

Original Article

Chemotherapy-induced leukopenia as a prognostic factor in patients with metastatic non-small cell lung cancer treated with platinum-based chemotherapy

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Abstract: Platinum-based chemotherapy is the front-line treatment in patients with metastatic non-small cell lung cancer (NSCLC). Leukopenia is one of its common side effects. The aim of this study was to analyze the association between the grade of platinum-based chemotherapy induced leukopenia and the clinical outcome of NSCLC patients. Three hundred nine patients with metastatic NSCLC, treated with platinum-based chemotherapy, were retrospectively analyzed. Patients were divided into 3 groups according to the presented worst leukopenia grade: absent (grade 0), mild (grade I/II) and severe (grade III/IV). The associations between platinum-based chemotherapy induced leukopenia and time to tumor progression (TTP) and overall survival (OS) were evaluated and correlated to response rate (RR) and disease control rate (DCR). The results showed RR, DCR, TTP and OS were significantly better in patients developing any grade of leukopenia compared with those without leukopenia. The median TTPs were 2.0, 5.88, 7.44 months for absent, mild and severe leukopenia, respectively; the median OSs were 7.64, 14.69, 13.72 months for the same groups, respectively. Multivariate analysis revealed that mild chemotherapy-induced leukopenia was an independent factor associated with a better TTP and OS. In conclusion, platinum-based chemotherapy induced leukopenia was emerged as an independent prognostic factor. Our study suggests that chemotherapy-induced leukopenia can be regarded as a surrogate marker for optimal dosing of anticancer drugs.

Keywords: Chemotherapy, leukopenia, non-small cell lung cancer, platinum, prognosis

Introduction

Non-small cell lung cancer (NSCLC) comprises 80% of the lung cancer and is the leading cause of cancer-related death in both male and female [1]. Compared to the supportive care alone, systemic chemotherapy in patients with advanced NSCLC improves survival and alleviates symptoms [2]. Platinum-based chemotherapy represents the main therapeutic choice in NSCLC [3, 4] and possesses an advantage on death risk reduction and 1-year survival rate improvement [5]. However, several studies suggested that no significant improvement on the time to tumor progression (TTP) and overall survival (OS) in NSCLC patients after the employment of platinum-base chemotherapy [6-8].

It is reported that substantial toxicity especially hematological toxicity could be caused by cytotoxic chemotherapy, which could result in treat-

ment delays, treatment discontinuation and even treatment related deaths [9]. Repetto et al. verified that myelotoxicity occurred in a substantial proportion of cancer patients receiving chemotherapy and had an impact on chemotherapy dose delivery [10]. Kvinnsland et al. proposed that hematological toxicity could be used as an indicator of cytotoxic drug [11]. Moreover, several studies suggested that better clinical outcome could be expected in breast cancer patients presented with serious adverse events [12-15]. In addition, chemotherapy-induced myelosuppression was reported to be associated with the clinical outcome of patients with testicular cancer, ovarian cancer and lymphoma [16-18]. In advance NSCLC, Pallis et al. suggested that chemotherapy-induced neutropenia could be employed as a prognostic fact in patients with NSCLC treated with chemotherapy [19]. However, most of current studies were focused on the neutropenia or anemia, while

