

# Incidence of interstitial pneumonitis in non-Hodgkin's lymphoma patients receiving immunochemotherapy with pegylated liposomal doxorubicin and rituximab

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Received: 4 July 2017 / Accepted: 23 October 2017 / Published online: 31 October 2017  
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**Abstract** Pneumonitis is a rare but severe and potentially fatal adverse effect in chemotherapy of lymphoma. This study is aimed to investigate the incidence of interstitial pneumonitis in non-Hodgkin's lymphoma (NHL) patients receiving immunochemotherapy with pegylated liposomal doxorubicin and rituximab. Lymphoma patients were retrospectively reviewed, and eligible patients were included in this study. According to the chemotherapy regimens, patients were classified in four groups: combination of vincristine, cyclophosphamide, doxorubicin, and prednisone (CHOP group) with rituximab (RCHOP group) and combination of vincristine, cyclophosphamide, pegylated liposomal doxorubicin and prednisone (CDOP group) with rituximab (RCDOP group). Incidence and severity of interstitial pneumonitis were compared among the four groups. Among 757 patients reviewed, 207 patients were included in final analysis. Thirteen patients developed chemotherapy-induced interstitial pneumonitis, and the mean cycle of chemotherapy before the onset of pneumonitis was 4. Incidence rates of pneumonitis were 0, 1.8, 17.4, and 21.1% in CHOP, RCHOP, CDOP, and RCDOP groups, respectively ( $p < 0.001$ ). The mean grades of pneumonitis were 0, 2, 2.5, and 3 in four groups, respectively ( $p < 0.001$ ). After adjustment of confounders, chemotherapy regimens (OR 3.491, 95% CI 1.527–7.981,  $p = 0.003$ ) and neutropenia in previous cycles (OR 2.186, 95% CI 1.281–3.731,  $p = 0.004$ ) were independently associated with the

incidence of pneumonitis. Interstitial pneumonitis should be highlighted in NHL patients who received more than 4 cycles of RCDOP chemotherapy regimen, especially in those who had grade 4 neutropenia in the previous cycles of chemotherapy.

**Keywords** Non-Hodgkin's lymphoma · Interstitial pneumonitis · Pegylated liposomal doxorubicin · Rituximab · Chemotherapy

## Introduction

Non-Hodgkin's lymphoma (NHL) is one of the most common tumors in the world [1, 2], and its incidence has significantly increased in recent decades [3]. It comprises a group of diverse subtypes, such as diffuse large B cell lymphoma (DLBCL), Follicular lymphoma (FL), mucosa-associated lymphoid tissue lymphoma (MALT), mantle cell lymphoma (MCL), and peripheral T cell lymphoma (PTCL) [4, 5]. Among the diverse subtypes of NHL, DLBCL is the most frequent subtype and represents more than 30% of NHL in adults [6]. Ever since the anti-CD20 monoclonal antibody rituximab was developed and used clinically, the prognosis of NHL was dramatically improved [7–9]. At present, the combination of vincristine, cyclophosphamide, doxorubicin, and prednisone (CHOP) with rituximab (R) is the standard treatment for non-Hodgkin's lymphoma [10].

However, NHL patients receiving RCHOP regimen always suffer several treatment-related adverse effects including hematologic toxicities, infections, alopecia, or cardiologic complications [11, 12], and doxorubicin is the agent with most frequent side effects in the RCHOP regimen, especially cardiac toxicity [13, 14]. A new formulation of doxorubicin, called pegylated liposomal doxorubicin, has extended circulation

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time and reduced volume of distribution than doxorubicin [15]. Previous studies suggested that the cardiotoxicity of pegylated liposomal doxorubicin was less than doxorubicin [16–19], and the combination of vincristine, cyclophosphamide, pegylated liposomal doxorubicin, and prednisone (CDOP) with rituximab (R) was an alternative regimen for non-Hodgkin's lymphoma used in clinical practice [18, 20, 21].

Apart from cardiotoxicity, pneumonitis is also a severe and potentially fatal adverse effect in chemotherapy of lymphoma. It was reported that the addition of rituximab to CHOP regimen increased the incidence of interstitial pneumonitis in patients with NHL [22–25]. In addition, several case reports [26–28] or small sample studies [20, 29–32] highlighted that interstitial pneumonitis was a more frequent and potentially fatal side effect of pegylated liposomal doxorubicin.

To date, there is still lack of studies focused on incidence of pneumonitis in NHL patients receiving immunochemotherapy of RCDOP, and whether the combination of rituximab and pegylated liposomal doxorubicin increase the incidence of pneumonitis is still unclear. Therefore, the aim of this study is to investigate the incidence and severity of treatment-related interstitial pneumonitis among patients receiving chemotherapy of CHOP, RCHOP, CDOP, and RCDOP and also to identify variables associated with incidence of pneumonitis.

## Methods

### Patients and data collection

Lymphoma patients between December 2014 to June 2017 who were treated in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology were retrospectively reviewed. Patients who received RCHOP, CHOP, RCDOP, or CDOP were included in this study. Patients who had uncertain diagnosis or received less than 2 cycles of chemotherapy were excluded. This study was reviewed and approved by the Tongji Medical College Research Ethics Board.

