of chemotherapy, and treatment efficacy was evaluated by comparing the baseline metastatic lesions. The response to chemotherapy was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1 criteria). The diameter of measurable lesions should be longer than 10 mm, which was the detection limit for CT scans or echography [9]. Complete remission (CR) was defined as the complete disappearance of all target lesions. A decrease in the cross-sectional area of all target lesions of at least 30% was defined as a partial response (PR). Progressive disease (PD) was defined as an increase of at least 20% in the tumour mass of metastatic nodes or at least one lesion or the appearance of a new lesion. Stable disease was defined as a decrease in lesion size of less than 30% or an increase of less than 20% [10-12].

Evaluation of neutropenia and supportive therapy

Routine blood samples were taken from all patients on the day before treatment and after approximately 4, 7 and 10 days of chemotherapy during each chemotherapy cycle. CIN was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) as follows: CIN Grade 1 (between 1.5 × 10^9/L and 2.0 × 10^9/L), CIN Grade 2 (between 1.0 × 10^9/L and 1.5 × 10^9/L), CIN Grade 3 (between 0.5 × 10^9/L and 1.0 × 10^9/L), and CIN Grade 4 (<0.5 × 10^9/L). The worst grade of CIN was defined as the lowest recorded neutropenia count after six cycles of DCF chemotherapy for a given patient. To evaluate chemotherapy-induced neutropenia, CIN was classified into the following four categories: absent (grade 0), mild (grade 1~2), moderate (grade 3), and severe (grade 4). In our study, we further categorized the CIN according to the timing of neutropenia as follows: early-onset neutropenia was defined as the lowest grade neutropenia during cycle 1-3; late-onset neutropenia was defined as the worst grade of CIN during cycles 4-6, including the absence of neutropenia [9,13].

Statistical analysis

Overall survival (OS) was the primary study endpoint. The secondary endpoints were progression-free survival (PFS) and the disease control rate (DCR). OS was defined as the interval from the onset of the DCF regimen to the date of death or loss follow-up. PFS was defined as the interval between the onset of chemotherapy and the date of progression or death due to any cause. DCR included patients in complete or partial radiographic remission and patients with stable disease. The survival curves of the four categories were estimated using the Kaplan-Meier method and compared with the log-rank test. The distribution of subject characteristics was assessed using the χ^2 test, and the response rates were evaluated using Fisher's exact test, as appropriate. The mean of continuous variables was determined using Student's t-test. To evaluate the association between clinical pathological features and OS, univariate and multivariate cox proportional hazards modelling was applied. All statistical tests and P values were two-sided, and P values <0.05 were considered significant.

Results

The demographics and clinical characteristics of 110 patients

A total of 110 patients who fulfilled the inclusion criteria were included in this retrospective analysis, including 90 (82%) males and 20 (18%) females, and the median age was 55 years (range: 20-75 years). In the entire population, 55 (50%) patients suffered from liver metastases, whereas 55 patients had no evidence of liver metastases. Although 57 (52%) patients harboured only 1-2 metastatic lesions, 53 (48%) patients exhibited 3 or more metastases. Among the 110

patients, 15 (13.6%) patients did not exhibit CIN (grade 0), 54 (49.1%) patients experienced mild CIN (grade 1-2), 22 (20.0%) patients had moderate CIN (grade 3), and 19 (17.3%) patients developed severe CIN (grade 4) during first-line chemotherapy. Early-onset CIN and late-onset CIN developed in 60% (66/110) and 40% (44/110) of patients. The demographics and clinical characteristics of these 110 patients, such as gender, age, BSA, and tumour differentiation, were categorized according the CIN, as shown in Tables 1 and 2. These characteristics did not significantly differ between the four neutropenia groups (P values <0.05 were considered significant). The relative dose intensity and cycles of first-line chemotherapy did not significantly differ between groups.