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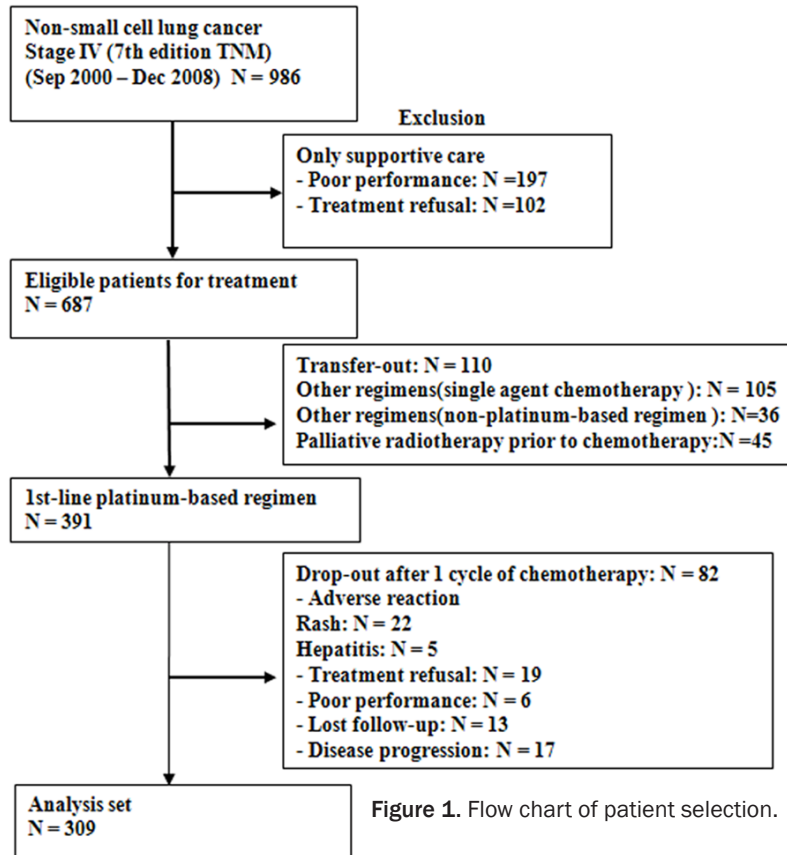


Figure 1. Flow chart of patient selection.

Table 1. Patients' characteristics according to worst leukopenia grade

Parameters	0 (n=62)		I/II (n=145)		III/IV (n=102)	
	(n, %)	(n, %)	(n, %)	(n, %)	P value	P value
Age (years)						
Median (range)	56.5 (38-84)	59 (33-80)	0.743	60 (29-77)	0.600	
Gender			0.220		0.205	
Male	46 (74.2%)	95 (65.5%)		66 (64.7%)		
Female	16 (25.8%)	50 (34.5%)		36 (35.3%)		
Stage			0.827		0.404	
IIIB	1 (1.6%)	3 (2.1%)		4 (3.9%)		
IV	61 (98.4%)	142 (97.9%)		98 (96.1%)		
Histology			0.036		0.440	
Squamous	33 (53.2%)	105 (72.4%)		61 (59.8%)		
Adenocarcinoma	15 (24.2%)	18 (12.4%)		16 (15.7%)		
Undifferentiated	11 (17.7%)	14 (5.5%)		16 (15.7%)		
Others	3 (4.8%)	8 (9.7%)		9 (8.8%)		
Number of circles			0.001		0.03	
<6 circles	53 (85.5%)	90 (62.1%)		72 (70.6%)		
≥6 circles	9 (14.5%)	55 (37.9%)		30 (29.4%)		

the efficacy of other hematological indicators such as leukopenia has not yet been explored.

Here we collected 309 cases of NSCLC patients treated with front-line platinum-based chemotherapy and performed a retrospective study to investigate the association between leukopenia and TTP and OS of the patients.

Patients and methods

Patients and treatments

This retrospective analysis included 309 patients with NSCLC who received platinum-based chemotherapy between 2000 and 2008 in Shanghai Chest Hospital (Shanghai, China). The patient selection process was shown in **Figure 1**. The median age of included patients was 57 years old (range from 29 to 84 years old). Of them, 207 were males and 102 were females. All the included patients had an Eastern Cooperative Oncology Group Performance status (PS) of 0-1, inoperable locally advanced stage IIIB or metastatic stage IV NSCLC and had applied with platinum-based chemotherapy as the treatment. The study protocol was approved by the Ethics and Scientific Committees of Shanghai Chest Hospital, and written informed consent was provided by all the included patients. This study was performed according to the Helsinki Declaration.

