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Incidence and non-genetic risk factors of irinotecan-induced severe neutropenia in Chinese adult inpatients

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Abstract

To analyze the incidence and nongenetic risk factors of irinotecan-induced severe neutropenia in the hospital, and provide additional reference and help for clinical treatment. A retrospective analysis of patients who received irinotecan based chemotherapy from May 2014 to May 2019 in Renmin Hospital of Wuhan University was conducted. Univariate analysis and binary logistic regression analysis with the forward stepwise method were used to assess the risk factors associated with severe neutropenia induced by irinotecan. Of the 1312 patients treated with irinotecan-based regmines, only 612 patients met the inclusion criteria, and 32 patients developed irinotecan-induced severe neutropenia. In the univariate analysis, variables associated with severe neutropenia were tumor type, tumor stage, and therapeutic regimen. In the multivariate analysis, irinotecan plus lobaplatin, lung cancer or ovarian cancer, tumor stage T_2, T_3, and T_4, were identified as risk factors that contributed independently to irinotecan-induced severe neutropenia ($P < .05$), respectively. The results showed that the incidence of irinotecan–induced severe neutropenia was 5.23% in the hospital. The risk factors included tumor type (lung cancer or ovarian cancer), tumor stage (T_2, T_3, and T_4) and therapeutic regimen (irinotecan plus lobaplatin). Therefore, for patients with these risk factors, it might be advisable to actively consider optimum management to reduce the occurrence of irinotecan–induced severe neutropenia.

Abbreviations: ANC = absolute neutrophil count, FN = febrile neutropenia, SN-38 = 7-ethyl-10-hydroxycamptothecin, WBC = white blood cell.

Keywords: incidence, irinotecan, risk factor, severe neutropenia, therapeutic regimen

1. Introduction

It was well known that irinotecan was effectively and widely used in many kinds of cancers, such as metastatic colorectal cancer, lung cancer, and gynecological cancers. However, the serious issue of irinotecan in clinical practice was its dose-limiting toxicity, including severe neutropenia, regardless of any cancers.[1–3]

Irinotecan is also a potent inhibitor of topoisomerase I, is initially hydrolyzed to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), which is then subsequently inactivated through UGT1A1-mediated glucuronidation.[4] Irinotecan-induced neutropenia is a complex, polygenic phenotype. Several additional genetic variants contribute to both variability in irinotecan pharmacokinetics and the risk of severe neutropenia.[5] However, other nongenetic factors, such as organ functions, age, gender, comorbidities, and performance status, should therefore be comprehensively considered in predicting the risk of severe irinotecan-related toxicities.[4,6–10] The other study also suggests the risk of severe neutropenia induced by irinotecan based regimens can not be predicted solely on the basis of UGT1A1 genotype and the administered dose of irinotecan, potential effects of other nongenetic factors such as patients clinical characteristics must also be considered.[11] In general, the risk of developing neutropenia and/or febrile neutropenia (FN) is dependent on a variety of factors including the type of cancer, the chemotherapy regimen used, patient characteristics, and including a low neutrophil count at baseline.[12]

SZ and JY contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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The guidelines recognize older age (particularly > 65 years), previous chemotherapy or radiotherapy, preexisting neutropenia or tumor involvement in the bone marrow, poor performance status, comorbidities(e.g., renal or liver dysfunction), and pre–existing conditions (e.g., infection) as risk factors for developing severe neutropenia.[13]

Up to now, the risk factors of irinotecan–induced severe neutropenia are often associated with genetic polymorphisms in UGT1A1, but nongenetic risk factors were seldom reported in detail. Therefore, we aim to analyze the incidence and nongenetic risk factors of irinotecan-induced severe neutropenia in Renmin Hospital of Wuhan University, and to provide additional evidence for clinical prevention and treatment of irinotecan-induced severe neutropenia.

2. Materials and methods

2.1. Study design and participants

The medical records of 1312 patients receiving irinotecan based chemotherapy at Renmin Hospital of Wuhan University from May 2014 to May 2019 were collected. A retrospective analysis of 612 patients was finalized according to the inclusion and exclusion criteria below.

