Timing of chemotherapy-induced neutropenia is a prognostic factor in patients with diffuse large B-cell lymphoma: a retrospective study

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Research Article

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Abstract

Background

Chemotherapy-induced neutropenia (CIN) has been shown to be associated with improved clinical outcomes in patients with various solid tumors. The aim of this study was to investigate the relationship between the timing and degree of chemo-induced neutropenia (CIN) and short-term efficacy and survival in newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL).

Methods

A retrospective study was conducted on 236 newly diagnosed DLBCL patients who received at least 6 cycles of R-CHOP (like) or CHOP (like) between January 2012 and December 2018. According to the occurrence time of CIN, subjects were divided into CIN-absent group, early-onset CIN group and late-onset CIN group. According to the degree of CIN, they were divided into CIN-absent group, mild (grade 1-2) CIN group, and severe (grade 3-4) CIN group. Short-term efficacy was evaluated after 4 cycles of treatment. The Kaplan-Meier method was used to draw the survival curve, and the Cox proportional hazards model was applied to determine the correlation between the timing and extent of CIN and clinical features, short-term efficacy, progression-free survival (PFS) and overall survival (OS).

Results

After 4 treatment cycles, the objective response rate (ORR) of the early-onset group was higher than that of in the late-onset group and CIN absent group (95.7% VS 88.4% VS 81.0%). Multivariate analysis, Ann Arbor staging, choice of treatment plan and CIN timing were the independent prognostic factors for OS and PFS. OS and PFS in the early-onset group were longer than those of in the absent group [OS (*HR*:0.241; *95%CI*: 0.110-0.530; *P* < 0.001), PFS (*HR:* 0.313; *95%CI*: 0.169-0.579; *P* < 0.001)] and late-onset group [OS (HR: 0.332; *95%CI*: 0.161- 0.685; *P* = 0.003), PFS (*HR*: 0.376; *95%CI*: 0.204-0.693; *P* = 0.002)].

Conclusions

The timing of CIN is an independent predictor of prognosis in DLBCL patients treated with R-CHOP (like) or CHOP (like) regimens, and patients with early-onset CIN have longer survival times. The degree of CIN is not an independent predictor of prognosis in patients with DLBCL.

Background

DLBCL is the most common subtype of adult non-Hodgkin's lymphoma [1, 2], and its morbidity and mortality rates have been steadily increasing in China[3, 4]. The current first-line standard treatment for DLBCL is a combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) or the latter 4 without rituximab (CHOP) [5], both of which can cure about 50–60% of patients. However, for patients who had failed prior treatment or relapsed after remission, outcomes were particularly poor[6]. In the past, when exploring better initial treatment options, other treatment schemes have failed to show a better effect than CHOP or R-CHOP; therefore, improving the therapeutic effect of CHOP or R-CHOP and improving DLBCL prognosis are areas worth exploring.

DLBCL is a chemotherapy-sensitive cancer, and the curative effect is proportional to the drug dose to a certain extent; therefore, it is worth studying individualised therapeutic doses to improve the curative effect. Through evaluations before and during treatment, an individualised chemotherapy plan can be made by adjusting the dose in time to determine the ideal amount for each patient. In R-CHOP or CHOP treatment regimens, the common adverse reaction is

neutropenia[7, 8], a major factor that leads to the reduction of subsequent doses and additional treatment costs[9, 10]. However, the occurrence of CIN seems to represent dose intensity, and may be related to DLBCL prognosis. Michael et al. [11]studied the relationship between CIN severity and prognosis in 965 DLBCL patients after the first cycle of R-CHOP treatment, and found that grade 1–2 CIN had the best prognosis (Grade 0 patients had a 67% 5-year overall survival rate grade 1–2: 78%, grade 3: 64%, and grade 4: 57%.). Similarly, for gastric cancer[12], lung cancer[13], pancreatic cancer[14], breast cancer[15], colorectal cancer[16] and other diseases, it has been shown that the occurrence of CIN is related to prognosis. Additionally, CIN timing also seems to be associated with survival, although previous research has shown that the dividing line between early and late occurrence differs. At present, studies have shown that the early onset of CIN in gastric cancer[17], lung cancer[18, 19], pancreatic cancer [20] and colon cancer [21] indicates a longer survival time. However, the relationship between CIN timing and DLBCL prognosis is not clear.