Assessment of leukopenia

Leukopenia was assessed according to WHO criteria [20]. The grade of leukopenia was based on the lowest recorded WBC count for a given patient

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Table 2. Response rate according to worst leukopenia grade

Response	0 (n=60)	I/II (n=145)	III/IV (n=102)	I/IV (n=247)
CR	0	0	0	0
PR	2 (3.2%)	21 (14.5%)	26 (25.5%)	47 (19.0%)
ORR (CR+PR)	2 (3.2%)	21 (14.5%)	26 (25.5%)	47 (19.0%)
SD	15 (24.2%)	84 (57.9%)	58 (56.9%)	142 (57.5%)
DCR (CR+PR+SD)	17 (27.4%)	105 (72.4%)	84 (82.4%)	189 (76.5%)
PD	43 (72.6%)	40 (27.6%)	18 (17.6%)	58 (23.5%)

CR: complete response; PR: partial response; SD: Stable Disease; PD: progressive disease; ORR: overall response rate; P<0.001 (0 vs. I/II), P<0.001 (0 vs. III/IV), P=0.042 (I/II vs. III/IV), P<0.001 (0 vs. I/IV).

Table 3. Time to tumor progression (TTP) according to leukopenia grade

	0 (n=52)	I/II (n=94)	III/IV (n=62)
TTP (median; month)	2.0	5.88	7.44
Minimum-maximum	0.96-9.57	0.99-24.00	1.87-21.17
95% CI	1.85-3.42	5.46-8.14	6.47-8.40
1 year without tumor progression	0%	11.00%	10.80%

TTP: time to tumor progression; CI: confidence interval; P<0.001 (0 vs. I/II); P<0.001 (0 vs. III/IV); P=0.597 (I/II vs. III/IV).

between the first day of chemotherapy administration and 3 weeks after the last chemotherapy. In all patients a complete blood cell count with differential and platelet count had to be performed before chemotherapy. A complete blood cell count was performed at least twice a week during the chemotherapy period; patients with severe leukopenia were followed up with daily blood counts and received human recombinant granulocyte-colony-stimulating factor (G-CSF).

Statistical analysis

According to worst WHO leukopenia grade recorded during the treatment, patients were divided into three groups: absent (grade 0), mild (grade I/II), severe (grade III/IV). Descriptive statistics for the patient group were reported as mean, median, and range. Statistical comparisons between group rates (proportions) were assessed by Pearson's χ^2 -test. The survival curves were constructed by Kaplan-Meier method and differences between groups were evaluated by log-rank test. OS was measured from entry into the study until death while TTP was measured from the time of enrollment to the study to the time of local recurrence or metastasis. The Cox proportional hazards regression model was used to estimate hazard ratios (HRs) of OS and TTP, both in a univariate

and multivariate setting, where the effect of one factor or the combined effects of two or more factors were assessed [21]. Confidence intervals (CI) at 95% for HRs were calculated. All the statistical analyses were performed using SPSS version 18.0 (SPSS Inc. Chicago, IL, USA). P<0.05 was considered as statistical significance.

Results

Characteristics of patients

Patient's characteristics according to worst leukopenia grade were listed in **Table 1**. Grade I/II (mild) and grade III/IV (severe) leukopenia was observed in 145 and 102 patients,

respectively. There was no statistical difference among the three groups according to the age, gender, and disease stage. There was a significantly higher proportion of squamous carcinoma who developed mild leukopenia (72.4%) compared with that of patients in the absent group (53.2%, P=0.036). Moreover, among patients who developed mild and severe leukopenia, there were a significantly higher percentage of patients with ≥ 6 cycles chemotherapy compared with the absent group (mild 37.9% vs. 14.5%, P=0.001; severe 29.4% vs. 14.5%, P=0.03).

Response to treatment

The response ratio according to leukopenia status was shown in **Table 2**. Patients who presented with any grade of leukopenia had significantly higher overall response rate (ORR; mild: 14.5%, P<0.001; severe: 25.5%, P<0.001) compared with those without leukopenia (absent group: 3.2%). Similarly, the disease control rate (DCR) was also significantly higher in mild (72.4%, P<0.001) or severe (82.4%, P<0.001) leukopenia than in absent patients (27.4%).