The inclusion criteria were as follows: Patients ≥ 18 years old; normal range of white blood cell (WBC) and absolute neutrophil count (ANC) tests at baseline before chemotherapy; conduction of follow-up laboratory data adequate for assessing neutropenia; and reasonable prescription of irinotecan. The exclusive criteria were: liver and kidney trans-plantation prior to the onset of neutropenia; neutropenia induced by other drugs before chemotherapy; and disease of blood and hematopoietic system such as leukemia, thrombocytopenic purpura, and so on.

The chemotherapy regimens and dose of irinotecan in this study: irinotecan alone (125mg/m^2, d1, d8, d15, and d22, repeated every 6 weeks; 350mg/m^2, dL, repeated every 3 weeks), irinotecan plus 5-Fluorouracil (180mg/m^2, dL, repeated every 2 weeks), irinotecan plus capecitabine (250 mg/m^2, dL, repeated every 3 weeks), irinotecan plus cisplatin (60mg/m^2, dL, d8, and d15, repeated every 4 weeks; 65mg/m^2, dL, d8, and d15, repeated every 3 weeks), irinotecan plus lobaplatin (80 mg/m^2 or 90mg/m^2, dL, d8, repeated every 3 weeks), irinotecan plus nedaplatin (60mg/m^2 or 65mg/m^2, dL, d8, repeated every 3 weeks), irinotecan plus bevacizumab (125mg/m^2, dL, repeated every 2 weeks) and irinotecan plus raltitrexed (150 or 180mg/m^2, dL, repeated every 2 weeks; 240mg/m^2, dL, repeated every 3 weeks). Dose and schedule of irinotecan was modified according to patient age, medical condition and the combination with other anticancer drugs by each attending physician decision.

2.2. Data collection

We retrospectively reviewed all serum laboratory data that were collected from inpatient records from May 2014 to May 2019. Our search through individual review of their electronic medical records to determine whether inpatients could meet the inclusion and exclusion criteria.

2.3. Definition of severe neutropenia[14]

Neutropenia is a decrease in circulating neutrophils in the nonmarginal pool and is defined in terms of ANC, with a healthy person having an ANC of 1.5 to 8.0×10^9 cells/L. In this study, severe neutropenia is defined as granulocyte count < 0.5×10^9 cells/L. Recovery from severe neutropenia is defined as a granulocyte count restored to 0.5×10^9 cells/L and more. FN is defined as an oral temperature > 38.5°C or 2 consecutive readings of > 38.0°C for 2 hours and an absolute neutrophil count < 0.5×10^9 cells/L, or expected to fall below 0.5×10^9 cells/L.

2.4. Statistical analysis

SPSS 24.0 (IBM Corp., Armonk, NY) was used for statistical analyses. The categorical variables were subject to chi square test, the unidirectional ordered data was subject to Mann–Whitney test of independent samples, and the bidirectional ordered data was subject to Kappa consistency test. In the chi square test, the exact method adopted the progressive only method. If the number of cells whose expected count was < 5 was > 25%, Fisher exact probability method was used to re-test. A bilateral P value < .05 was considered statistically significant. All patient factors with a P value of $.05 \pm 0.005$ in the univariate analysis were considered for inclusion in the multivariate analysis. A multivariate analysis of risk factors for irinotecan-induced severe neutropenia was performed using logistic regression with a forward conditional method, and Homos–Lemeshow test was used to evaluate the goodness of fit. Patient characteristics hypothesized to be strong predictors of severe neutropenia and variables that were significantly associated with severe neutropenia in bivariate analyses were included.

2.5. Ethical review and informed consent of patients

The study was approved by the Renmin Hospital Ethics Committee of Wuhan University(2018KC124). In view of the retrospective and observational nature of the study with no interventions performed, the need for informed consent was waived.