Table 1. *Baseline demographics and clinical characteristics in all patients and in subgroups stratified according to the worst grade of neutropenia during six cycles.*

	Case N (%)	G0 (absent)	G1-2 (mild)	G3 (moderate)	G4 (severe)	P
Gender						
Male	90 (82)	13	45	14	18	0.062
Female	20 (18)	2	9	8	1	
Age (years)						
≤ 60	31 (28)	3	15	9	4	0.434
>60	79 (72)	12	39	13	15	
RDI						
Docetaxel	0.88	0.88	0.91	0.87	0.86	0.166
Cisplatin	0.89	0.9	0.92	0.89	0.87	0.257
5-FU	0.87	0.86	0.9	0.86	0.85	0.12
Cycles of chemotherapy						
(mean ± SD)	5.5 ± 0.3	5.7 ± 0.2	5.5 ± 0.4	5.4 ± 0.3	5.2 ± 0.3	0.106
Differentiation						
Poorly	54 (49)	10	22	10	12	0.173
Moderately-well	56 (51)	5	32	12	7	
BSA						
≤ 1.6 m^2	28 (25)	3	13	7	5	0.857
>1.6 m^2	82 (75)	12	41	15	14	
ECOGPS						
0-1	50 (45)	4	27	11	8	0.415
2-3	60 (55)	11	27	11	11	
Her-2						
Negative	53 (48)	3	29	9	12	0.55
Positive	57 (52)	12	25	13	7	
Liver metastasis						
No	55 (50)	5	28	12	10	0.578
Yes	55 (50)	10	26	10	9	
Metastasis site						
1-2	57 (52)	4	28	10	11	0.277
3 or more	53 (48)	11	26	12	8	
Tumour location						

Upper	46 (42)	7	22	7	10	
Middle	25 (23)	2	15	5	3	0.707
Lower	39 (35)	6	17	10	6	

Table 2. *Baseline demographics and clinical characteristics in all patients and in subgroups stratified according to the timing of neutropenia during six cycles.*

	Case	Early-onset neutropenia	Late-onset neutropenia	P
	N (%)	N=66 (60%)	N=44 (40%)	
Gender				
Male	90 (82)	52	38	0.052
Female	20 (18)	14	6	
Age (years)				
≤ 60	31 (28)	18	13	0.224
>60	79 (72)	48	31	
RDI				
docetaxel	0.88	0.91	0.85	0.106
Cisplatin	0.89	0.92	0.87	0.147
5-FU	0.87	0.89	0.86	0.09
Cycles of chemotherapy				
(mean ± SD)	5.5 ± 0.3	5.4 ± 0.3	5.7 ± 0.3	0.125
Differentiation				
poorly	54 (49)	38	16	0.273
Moderately-well	56 (51)	28	28	
BSA				
≤ 1.6 m^2	28 (25)	12	16	0.657
>1.6 m^2	82 (75)	54	28	
ECOGPS				
0-1	50 (45)	40	10	0.515
2-3	60 (55)	26	34	
Her-2				
Negative	53 (48)	31	22	0.411
Positive	57 (52)	35	22	
Liver metastasis				
No	55 (50)	35	20	0.338
Yes	55 (50)	31	24	
Metastasis site				
1-2	57 (52)	27	30	0.207
3 or more	53 (48)	39	14	
Tumour location				
Upper	46(42)	21	25	0.517
Middle	25(23)	13	12	
Lower	39(35)	32	7	

Relationship between chemotherapy-induced neutropenia (CIN) and survival

The median follow-up time at the time of this study was 30 months. The median progression-free survival (PFS) of these 110 patients was 6.0 months (95% CI: 5.5~6.6 months), and the median overall survival (OS) of these 110 patients was 12.7 months (95% CI: 11.2~14.2 months). Kaplan-Meier survival curves based on chemotherapy-induced neutropenia (CIN) are shown in Figure 1 (PFS) and Figure 2 (OS). The median progression-free survival times for absent (grade 0), mild (grade 1-2), moderate (grade 3) and severe (grade 4) CIN were 3.5 months, 7.0 months, 6.0 months, and 4.3 months, respectively. The median overall survival times were 7.3 months, 16.0 months, 12.2 months, and 10.7 months for absent (grade 0), mild (grade 1-2), moderate (grade 3) and severe (grade 4) CIN, respectively. Furthermore, patients exhibiting early-onset neutropenia experienced significantly better clinical outcomes (PFS and OS) than patients exhibiting late-onset neutropenia, with median PFS times of 6.8 months and 5.6 months, respectively ($P<0.05$) and median OS times of 14.9 months and 12.1 months, respectively ($P<0.05$). The overall survival rates of the 110 patients were 83%, 39%, and 16% at 6 months, 1 year, and 2 years, respectively.