The purpose of this study was to examine the relationship between the timing and degree of CIN in newly diagnosed DLBCL patients treated with R-CHOP and the short-term efficacy and prognosis, in order to improve the initial treatment efficacy of DLBCL and achieve a better prognosis.

Methods

Patients

Patients diagnosed with DLBCL and admitted to Shandong Cancer Hospital from November 2011 to December 2018 were enrolled in this retrospective study. Approval was granted by the Ethics Committee of Shandong Cancer Hospital, and all clinical records came from the electronic medical record database of Shandong Cancer Hospital.

The study criteria were as follows: 1) confirmation of DLBCL by pathological diagnosis with no prior treatment; 2) at least 6 cycles of CHOP or CDOP (liposome doxorubicin instead of epirubicin) or R-CHOP or R-CDOP regimen after diagnosis and a standard dose initial treatment regimen; 3) no bone marrow infiltration. The exclusion criteria were as follows: 1) incomplete bone marrow toxicity records; 2) lack of follow-up; 3) primary diffuse large B-cell lymphoma of the central nervous system or transformed large B-cell lymphoma of the central nervous system; 4) primary treatment in other hospitals; 5) presence of second or multiple cancers. According to the inclusion and exclusion criteria, 236 patients with DLBCL were identified and chosen for this study. The specific selection criteria are shown in Figure 1.

Treatment regimen and dose intensity

To reduce the deviation caused by the number of treatment cycles, all patients received at least 6 cycles of first-line treatment with CHOP (like) or R-CHOP (like) regimens. The initial chemotherapy doses were cyclophosphamide (750 mg/m2, Vi, d1), doxorubicin (50 mg/m^2, Vi, d1-2), vincristine (1.4 mg/m^2, maximum 2 mg, Vi, d1) and prednisone (100 mg, d1-5) with or without rituximab (375 mg Vi, d0). Each cycle was 21 days. Granulocyte colony-stimulating factor (G-CSF) was used when there was grade 3-4 neutropenia, but prophylactic treatment without neutropenia was prohibited.

Assessment of neutropenia

Routine blood tests were performed every 3-5 days from the first day of chemotherapy until the following cycle. In this study, CIN severity was determined by the minimum absolute neutrophil count (ANC) in the peripheral blood tested during this period. According to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0), CIN severity is defined as follows: Grade 1, ANC 1.5-2.0 x 10^9 / L; Grade 2, ANC 1.0-1.5 x 10^9 / L; Grade 3, ANC 0.5-1.0 x 10^9 / L; and Grade 4, ANC 0-0.5 x 10^9 / L. Absence of CIN is defined as ANC > 2.0 x 10^9 / L. Grade 1 and Grade 2 neutropenia are considered mild neutropenia, and Grade 3 and Grade 4 neutropenia are considered severe neutropenia. According to the CIN occurrence times, CIN occurring during the third cycle of treatment

was regarded as the bound, early-onset was CIN occurring during weeks 1-3, late-onset was CIN occurring during the fourth cycle or later, and absence of CIN was no CIN occurrence during the entire treatment. Among them, the late-onset group and CIN-absent group were collectively referred to as the non-early-onset group.

Efficacy and survival assessment

Efficacy was evaluated according to imaging remission (CT/MRI) or metabolic remission (PET/CT)[22] as per the revised 2014 Lugano criteria. Efficacy was evaluated every two cycles after treatment and divided into complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD). The objective response rate (ORR) was the proportion of patients with CR and PR.

The follow-up end points were OS and PFS, and the follow-up deadline was January 30, 2021. OS is defined as the duration from the beginning of treatment to date of death for any cause. PFS is defined as the duration from the beginning of treatment to time of tumor progression or death of any cause.

Statistical analysis

IBM SPSS Statistics software (version 22.0) and GraphPad Prism software (version 5.0) were used for the statistical analysis and to generate the graphs. Descriptive statistics was used to describe the baseline characteristics of patients, and a chi-square test was used to compare the baseline characteristics. The Kaplan-Meier method (logarithmic rank test) was used to construct the survival curve. Prognostic factors of OS and PFS were determined through univariate and multivariate Cox regression (enter method) analyses. Variables with $P<0.1$ from the univariate analysis were entered into multivariate analysis. $P < 0.05$ was defined as a statistically significant difference.