Time to tumor progression

Patients who developed any grade of leukopenia had significantly longer median TTP com-

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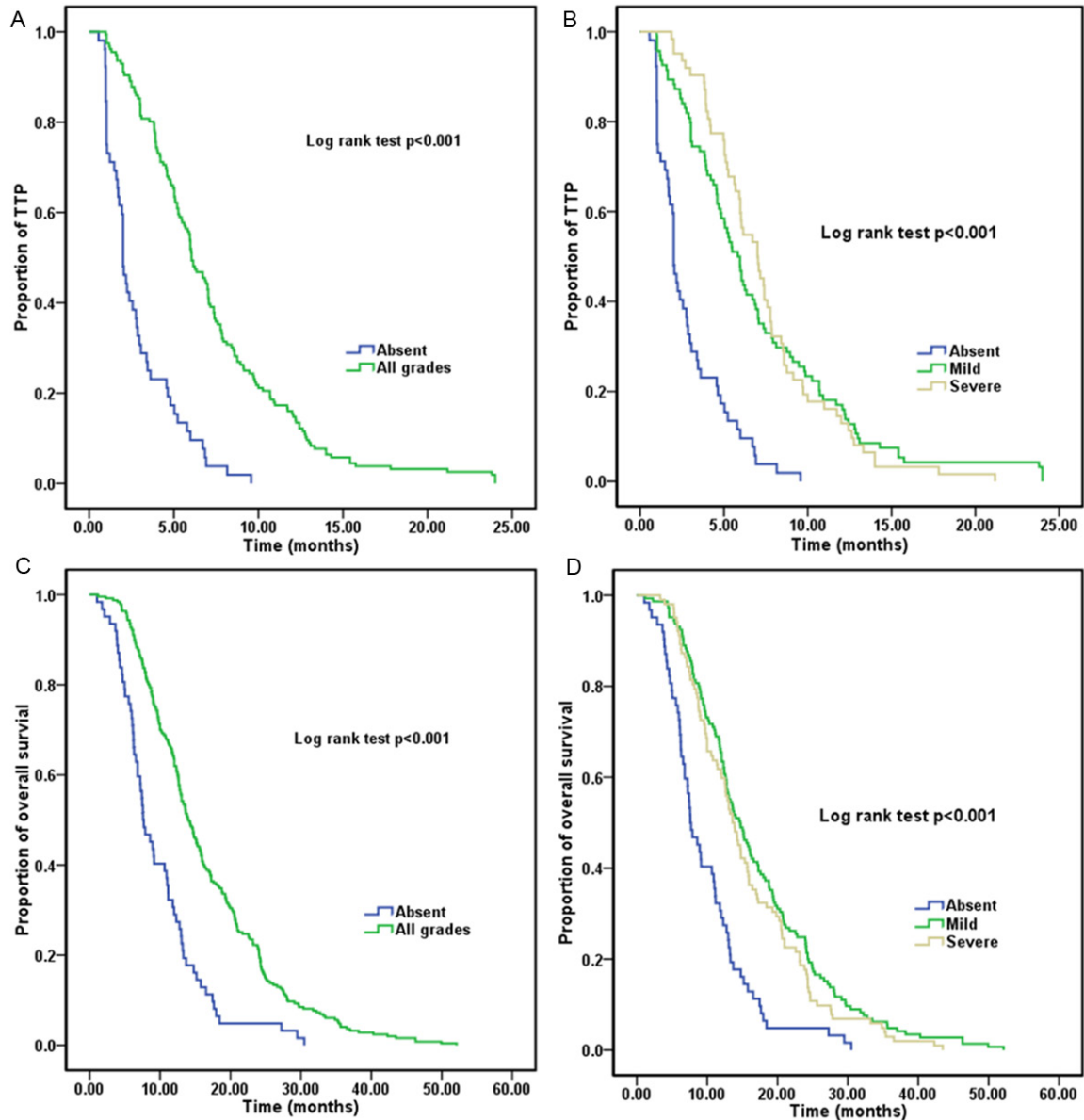


Figure 2. Kaplan-Meier curve of time to tumor progression (TTP) and overall survival (OS). A. TTP in patients with any grade of leukopenia compared with those in absent group; B. TTP in patients with different leukopenia severity; C. OS in patients with any grade of leukopenia compared with those in absent group; D. OS in patients with different leukopenia severity.