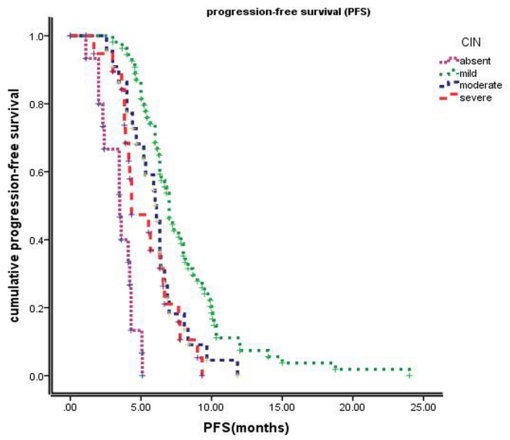

Figure 1. *Kaplan-Meier curves of progression-free survival (PFS) for all patients stratified by CIN.*

Univariate and multivariate analysis focused on neutropenia and other clinicopathological parameters of advanced gastric

cancer (Tables 3 and 4), including gender (male *vs.* female), age (≤ 60 *vs.* >60), differentiation (poorly *vs.* moderately-well), BSA (body surface area) (≤ 1.6 m^2 *vs.* >1.6 m^2), performance status (0-1 *vs.* 2-3), presence of a liver metastasis (yes *vs.* no), her-2 amplification (positive *vs.* negative), metastasis site (1-2 *vs.* 3 or more), and tumour location (upper *vs.* middle *vs.* lower). Table 3 shows that the timing and degree of CIN, differentiation, PS (performance status), presence of a liver metastasis, her-2 amplification, and metastasis site significantly correlated with a better PFS and OS in the univariate analysis. Table 4 shows that the timing and degree of CIN, performance status, presence of a liver metastasis, and her-2 amplification served as independent prognosticators of improved PFS, whereas the timing and degree of CIN and presence of a liver metastasis independently predicted better OS in a multivariate analysis. The result of a Cox regression analysis for the association between CIN and survival is shown in Table 4.

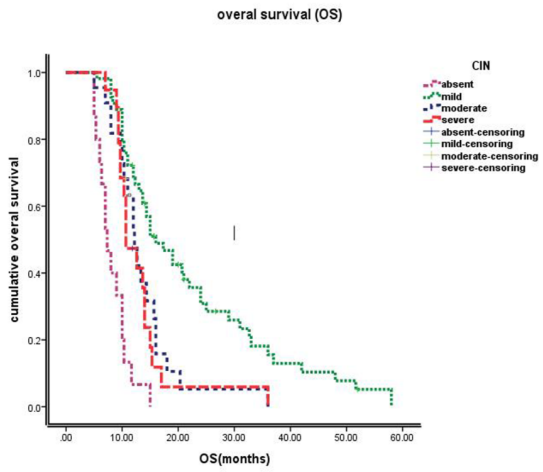

Figure 2. *Kaplan-Meier curves of overall survival (OS) for all patients stratified by CIN.*

For progression-free survival (PFS), the HR for mild CIN (grade 1-2) compared with absent CIN (grade 0) was 0.268 (95% CI: 0.123-0.582, P<0.001), which represented a 73.2% lower risk of disease progression; similarly, the HR for moderate CIN (grade 3) compared with absent CIN (grade 0) was 0.595 (95% CI: 0.368-0.720, P=0.00), which corresponded to a 40.5% lower risk of disease progression; the HR for severe CIN (grade 4) compared with absent CIN (grade 0) was 0.712 (95% CI: 0.380-1.333, P=0.001), which indicated a 28.8% lower risk of disease progression. The hazard ratio for disease progression was significantly lower for early-onset CIN than late-onset CIN (HR=0.713, [95% CI=0.532-0.897], P=0.035).

Table 3. *Univariate analysis for the association between chemotherapy-induced neutropenia and survival.*