Results

Demographics

A total of 236 eligible patients were included in this study. The ratio of males to females was approximately 1:1.3, and the median age was 54.9 years (18-80 years). 165/236 patients (69.9%) were treated with a R-CHOP (like) regimen, and 71/236 patients (30.1%) were treated with a CHOP (like) regimen. During treatment, 42/236 patients (17.8%) were CIN-absent, 166/236 (70.3%) had early-onset CIN, and 28/236 (11.9%) had late-onset CIN. In addition to CIN degree, there was a balanced distribution among patients with different CIN timings in terms of sex, age, IPI score, Ann Arbor stage and treatment regimen. Baseline characteristics of the 236 patients and the distribution among groups according to CIN timing are shown in Table 1(See the table at the end of this article).

CIN and short-term efficacy

A total of 232 patients who underwent 4 treatment cycles were evaluated by imaging, of which 214 patients achieved ORR. The correlation between the efficacy of 4 treatment cycles and CIN timing is shown in Table 2 (See the table at the end of this article). The ORR of the early-onset group was higher than that of the late-onset group and CIN-absent group (95.7% VS 88.4% VS 81.0%).

Survival analysis

The median follow-up period of all 236 patients was 42.5 months (5-109 months), and total PFS and total OS were not achieved during the median period. During the follow-up period, 53/236 patients (22.5%) died and 81/ 236 (34.3%) relapsed. The Kaplan-Meier survival curves drawn according to CIN timing and CIN degree are shown in Figure 2 and Figure 3, respectively. As shown in Figure 2, when using Kaplan-Meier analysis, every survival curve was meaningful

regardless of the treatment regimen used, and the OS and PFS of the early-onset group were longer than those of the non-early-onset group.

To evaluate the prognostic values of CIN timing and degree, we performed univariate and multivariate COX regression analysis. The analysis results are shown in Table 3(See the table at the end of this article). Univariate analysis showed that IPI score, Ann Arbor stage, treatment regimen, CIN degree and CIN timing were significant factors affecting the prognosis of OS and PFS. Multivariate analysis showed that Ann Arbor stage, choice of treatment and CIN timing were independent prognostic factors of OS and PFS. The OS and PFS in the early-onset group were longer than those of in the absent group [OS (*HR*:0.241; *95%CI*: 0.110-0.530; $P < 0.001$), PFS (*HR*: 0.313; *95%CI*: 0.169-0.579; $P < 0.001$)] and late-onset group [OS (*HR*: 0.332; *95%CI:* 0.161-0.685; $P = 0.003$), PFS (*HR*: 0.376; *95%CI*: 0.204-0.693; $P = 0.002$)]. However, no independent correlation was observed between CIN degree and PFS and OS.

Discussion

Although CIN is the most common adverse reaction in cancer patients post-treatment, its occurrence and severity does not represent a poor prognosis. This study is the first to report on the relationship between CIN timing and degree and survival in DLBCL patients. Studies have shown that CIN timing is an independent prognostic factor for patients with DLBCL. We found that the PFS and OS in the early-onset CIN group were significantly longer than those of in the non-early-onset group (late-onset and absent CIN), which is consistent with the findings of previous studies on other types of cancers.

In several different cancers, the early occurrence of CIN represents a good prognosis. He et al.[23] studied the relationship between CIN timing and survival after 6 cycles of carboplatin combined with paclitaxel in patients with primary serous ovarian cancer. They found that the median PFS of the early-onset group VS non-early-onset group was 23 months VS 9 months ($P < 0.001$), and the median OS of the early-onset group VS non-early-onset group was 55 months VS 24 months ($P < 0.001$), and concluded that the early onset of CIN can significantly improve PFS and OS. Similar results have also been found in studies on gastric cancer[17], colorectal cancer [21] and other diseases. Although these findings are consistent with our results, it is worth noting that our results also showed no difference in PFS（$P=0.645$） and OS（$P=0.500$）between patients with late-onset CIN and absent CIN in the non-early-onset group.