Table 4. Overall survival (OS) according to leukopenia grade

	0 (n=62)	I/II (n=145)	III/IV (n=102)
OS (median; months)	7.64	14.69	13.72
Minimum-maximum	1.50-30.48	1.18-52.11	3.32-43.50
95% CI	7.21-11.36	14.42-18.68	12.93-17.33
1-year survival	29%	67.60%	61.80%
2-year survival	4.80%	24.80%	17.60%

OS: overall survival; CI: confidence interval; $P < 0.001$ (0 vs. I/II); $P < 0.001$ (0 vs. III/IV); $P = 0.217$ (I/II vs. III/IV).

pared with those in absent group (**Table 3** and **Figure 2A**). The median TTP was 2.0, 5.88, 7.44 months for the groups with absent, mild and severe leukopenia, respectively (absent vs. mild: $P = 0.000$; absent vs. severe: $P = 0.000$). There was no difference in terms

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Table 5. Univariate analysis for time to tumor progression (TTP) and overall survival (OS)

	Log-rank test	Hazard	95% CI	P value
TTP				
Leukopenia				
0 vs. 1-2	47.625	4.131	2.795-6.104	<0.001
0 vs. 3-4	58.979	1.017	0.735-1.408	<0.001
Thrombopenia				
0 vs. 1-2	17.545	1.765	1.151-2.705	<0.001
0 vs. 3-4	7.047	0.879	0.552-1.401	0.008
Erythropenia				
0 vs. 1-2	12.418	1.495	0.897-2.491	<0.001
0 vs. 3-4	2.935	0.876	0.529-1.452	0.087
Age				
<65 vs. ≥65	0.220	1.077	0.787-1.473	0.639
Stage				
IV vs. IIIB	2.444	0.554	0.260-1.180	0.118
Gender				
Male vs. Female	5.561	1.403	1.054-1.869	0.018
OS				
Leukopenia				
0 vs. 1-2	35.694	2.093	1.441-3.040	<0.001
0 vs. 3-4	21.896	0.836	0.641-1.090	<0.001
Thrombopenia				
0 vs. 1-2	12.782	1.237	0.843-1.813	<0.001
0 vs. 3-4	3.370	0.892	0.617-1.289	0.066
Erythropenia				
0 vs. 1-2	0.065	0.513	0.326-0.806	0.799
0 vs. 3-4	1.158	0.655	0.434-0.989	0.282
Age				
<65 vs. ≥65	0.593	1.155	0.905-1.476	0.441
Stage				
IV vs. IIIB	0.322	0.816	0.404-1.651	0.571
Gender				
Male vs. Female	12.526	1.568	1.228-2.003	<0.001

Table 6. Multivariate analysis for time to tumor progression (TTP) and overall survival (OS)

	Hazard	95% CI	P value
TTP			
Leukopenia			
0 vs. 1-2	3.218	2.058-5.031	<0.001
0 vs. 3-4	0.976	0.698-1.364	0.885
OS			
Leukopenia			
0 vs. 1-2	1.809	1.272-2.573	0.001
0 vs. 3-4	0.797	0.613-1.037	0.091
Gender			
Male vs. Female	1.570	1.227-2.010	<0.001

of TTP between the mild and severe leukopenia groups ($P=0.597$, **Figure 2B**). The univariate analysis to define factors which influence the TTP such as leukopenia, thrombopenia, erythropenia, age, stage and gender, revealed the presence of leukopenia, thrombopenia, erythropenia and gender as the factors with a significant influence on TTP (**Table 5**). A proportional hazards (Cox) regression analysis demonstrated that mild leukopenia had a significant effect on the hazard of disease progression (**Table 6**).

Overall survival

Patients who developed any grade of leukopenia had significantly longer median OS compared with those in absent group (**Table 4** and **Figure 2C**). The median OS was 7.64, 14.69, 13.72 months for the groups with absent, mild and severe leukopenia, respectively (absent vs. mild: $P<0.001$; absent vs. severe: $P<0.001$). There was no difference in terms of OS between the mild and severe leukopenia groups ($P=0.217$, **Figure 2D**). The

univariate analysis to define factors which influence the OS such as leukopenia, thrombopenia, erythropenia, age, stage and gender, revealed the presence of leukopenia, thrombopenia and gender as the factors with a significant influence on OS (**Table 5**). A proportional hazards (Cox) regression analysis demonstrated that mild leukopenia and gender had a significant effect on the hazard of OS (**Table 6**).