	Case	PFS (m)			OS (m)		
	N (%)	Median	χ^2	P value	Median	χ^2	P value
Gender							
Male	90 (82)	6	0.001	0.979	12.7	0.004	0.948
Female	20 (18)	6.2			12.6		
Age (years)							
≤ 60	31 (28)	6.3	0.012	0.911	13.7	0.265	0.607
>60	79 (72)	6			12.2		
Differentiation							
Poorly	54 (49)	5.1	8.403	0.004<0.05	10.3	4.845	0.028<0.05
Moderately-well	56 (51)	6.4			15		
BSA							
≤ 1.6 m^2	28 (25)	6.2	0.029	0.865	13.3	0.394	0.53
>1.6 m^2	82 (75)	6			12.3		
ECOGPS							
0-1	50 (45)	7.2	17.065	0.000<0.05	15	4.261	0.039<0.05
2-3	60 (55)	4.7			10.7		
Her-2							
Negative	53 (48)	7	20.994	0.000<0.05	15	5.106	0.024<0.05
Positive	57 (52)	5.3			11		
Liver metastasis							
No	55 (50)	6.6	6.886	0.009<0.05	15	16.614	0.00<0.05
yes	55 (50)	5.4			10.3		
Metastasis site							
1-2	57 (52)	6.6	7.809	0.005<0.05	15	12.544	0.00<0.05
3 or more	53 (48)	5.4			10.3		
Tumour location							
Upper	46(42)	6	0.543	0.762	12.2	1.578	0.454
Middle	25(23)	6			14.3		
Lower	39(35)	6.3			12		
Timing of CIN							
Early-onset	66(66)	6.8	9.804	0.010<0.05	14.9	3.375	0.01<0.05
Late-onset	44(44)	5.6			12.1		
Degree of CIN							
G0	15 (14)	3.5	72.144	0.00<0.05	7.3	50.123	0.00<0.05
G1~2	54 (49)	7			16		
G3	22 (20)	6			12.2		
G4	19 (17)	4.3			10.7		
G1~2 *vs.* G0	-	-	69.669	0.00	-	40.017	0.00
G3 *vs.* G0	-	-	20.897	0.00	-	14.406	0.00
G4 *vs.* G0	-	-	10.894	0.001	-	10.886	0.001

G1~2 *vs.* G3	-	-	6.961	0.008	-	7.785	0.005
G1~2 *vs.* G4	-	-	12.755	0.00	-	9.158	0.002
G3 *vs.* G4	-	-	0.839	0.36	-	0.392	0.531

For overall survival (OS), the HR for mild CIN (grade 1-2) compared with absent CIN (grade 0) was 0.362 (95% CI: 0.178-0.736, P<0.001), which represented a 63.8% lower risk of death; similarly, the HR for moderate CIN (grade 3) was 0.765 (95% CI: 0.448-0.997, P=0.002), which corresponded to a 23.5% lower risk of death; the HR for severe CIN (grade 4) was 0.791 (95% CI: 0.470-1.688, P=0.005), which indicated a 20.9% lower risk of death. The hazard ratio for death was significantly lower for early-onset CIN than late-onset CIN (HR=0.688, [95% CI=0.499-0.874], p=0.040).

Table 4. *Multivariate Cox models for the association between chemotherapy-induced neutropenia and survival.*

	PFS(m)				OS(m)			
	Wald	P	HR	95% CI	Wald	P	HR	95% CI
Differentiation								
Poorly	-	0.161	-	-	-	0.194	-	-
Moderately-well	-	-	-	-	-	-	-	-
ECOG PS								
0-1	8.111	0.004	0.527	0.339-0.819		0.35		
2-3	-	-	-	-	-	-	-	-
Her-2								
Negative	6.836	0.009	0.522	0.320-0.850		0.464		
Positive	-	-	-	-	-	-	-	-
Liver metastasis								
No	5.19	0.023	0.629	0.423-0.937	16.705	0.000	0.389	0.247-0.611
Yes	-	-	-	-	-	-	-	-
Metastasis site								
1-2		0.743				0.807		
3 or more	-	-	-	-	-	-	-	-
Timing of CIN								
Early-onset	4.233	0.035	0.713	0.532-0.897	10.151	0.040	0.688	0.499-0.874
Late-onset	-	-	-	-	-	-	-	-
Degree of CIN	50.176	0.00	-	-	38.917	0.000	-	-
G1~2	11.065	0.001	0.268	0.123-0.582	7.876	0.005	0.362	0.178-0.736
G3	17.885	0.000	0.595	0.368-0.720	11.815	0.001	0.765	0.448-0.997
G4	1.126	0.009	0.712	0.380-1.333	0.125	0.023	0.791	0.470-1.688

Response to chemotherapy

The overall response rate (ORR) and disease control rate (DCR) is summarized in Table 5. The clinical effects of 6 cycles of DCF chemotherapy in 110 patients were as follows: no patients achieved CR, 43 (39%) patients exhibited PR, 29 (26%) patients attained SD, and 38 (35%) patients experienced PD. The total ORR and DCR among these 110 patients were 39% and 65%, respectively. In a subgroup analysis, the overall response rates for absent (grade 0), mild (grade 1-2), moderate (grade 3) and severe (grade 4) CIN were 13.3%, 53.7%, 45.5%, and 10.5%, respectively, and the disease control rates were 33.3%, 75.9%, 68.2%, and 57.9%, respectively. Overall, chemotherapy-induced neutropenia (CIN) also predicted improved disease control in advanced gastric cancer.