The specific mechanism of the good survival of patients with early-onset CIN is not clear, which may be related to the following points: 1) Early-onset CIN may indicate that patients are sensitive to drugs. Kvinnsland [24]stated that the sensitivity of treatment is a reflection of genetic susceptibility, and the sensitivity of neutrophils and cancer cells to drugs is theoretically the same. Non-early-onset CIN indicates less chemosensitivity and drug resistance, which possibly explains why the short-term effect seen in the early-onset group was better than that of the late-onset group and absent group. 2) CIN reflects the chemotherapy dose and pharmacokinetics of patients. The standard dose of R-CHOP or CHOP is calculated based on body surface area (BSA). However, due to individual differences in pharmacokinetics and pharmacodynamics, the drug dose calculated by BSA may lead to drug dose deficiency in certain patients[25-27]. CIN occurrence may indicate that a patient received an adequate treatment dose. 3) Neutrophils are related to the progression or prognosis of tumours. Studies have shown that neutrophils play an important role in cancer progression by interacting with cancer cells and immune cells in the blood and tumour microenvironment (TME). They are involved in a variety of functions that promote tumour growth, including proliferation, invasiveness and spread, and immunosuppression[28-30]. In addition, tumour-related neutrophils (TANs) are closely related to a patient's prognosis. Manfroi et al. [31] analysed the relationship between TANs and prognosis in 233 DLBCL patients using the R-CHOP regimen, and used the neutrophil elastase (ELANE) gene as a marker of TAN infiltration. The results

showed that the high expression of ELANE was associated with decreased overall survival (*HR*=2.3, *95% CI*: 1.2-4.3, *P*=0.01), which suggests that DLBCL patients with increased TANs may have a poor prognosis.

Additionally, our study shows that CIN occurrence is not an independent prognostic factor of PFS and OS, which differs from the results of Michael et al.[11], who found that grade 1-2 CIN leads to the best prognosis (5-year overall survival rate of patients with grade 0 was 67%, grade 1-2 was 78%, grade 3 was 64%, and grade 4 was 57%). The reasons for the differences in results may be as follows: 1) the cut-off points for evaluating CIN degree between the two studies were different. The cut-off point for Michael et al.'s study was the CIN degree after the first treatment cycle, while our study was based on the third cycle. If CIN occurred during the first three cycles, the lowest CIN degree of the previous three cycles was taken as the cut-off point. Otherwise, the cut-off point was the lowest CIN degree that occurred in the following cycle. 2) The total number of treatment cycles was different. There was no requirement for the number of treatment cycles in Michael et al.'s study, but at least 6 treatment cycles were required in this study, which may have excluded certain patients who could not complete 6 cycles of chemotherapy due to age, poor physique, severe myelosuppression and other reasons.

However, there were several limitations in this study. 1) This study was a single-center retrospective study, and the sample size was limited.2) The follow-up time was relatively short, and no end point event occurred in many patients. Despite these limitations, our study still suggests that it seems possible to adjust the dose according to the presence of CIN in 1-3 cycles and choose the appropriate dose for each patient to achieve a better therapeutic efficacy of DLBCL. Of course, this needs to be verified by prospective tests.

Conclusion

The results of the present study suggest that CIN timing onset is a potential prognostic marker in newly diagnosed DLBCL patients who receive 6 cycles of R-CHOP or CHOP regimens, and early onset CIN leads to a better prognosis.

Abbreviations

CIN: Chemotherapy-induced neutropenia

DLBCL: Diffuse large B-cell lymphoma

PFS: Progression-free survival

OS: Overall survival

ORR: Objective response rate

G-CSF: Granulocyte colony-stimulating factor

ANC: Absolute neutrophil count

NCI: National Cancer Institute

CTCAE: Common Terminology Criteria for Adverse Events

CR: Complete response

PR: Partial response

SD: Stable disease

PD: Progression disease

BSA: Body surface area

TME: Tumor microenvironment

TAN: Tumor-related neutrophil

Declarations

Ethics approval and consent to participate

The research was performed following international and national regulations in accordance with the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of the Shandong Cancer Hospital (No. SDTHEC2021001023). Prior to treatment, all patients or legal guardians had signed a written informed consent

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

LHS and JQ carried out the studies, participated in collecting data, and drafted the manuscript. JQ and BXZ performed the statistical analysis and participated in its design. BB and SF helped to draft the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Clinical characteristics of DLBCL patients according to the occurrence time of CIN