Discussion

This retrospective analysis was performed in order to investigate a possible correlation between the development of leukopenia and

OS in NSCLC patients treated with platinum-based chemotherapy as first-line treatment. Our results demonstrated that the development of chemotherapy-induced leukopenia is a significant prognostic factor for improving clinical outcome of NSCLC patients. Here, patients who developed leukopenia after receiving platinum-based chemotherapy had significantly higher ORR, TTP and OS. Moreover, the influence of leukopenia on both TTP and OS was verified by univariate and multivariate analysis. Especially, the multivariate analysis revealed mild leukopenia as an independent factor with a significant effect on the hazard of TTP and OS. In addition, gender was also confirmed as an independent prognostic factor associated with an improved OS. To the best of our knowledge, this is the first study showed that the benefit of platinum-based chemotherapy was associated with leukopenia.

A possible bias might exist in the association observed between the chemotherapy-induced leukopenia and the improvement of clinical outcome. Patients with longer survival time could receive additional chemotherapy cycles and might present a higher risk to leukopenia development. However, given that majority of patients received <6 cycles chemotherapy, this is unlikely to present in our opinion. Furthermore, in a landmark reported by Di Maio et al. [22], they restricted the primary analysis to patients who had completed six cycles of treatment and had confirmed the presence of an association between neutropenia and improved clinical outcome.

A possible explanation for the association between chemotherapy-induced leukopenia and clinical outcome improvement is that the absence of leukopenia may suggest a lack of efficacy of the administered chemotherapy regimen due to different pharmacogenetic background of individual patients and various metabolism patterns of different anticancer drugs. According to previous study, application of conventional dosage of chemotherapy drugs in patients with normal organ functions could lead to obvious variations in different individuals and this is not associated with the complex process of cytotoxic drug elimination [18]. This might result in over or under treatment in patients associated with unwarranted toxicity, and unpredictable treatment efficacy. Bergh et

al. previously suggested that patients who are inadvertently under-dosed are at risk of a significantly reduced treatment efficacy [23]. In addition, we could not exclude that leukopenia may be caused by decreased drug metabolism because of downregulation of factors associated with the metabolism of anticancer drugs, and thus an increased cytotoxicity against both normal and malignant cells could be observed. Furthermore, the association between gender and OS was also found in this study. A possible explanation is the relationship between sex hormones and lung cancer. Several studies have shown that estrogen receptor- β (ER β) was presented in the majority of tested NSCLC tumors, suggesting a potential role of estrogen in NSCLC [24, 25]. Moreover, in a murine xenograft model of NSCLC, Stabile et al. reported the response of NSCLC after the activation of ER β [24]. Ganti et al. showed that continued use of female sex hormones after diagnosis of lung cancer worsened outcome [26], and in a randomized Women's Health Initiative (WHI) trial, the combination use of estrogen and progestin significantly increased lung cancer mortality in postmenopausal women [27, 28]. In addition, estrogen exerts a certain effect on angiogenesis as proved by discovery of estrogen response elements in vascular endothelial growth factor (VEGF) [29]. Another potential explanation is that women may be more susceptible than men to chemotherapy due to decreased DNA repair capacity [30, 31]. Further study is necessary to understand this phenomenon.

There were also some limitations in this study. The properties of a single-center retrospective study other than double blind randomized controlled trial could result in incomplete information on the follow-up and long-term effect. Moreover, we only included a small number of patients in this study and certain patient selection bias might be produced due to the patient number. Furthermore, we did not include a group of patients with non-platinum based chemotherapy. In the future, large number of patients and appropriate non-platinum based chemotherapy group should be included to accurately access the efficacy of the prognostic effect of leukopenia.

In conclusion, the chemotherapy-induced leukopenia can be a prognostic factor to the

advanced NSCLC treated with platinum-based chemotherapy. Our study suggests that chemotherapy-induced leukopenia can be regarded as a surrogate marker for optimal dosing of anticancer drugs. A prospective randomized trial should be executed to explore the best method of dose individualization.

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Disclosure of conflict of interest

None.

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