Table 5. *Response rates and disease control rates.*

	Degree of CIN				
	G0	G1~2	G3	G4	P value
ORR (%)	13.3 (2/15)	53.7 (29/54)	45.5 (10/22)	10.5 (2/19)	0.001

	33.3	75.9	68.2	57.9	
DCR (%)	(5/15)	(41/54)	(15/22)	(11/19)	0.018

Discussion

In conclusion, a subgroup analysis indicated that mild, moderate and severe CIN tended to be associated with improved prognosis compared with absent CIN. Additionally, patients who experienced mild (grade 1-2) CIN had a more favourable prognosis than patients with either moderate (grade 3) or severe (grade 4) CIN. Nevertheless, both moderate and severe CIN favourably impacted patients to almost the same degree. Furthermore, the timing of CIN was associated with PFS and OS as follows: the early-onset neutropenia group demonstrated significantly better clinical outcomes than the late-onset neutropenia group. Based on this analysis, univariate and multivariate analyses confirmed that CIN during first-line chemotherapy for advanced gastric cancer was associated with better survival.

Chemotherapy-induced neutropenia is well known to be one of the most important dose-limiting toxicities of cytotoxic drugs that often necessitates a reduction in the initial dosage [12]. In this study, we investigated the association between chemotherapy-induced neutropenia and prognosis in patients with advanced gastric cancer. Monitoring neutropenia in patients who receive chemotherapy may contribute to improved drug efficacy and survival [5]. We herein described a retrospective analysis of 110 consecutive patients treated with DCF as first-line chemotherapy for advanced gastric cancer. We found that early-onset CIN and the degree of CIN (any grade) was associated with improved prognosis. Specifically, the mild, moderate, severe CIN all favourably impacted patient outcomes (PFS: HR=0.268 for mild CIN, HR= 0.595 for moderate CIN, and HR=0.712 for severe CIN; OS: HR=0.362 for mild CIN, HR=0.765 for moderate CIN, and HR=0.791 for severe CIN). The hazard ratios for disease progression and death were significantly lower for early-onset CIN than late-onset CIN (HR=0.713, [95% CI=0.532-0.897], p=0.035 and HR=0.688, [95% CI=0.499-0.874], p=0.040, respectively). To the best of our knowledge, this study was the first to examine the prognostic role of the timing and degree of CIN in advanced gastric cancer patients receiving the DCF regimen.

Chemotherapy-induced neutropenia is reportedly favourably associated with survival in a variety of solid tumours, including non-small cell lung, colorectal, gastric, breast, cervical and ovarian cancer [5,13-22]. Since the late 1990s, many studies have reported better clinical outcomes for patients with chemotherapy-induced neutropenia. Di-Maio et al. demonstrated a positive correlation between chemotherapy-induced neutropenia and survival in by analysing pooled data from three randomized trials of 1265 patients with non-small cell lung cancer [5]. They concluded that both mild (grade 1-2) and severe (grade 3-4) neutropenia improved survival and chemotherapy efficacy compared with absent (grade 0) neutropenia. A similar result was reported for mCRC (metastatic colorectal cancer). Specifically, Shitara et al. retrospectively analysed 153 patients with advanced colorectal cancer receiving FOLFOX with or without bevacizumab as a first-line chemotherapy and found that any degree of CIN was associated with a favourable outcome [13]. Rambach et al. extended this study to a larger population receiving different chemotherapy regimens and found that the favourable prognostic role of neutropenia during treatment for mCRC was a common phenomenon that may not depend on the type of chemotherapy [23]. Jang et al. retrospectively analysed a total of 123 patients with stage IV NSCLC receiving at least two cycles of first-line doublet chemotherapy (gemcitabine plus platinum) and found that early-onset CIN may be a surrogate marker for improved disease control and favourable prognosis in patients with metastatic NSCLC [9]. These findings prompted us to rigorously quantify the prognostic value of the degree and timing of chemotherapy-induced neutropenia with respect to survival outcomes and treatment response in advanced gastric cancer patients undergoing first-line chemotherapy with DCF.