	No.（%） (n=236)	Timing of CIN			*P* value
		absent group (n=42)	Early-onset (n=166)	Late-onset (n=28)	
Sex					0.281
Male	103(43.6)	21（50.0）	67（40.4）	15（53.6）	
Female	133(56.4)	21(50.0）	99（59.6）	13(46.4）	
Age (years)					0.780
≤60	162(68.6)	27(64.3)	116(69.9)	19(67.9)	
＞60	74(31.4)	15(35.7)	50(30.1)	9(32.1)	
IPI score					0.570
0-2	146(61.9)	28(66.6)	104(62.6)	14(50.0)	
3-4	83(35.2)	13(31.0)	58(35.0)	12(42.9)	
DD[1]	7(2.9)	1(2.4)	4(2.4)	2(7.1)	
Ann Arbor staging criteria					0.338
I-II	116(49.1)	24(57.1)	81(48.8)	11(39.3)	
III-IV	120(50.9)	18(42.9)	85(51.2)	17(60.7)	
Treatment regimen					0.626
CHOP (like)	71(30.1)	15(35.7)	47(28.3)	9(32.1)	
R-CHOP (like）	165(69.9)	27(64.3)	119(71.7)	19(67.9)	
The degree of CIN					0.000
Grade 0	42(17.8)	42(100.0)	0(0.0)	0(0.0)	
Grade 1-2	94(39.8)	0(0.0)	76(45.8)	18(64.3)	
Grade 3-4	100(42.4)	0(0.0)	90(54.2)	10(35.7)	

Note: Data are displayed as a count or percentage.

1DD：Data Deficient

Table 2 CIN and short-term efficacy

	N (n=232)	CR+PR (n=214)	SD+PD (n=18)	*P* value
CIN-absent group	42	34	8	0.01
early-onset group	164	157	7	
late-onset group	26	23	3	

Table 3 Univariate and multivariate analyses of OS and PFS in relation to clinical parameters

Variable	Overall survival				Progression-Free Survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	AHR (95% CI)	p-value	HR (95% CI)	p-value	AHR (95% CI)	p-value
Sex								
Male	0.800(0.466-1.373)	0.419	-	-	1.012(0.652-1.571)	0.958	-	-
Female								
Age (years)								
≤60	1.408(0.807-2.457)	0.229	-	-	1.281(0.813-2.020)	0.286	-	-
>60								
IPI score								
0-2	4.137(2.294-7.461)	<0.001	2.012(0.983-4.123)	0.056	3.095(1.959-4.890)	<0.001	1.406(0.807-2.449)	0.229
3-5								
Ann Arbor staging criteria								
I-II	5.583(2.724-11.441)	<0.001	4.605(1.906-11.126)	0.001	4.332(2.563-7.321)	<0.001	4.331(2.243-8.363)	<0.001
III-IV								
Treatment regimen								
CHOP-like	0.368(0.214-0.632)	<0.001	0.282(0.156-0.510)	<0.001	0.533(0.342-0.830)	0.005	0.448(0.278-0.722)	0.001
R-CHOP-like								
The degree of CIN								
Grade 1-2 VS Grade 0	0.608(0.309-1.198)	0.151	1.061(0.447-2.521)	0.892	0.713(0.410-1.241)	0.232	1.188(0.586-2.108)	0.633
Grade 3-4 VS Grade 0	0.486(0.241-0.980)	0.044	0.727(0.288-1.836)	0.500	0.488(0.274-0.872)	0.015	0.832(0.379-1.823)	0.645
Grade 1-	1.251(0.666-	0.486	1.460(0.742-	0.273	1.461(0.881-	0.142	1.428(0.835-	0.193

2VS Grade 3-4	2.349)		2.875)		2.422)		2.443)	
Timing of CIN								
Early-onset VS Absence	0.410(0.213-0.788)	0.008	0.241(0.110-0.530)	<0.001	0.481(0.283-0.817)	0.007	0.313(0.169-0.579)	<0.001
Late-onset VS Absence	1.509(0.708-3.216)	0.287	0.727(0.288-1.836)	0.500	1.451(0.759-2.774)	0.260	0.832(0.379-1.823)	0.645
Early-onset VS Late-onset	0.271(0.139-0.531)	<0.001	0.332(0.161-0.685)	0.003	0.332(0.189-0.582)	<0.001	0.376(0.204-0.693)	0.002