3. Results

3.1. Characteristics of patients with severe neutropenia

Of the 1312 patients, some patients had been excluded due to incomplete test record (528), blood disease (36), Patients < 18 years old (84), abnormal range of WBC and ANC tests at baseline (32) or unreasonable prescription of irinotecan (20). For the remaining 612 patients, and 32 patients (5.23%, 32/612) developed irinotecan-induced severe neutropenia. 32 Patients with severe neutropenia had their WBC and ANC values (mean ± SD) were $(4.58 \pm 1.61) \times 10^9$ cells/L and $(3.17 \pm 1.19) \times 10^9$ cells/L before chemotherapy, respectively, at baseline measurement, and their values during chemotherapy were $(0.96 \pm 0.65) \times 10^9$ cells/L and $(0.3 \pm 0.14) \times 10^9$cells/L, respectively.

Of the 32 patients with irinotecan-induced severe neutropenia, 21 were male and 11 were female. The mean age was 58.90 ± 9.80 years (32–79 years) and the median hospital stay was 40.75 ± 20.04 days (8–63 days). In the study, 9 patients (28.13%, 9/32) had severe neutropenia within the first week, 12 patients (37.5%, 12/32) within the second week, 9 patients (28.13%, 9/32) within the third week and 2 patients (6.25%, 2/32) within the 4th week. In addition, the median time interval from the initiation of treatment to the onset of severe neutropenia was 12.34 ± 9.45days. 32 patients with severe neutropenia displayed the signs and symptoms: fever (78.13%, 25/32), hypodynamia (43.75%, 14/32), dizziness (40.63%, 13/32), anorexia (15.63%, 5/32), infectious signs (37.5%, 12/32), headache (9.38%, 3/32), tinnitus (3.13%, 1/32), muscle aches (9.38%, 3/32), stomach ache (3.13%, 1/32), pharyngalgia (6.25%, 2/32), and proctalgia (3.13%, 1/32) and urodynia (3.13%, 1/32). Notably, 20 patients were diagnosised as FN among 32 patients. With regards to outcome of severe neutropenia, 25 (78.13%,

25/32) patients were cured, 5 (15.63%, 5/32) patients were improved, 2 (6.25%, 2/32) patients were not unknown, and no death.

3.2. Risk factors for irinotecan-induced severe neutropenia in patients

Table 1 summarized differences in clinical and demographic variables between patients who did and did not develop severe neutropenia during chemotherapy. From Table 1, patients were divided into 2 groups based on the presence (n = 32) or absence (n = 580) of severe neutropenia. Age, gender, smoke, drink, and hypertension and diabetes did not differ between 2 groups. However, these variables, such as tumor type (P = .04), tumor stage (P = .000) and therapeutic regimen (P = .001), appeared to be related to irinotecan-induced severe neutropenia.

As shown in Table 1, according to tumor type, their incidences during chemotherapy were: lung cancer (10.46%), colonic cancer (3.66%), rectal cancer (3.80%), gastric cancer (3.13%) and ovarian cancer (5.00%), respectively. In the different tumor stage, the incidences of irinotecan-induced severe neutropenia were: T_0 to T_1(1.33%), T_2 (2.56%), T_3(4.56%) and T_4 (14.43%), respectively.

Notably, irinotecan plus platinum showed higher incidences of irinotecan–induced severe neutropenia in comparison with other chemotherapy regmens.

Therefore, the statistically relevant factors identified were then entered into a multivariate stepwise analysis. As a result, lung cancer (OR [95%CI], 1.026 [0.001–2.650]; P = .026) and ovarian cancer (OR [95% CI], 1.013 [0.001–2.572]; P = .025), tumor stage T_2(OR [95%CI], 1.120 [0.032–2.456]; P = .019), T_3(OR [95% CI], 2.327 [1.134–7.797]; P = .014) and T_4(OR [95%CI], 5.191 [0.025–12.584]; P = .002), and irinotecan plus lobaplatin regimen (OR [95% CI], 1.389 [0.943–3.689]; P = .046), were found to be significant risk factors for irinotecan-induced severe neutropenia among these patients, respectively (seeing Table 2).

4. Discussion

While irinotecan based chemotherapy is effective for the treatment of various types of cancers, it is also associated with the

Table 1

Summary of non-severe neutropenia and severe neutropenia groups.