In our study, the relative dose intensity did not significantly differ between patients with and without neutropenia. Therefore, the improved response to chemotherapy and prognosis of patients with CIN were not associated with a reduction in dose. Because patients surviving longer are more likely receive additional cycles of chemotherapy, the number of chemotherapy cycles directly correlated with the incidence of CIN. To avoid this bias, treatment was discontinued upon disease progression, severe toxicity or after six cycles of chemotherapy.

The cause of this inter-patient variation is unclear, but it may be due to gene polymorphisms related to drug elimination or metabolism. The pharmacokinetics of cytotoxic drugs is equal for tumour cells and healthy cells; therefore, the neutrophil count can serve as a surrogate marker of cytotoxic agents and chemotherapy sensitivity. The sensitivity of tumour cells reflects a genetic predisposition, which is the same for all cells [24]. Because certain subpopulations of cancer cells have inherited normal stem cell properties and genetic predispositions, including the capacity for self-renewal and the ability to differentiate and metastasize, cancer stem cell suppression correlates with normal stem cell suppression [25]. Therefore, neutropenia represents the adequate exposure of tumour cells to cytotoxic drugs [26]. In other words, the absence of neutropenia during treatment might be associated with under-dosing [17]. We usually determine the dose of cytotoxic agents based on the body surface area (BSA). However, several prospective randomized studies [27,28] have suggested that the BSA-based dosing system may be not appropriate in many cases, and the optimal dose of cytotoxic drugs is not necessarily determined by the use of BSA-dosing guidelines. In fact, the dose optimization and calculation of a tailored regimen taken into account not only the body surface area but also bodyweight, sex, and age. Nearly two decades ago, Gurney [27] described the limitations of BSA-based dosing, which cannot account for the complex processes of drug elimination and metabolism. Thus, up to 30% of patients receive treatment with unrecognized under-dosing, and these

patients at risk of reduced efficacy and ultimately, poor survival.

Neutrophils may promote the occurrence and development of a tumour via the following mechanism: accumulating evidence has shown that neutrophils contribute to tumour angiogenesis, and an increase in the neutrophil population induces resistance to anti-vascular endothelial growth factor therapy [29,30]. Recent studies suggest that neutrophils play an important role in the induction of the angiogenic switch in cancer, as illustrated in a transgenic mouse model of pancreatic h-cell carcinogenesis [31]. Consequently, neutrophils may be a surrogate indicator for tumour cells acquiring resistance to chemotherapy agents. Significant strengths of this study include that the patients were treated at a single institution by a limited number of physicians and follow-up was relatively long and complete. Unlike a typical exposure of interest, such as a chemotherapy regimen, chemotherapy-induced neutropenia is less likely to be influenced by the investigator's intention. Quality control was overseen by the National Cancer Institute and its data safety monitoring board. However, this study was also subject to several methodological limitations. First, this study is retrospective and examined a small sample, and patients were not randomly assigned to a chemotherapy procedure, which can lead to patient selection bias. Moreover, OS, which was the primary endpoint, may have been confounded by different subsequent chemotherapy regimens, radiotherapy treatment, etc.

In conclusion, our rigorous statistical study demonstrated that patients with early-onset CIN and any grade of CIN reaped greater survival benefits from the treatment than patients with late-onset CIN or patients who did not develop CIN. Specifically, the absence of neutropenia may be a sign of an inadequate chemotherapy dose. Mild neutropenia resulted in the best treatment efficacy and survival, but the treatment efficacy and survival benefit did not significantly differ between severe and moderate neutropenia. Our study suggests that chemotherapy-induced neutropenia can be used to individualize a pharmacologically active dose, and the use of CIN as a guide to tailor dosages warrants further attention. Prospective randomized trials are required to evaluate the ability of dosing adjustments based on neutropenia to improve chemotherapy efficacy and survival. An additional well-defined prospective trial to explore safe intra-patient dose escalation with the intent of achieving neutropenia is warranted.

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Ethical Approval and Informed Consent

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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