Figures

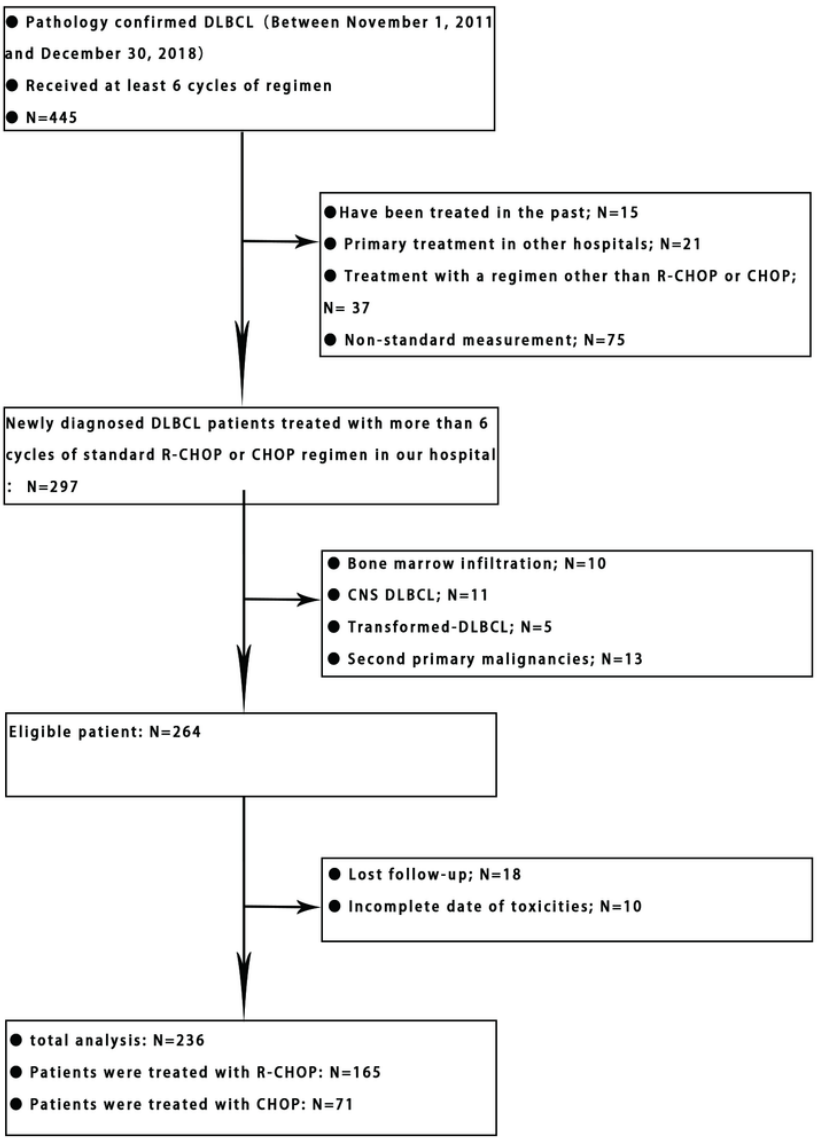

Figure 1

Study flowchart.