Variable	non-severe neutropenia (n = 580, 94.77%)	severe neutropenia (n = 32, 5.23%)	*P* value
Age, yr, n (%)			.48
18–44	87 (97.75)	2(2.25)	
45–59	249 (94.32)	15(5.68)	
≥60	254 (94.42)	15(5.58)	
Gender, n (%)			.96
Male	383 (94.80)	21(5.20)	
Female	197 (94.71)	11(5.29)	
Menopause, n (%)			.72
no	62 (95.39)	3(4.61)	
yes	135 (94.41)	8(5.59)	
History of disease			
Hypertension, n (%)			.81
no	424 (94.64)	24(5.36)	
yes	156 (95.12)	8(4.88)	
Diabetes, n (%)			.19
no	496 (94.30)	30(5.70)	
yes	84 (97.67)	2(2.33)	
Smoke, n (%)			.83
no	425 (94.65)	24(5.35)	
yes	155 (95.09)	8(4.91)	
Drink, n (%)			.39
no	494 (94.46)	29(5.54)	
yes	86 (96.63)	3(3.37)	
Tumor type, n (%)			.04*
Lung cancer	137 (89.54)	16(10.46)	
Colonic cancer	184 (96.34)	7(3.66)	
Rectal cancer	177 (96.20)	7(3.80)	
Gastric cancer	31 (96.87)	1(3.13)	
Ovarian cancer	19 (95.00)	1(5.00)	
Tumor stage, n(%)			.000*
T_0~T_1	74 (98.67)	1(1.33)	
T_2	152 (97.44)	4(2.56)	
T_3	272 (95.44)	13(4.56)	
T_4	83 (85.57)	14(14.43)	
Therapeutic regimen, n (%)			.001*
Irinotecan	80 (96.39)	3(3.61)	
Irinotecan + 5–fluorouracil	185 (97.88)	4(2.12)	
Irinotecan + capecitabine	88 (95.65)	4(4.35)	
Irinotecan + cisplatin	38 (86.36)	6(13.64)	
Irinotecan + lobaplatin	43 (82.69)	9(17.31)	
Irinotecan + nedaplatin	59 (93.65)	4(6.35)	
Irinotecan + bevacizumab	18 (94.74)	1(5.26)	
Irinotecan + raltitrexed	25 (96.15)	1(3.85)	

* Significant change between groups (P < .05).

Table 2

Logistic regression equation variables for severe neutropenia.

Variable	B	*P*	OR	95% CI
Lung cancer	3.664	.026	1.026	0.001–2.650
Colonic cancer	−2.449	.100	0.082	0.004–1.615
Rectal cancer	−2.281	.119	0.102	0.006–1.791
Gastric cancer	−2.256	.205	0.105	0.003–3.419
Ovarian cancer	4.356	.025	1.013	0.001–2.572
T_0–T_1	2.497	.128	1.082	0.009–4.760
T_2	2.118	.019	1.120	0.032–2.456
T_3	1.119	.014	2.327	1.134–7.797
T_4	0.009	.002	5.191	0.025–12.584
Irinotecan	0.175	.874	1.191	0.138–10.265
Irinotecan + 5-fluorouracil	−1.618	.152	0.198	0.022–1.811
Irinotecan + capecitabine	−0.042	.968	0.959	0.124–7.428
Irinotecan + cisplatin	2.462	.056	1.725	1.041–6.511
Irinotecan + lobaplatin	2.433	.046	1.389	0.943–3.689
Irinotecan + nedaplatin	1.356	.311	3.879	0.282–5.788
Irinotecan + bevacizumab	1.705	.453	2.931	0.177–48.575
Irinotecan + raltitrexed	−0.704	.603	0.495	0.035–7.015
Constant	0.026	.703		

B > 0, OR > 1, Risk factors; B < 0, OR < 1, Protective factors; B = 0, OR = 1, not affect.