Figure2

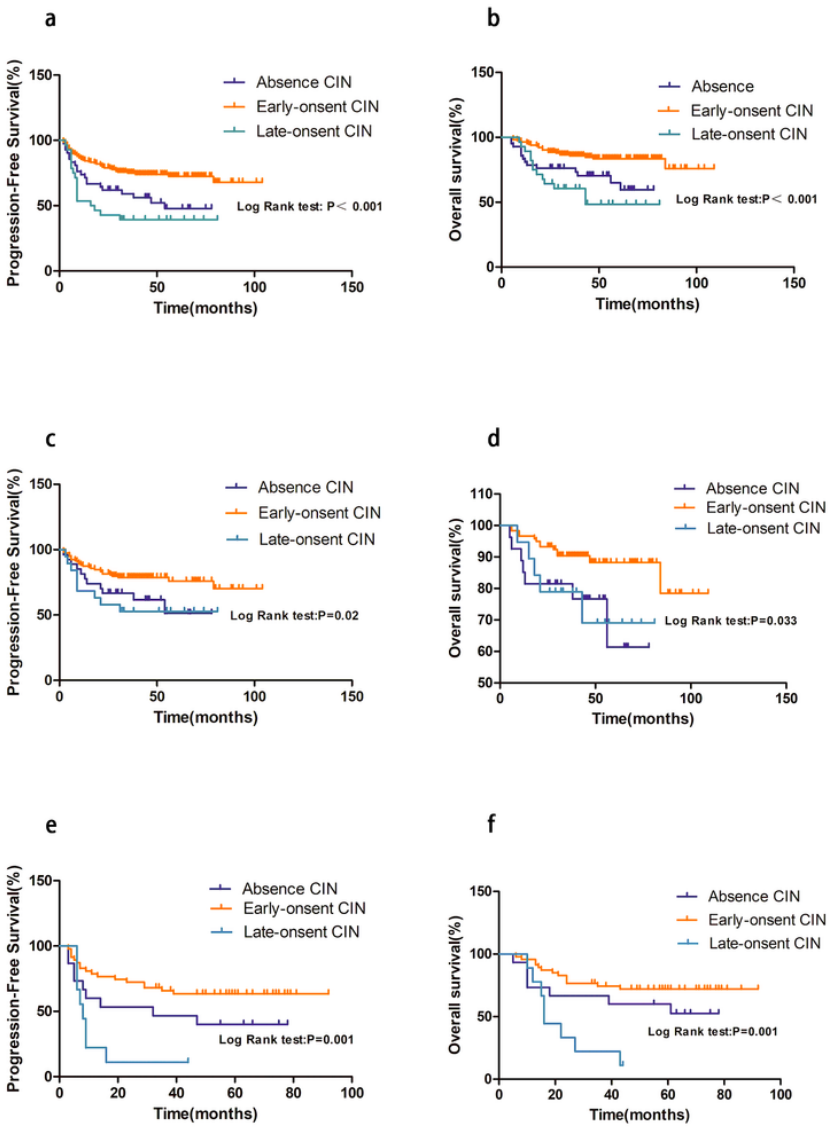

Figure 2

The Kaplan-Meier survival curves of total PFS (a) and total OS (b) were stratified according to the timing of CIN occurrence, and the Kaplan-Meier survival curves of PFS (c) and OS (d) treated with R-CHOP regimen were used, and the Kaplan-Meier survival curves of PFS (e) and OS (f) treated with CHOP regimen were used. No matter what treatment regimens were used, PFS and OS in the early-onset group were better than those in the non-early-onset group.

Figure3

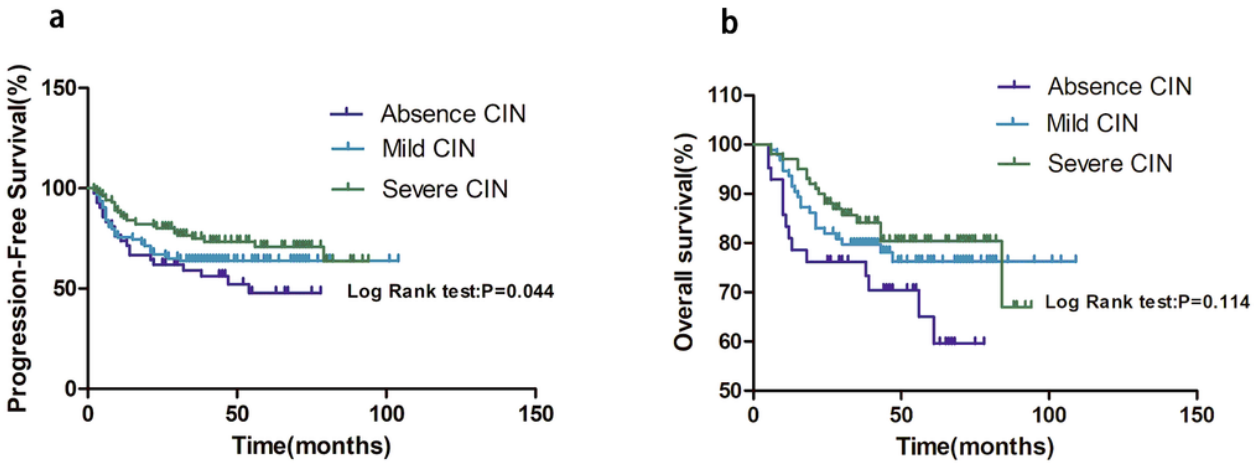

Figure 3

According to the stratification of the occurrence degree of CIN, the survival curves of PFS and OS are shown in figures 3a and 3b. 3a: The PFS of severe (grade 3-4) CIN group was better than that of mild (grade 1-2) CIN group and CIN deletion group. 3b: There was no significant difference in OS among the severe CIN group, mild CIN group and CIN deletion group.