CI = confidence interval, OR = odds ratio.

risk of severe neutropenia.[15] For example, 56 patients (20.3 %, 56/276) developed severe neutropenia in Chinese colorectal cancer patients. The incidence of severe neutropenia in female patients (27.3 %, 30/110) was significantly higher than male patients (15.7 %, 26/166; *P* = .019).[16] Yunami Yamada et al[15]reported severe neutropenia appeared in 53.8% of patients receiving irinotecan based chemotherapy regimens, with the incidence being significantly higher in patients receiving mFOLFIRINOX (78.4%) compared to other irinotecan based chemotherapy regimens. Yoshida et al[17] also reported that the incidence of grade ≥ 3 neutropenia was 83.9% in advanced pancreatic cancer patients receiving mFOLFIRINOX therapy in a phase II study. Recently, a study showed that 62 patients (51%) and 10 patients (8%) developed severe neutropenia and FN in patients with advanced pancreatic cancer, respectively.[18]

However, the analysis in this study showed the incidence of irinotecan induced severe neutropenia to be 5.23%, which was lower compared with that of irinotecan induced severe neutropenia in the other studies (20.3%–83.9%).[15–18] For instance, according to tumor type, their incidences during chemotherapy were: lung cancer (10.46%), colonic cancer (3.66%), rectal cancer (3.80%) and gastric cancer (3.13%), ovarian cancer(5.00%), respectively. The variation in the incidence of irinotecan induced severe neutropenia may be attributed to the differences in patients characteristics, genotypes of UGT1A1, tumor type, irinotecan based regmines, study design and the definition criteria of severe neutropenia (≥grade 3 or grade 4). Therefore, the results motivated us to further explore these risk factors of irinotecan induced severe neutropenia in order to reduce the incidence of severe neutropenia.

According to this study, the median time interval from the initiation of treatment to the onset of severe neutropenia was 12.34 ± 9.45days. Of the 32 patients with severe neutropenia, 9 patients had severe neutropenia during the first week of treatment, while 32 patients had severe neutropenia within 4 weeks, suggesting that all patients should be considered for universal ANC test particularly during the first week of treatment in order to identify asymptomatic severe neutropenia and apply appropriate intervention in time.

Risk factors other than the UGT1A1 genotype may contribute to irinotecan induced severe toxicity, such as neutropenia. These nongenetic factors, such as organ functions, age, gender, comorbidities, and performance status, should therefore be comprehensively considered in predicting the risk of severe irinotecan related toxicities.[4,6–10] It was also reported that 35 Chinese patients (gastric cancer: 35.7%, 15/42; esophageal cancer: 22.0%, 20/91) developed severe neutropenia. No associations were found between severe neutropenia and patients sex, age, chemotherapy regimens, and so on, both in gastric and in esophageal cancer patients.[19] However, in the study, age, gender, smoke, drink, and hypertension and diabetes had no significant association with the incidence of severe neutropenia. Noteworthily, tumor type (*P* = .04), tumor stage(*P* = .000) and therapeutic regimen (*P* = .001) were risk factors of irinotecan induced severe neutropenia, respectively.

Several studies reported that old age was a potential risk factor for severe neutropenia induced by irinotecan. For example, sever neutropenia were seen somewhat more frequently in patients aged > 65 years.[20] However, studies suggest that elderly patients aged > 70 years can safely be treated with irinotecan or with irinotecan and 5-Fluorouracil/leucovorin.[21–23] In the study, age displayed no significant difference between severe neutropenia group and non-severe neutropenia group, implying older patients do not significantly increase the risk of irinotecan induced severe neutropenia than younger patients.

Although early studies indicated no significant association of gender with grade 3 or 4 toxicities, more recent findings suggest that gender is an independent predictor of the pharmacokinetic behavior of irinotecan.[24,25] Previous studies also found no significant differences in the frequency of sever neutropenia by gender,[26] which is similar to our study results.

In a study of 190 patients, smokers were found to have a higher clearance of irinotecan (*P* = .001), lower systemic exposure to SN-38 (*P* < .001) and a higher metabolic conversion of SN-38 to its glucuronide (*P* = .006). In addition, smokers experienced less hematologic toxicity (grade 3 or 4 leucopenia *P* = .006, neutropenia *P* < .001) and there was a tendency towards lower incidence of grade 3 or 4 diarrhea in smokers.[27] However, smoke had no significant relation to sever neutropenia in the study.

The risk of developing neutropenia during chemotherapy is dependent on a variety of factors including the type of cancer, the chemotherapy regimen used, patient characteristics, and including a low neutrophil count at baseline.[13]

As shown in Table 1 and Table 2, therapeutic regimen was significant difference between non-severe neutropenia group and severe neutropenia group. Noteworthily, irinotecan platinum

combination therapy showed higher incidences of severe neutropenia in comparison with other irinotecan based regimens. The multivariate stepwise analysis exhibited that irinotecan plus lobaplatin regimen (OR [95% CI], 1.389 [0.943–3.689]; P = .046) was found to be significant risk factors for irinotecan induced severe neutropenia among these patients. Interestingly, irinotecan plus 5-fluorouracil was most frequently used in these patients receiving irinotecan based regimens, but its incidence of severe neutropenia was lower than the other irinotecan based regimens.

Although previous studies have analyzed irinotecan induced severe neutropenia during chemotherapy,[9] these studies seldom consider the difference among between these irinotecan based regimens. In the study, irinotecan plus platinum combination therapy (6.35%–17.31%) show higher incidence of irinotecan induced severe neutropenia than the other irinotecan based regimens (2.12%–5.26%). The further study results showed that irinotecan plus lobaplatin (OR [95% CI], 1.389 [0.943–3.689]; P = .046) could significantly increase the risk for severe neutropenia, while irinotecan plus 5-fluorouracil (2.12%) might be more safer during chemotherapy.

The previous studies have found advanced disease (i.e., higher disease stage or bone marrow involvement) to be a significant predictor of chemotherapy induced severe neutropenia or febrile neutropenia. These studies were performed in various cancers, including breast, ovarian, lung, colorectal, and prostate cancer.[12] In the study, the middle–advanced tumor stages (T_2–T_4 tumor stages, 2.56%–14.43%) showed the higher incidences of irinotecan induced severe neutropenia compared to T_0 to T_1 tumor stage (1.33%), respectively. The tumor stage T_2 (OR [95%CI], 1.120 [0.032–2.456]; P = .019), T_3 (OR [95%CI], 2.327 [1.134–7.797]; P = .014) and T_4 (OR [95%CI], 5.191 [0.025–12.584]; P = .002), were found to be significant risk factors for irinotecan induced severe neutropenia, which support those previous study results.[13]

In addition, the type of malignancy is also a significant predictor of severe and febrile neutropenia.[12] In the study, lung cancer (OR [95%CI], 1.026 [0.001–2.650]; P = .026) and ovarian cancer (OR [95%CI], 1.013 [0.001–2.572]; P = .025) might be potential risk factor of irinotecan induced severe neutropenia. Notably, lung cancer have the highest incidence of irinotecan induced severe neutropenia among those tumor types.

On the basis of above results, the middle advanced lung cancer patients might be more likely to have severe neutropenia during receiving irinotecan lobaplatin combination therapy.

There are some limitations in the study. First, the study may be limited by its retrospective design. The available data is not enough or completely dependent on the case record, and researchers could not follow the patients and manage severe neutropenia during therapy. Second, the study did not collect patients' information on performance status, bodyweight, hepatic function, renal function and comedication and dietary supplements, and which might be risk factors for severe neutropenia.

5. Conclusion

The incidence of irinotecan induced severe neutropenia in this study was 5.23%, was lower than that of previously studies, possibly reflecting the appropriate use of irinotecan in this clinical setting. Tumor type (lung cancer or ovarian cancer), tumor stage (T_2, T_3, and T_4) and therapeutic regimen (irinotecan plus lobaplatin), could increase the risk of developing severe neutropenia, and respectively. The vast majority of patients have a good prognosis after timely treatment. The middle advanced lung cancer patients might be more likely to have severe neutropenia during irinotecan lobaplatin combination therapy. Therefore, for patients with these risk factors, it may be advisable to actively consider optimum management to reduce the occurrence of irinotecan induced severe neutropenia.

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