Patients' baseline demographic and clinical characteristics including gender, age, lymphoma types, and Ann Arbor stages were collected from medical records. Chemotherapy-related information including chemotherapy regimen and cycles, chemotherapy-induced neutropenia, and chemotherapy-induced symptoms of pneumonitis (e.g., cough, fever, chest congestion, or dyspnea) were reviewed during the whole treatment. Moreover, information of chest computed tomography (CT) scans performed on patients with clinical indications of pneumonitis were recorded.

### Chemotherapy-induced interstitial pneumonitis

Patients with chest CT scans showed interstitial pulmonary infection and any concomitant symptoms of pneumonitis including fever, cough, chest congestion, or dyspnea were considered as symptomatic pneumonitis. Chemotherapy-induced pneumonitis was defined as symptomatic pneumonitis which occurred within 60 days of the most recent chemotherapy cycle that could not be explained by other factors, such as lymphoma pulmonary invasion or radiation-induced pneumonitis. Incidence and severity of symptomatic pneumonitis were investigated in this study.

### Statistical analysis

Patients' demographic and clinical characteristics were summarized by descriptive statistics. Category variables were compared among NHL patients receiving CHOP, RCHOP, CDOP, and RCDOP regimens through chi-square test, but when more than one-fifth expected frequencies  $< 5$  or one expected frequency  $< 1$ , Fisher's exact test was used instead. For continuous variables, one-way ANOVA was used for comparison of the four groups in variables with variance homogeneity; otherwise, Kruskal-Wallis Test was used instead. In order to adjust for confounders of baseline demographic and clinical characteristics, such as gender, age, Eastern Cooperative Oncology Group (ECOG), lymphoma types, stages, international prognostic index (IPI), and chemotherapy cycles, multivariate logistic regression was applied for analysis of factors associated with incidence of pneumonitis. SPSS version 18.0 was used for statistical analyses and  $p$  value  $< 0.05$  was defined as statistically significant.

## Results

A total of 757 patients with lymphoma were reviewed. Among them, 389 patients who did not receive CHOP, RCHOP, CDOP, or RCDOP as their chemotherapy regimen and 161 patients who received less than 2 cycles of chemotherapy were excluded. Finally, 207 patients with non-Hodgkin's lymphoma were included for analysis.

According to chemotherapy regimen, 207 patients were classified in four groups: CHOP group ( $n = 89$ ), RCHOP group ( $n = 57$ ), CDOP group ( $n = 23$ ), and RCDOP group ( $n = 38$ ). Patients' demographic and clinical characteristics were summarized in Table 1. The mean ages of the four groups were 52, 46, 49, and 51 years, respectively ( $p = 0.070$ ). Female patients were more than male patients in CHOP group (55.1%) and less than male patients in RCHOP (35.1%), CDOP (21.7%), and RCDOP (42.1%) groups ( $p = 0.012$ ). None of patients had Eastern Cooperative Oncology Group (ECOG) more than 3, and the majority of

**Table 1** Patients' demographic and clinical characteristics ( $n = 207$ )

	CHOP( $n = 89$ )	RCHOP( $n = 57$ )	CDOP( $n = 23$ )	RCDOP( $n = 38$ )	$p$ value
Mean age (SD) (years)	52(11)	46(13)	49(14)	51(16)	0.070
Gender					0.012
Male	40(44.9%)	37(64.9%)	18(78.3%)	22(57.9%)	
Female	49(55.1%)	20(35.1%)	5(21.7%)	16(42.1%)	
ECOG					0.252
0–1	71(79.8%)	42(73.7%)	16(69.6%)	24(63.2%)	
2–3	18(20.2%)	15(26.3%)	7(30.4%)	14(36.8%)	
Lymphoma types					0.065
DLBCL	61(68.6%)	45(78.9%)	14(60.9%)	34(89.4%)	
FL	13(14.6%)	6(10.5%)	3(13.1%)	2(5.3%)	
MALT	6(6.7%)	1(1.8%)	1(4.3%)	0	
MCL	3(3.4%)	3(5.3%)	0	2(5.3%)	
Others	6(6.7%)	2(3.5%)	5(21.7%)	0	
Stages					0.581
I	7(7.9%)	6(10.5%)	2(8.7%)	5(13.2%)	
II	39(43.8%)	23(40.4%)	5(21.7%)	13(34.2%)	
III	26(29.2%)	12(21.0%)	8(34.8%)	12(31.6%)	
IV	17(19.1%)	16(28.1%)	8(34.8%)	8(21.0%)	
IPI					0.306
0–1	37(41.6%)	25(43.9%)	9(39.1%)	15(39.5%)	
2	25(28.1%)	15(26.3%)	2(8.7%)	10(26.3%)	
3	20(22.5%)	10(17.5%)	7(30.4%)	5(13.1%)	
4–5	7(7.8%)	7(12.3%)	5(21.8%)	8(21.1%)	
Mean chemotherapy cycle (SD)	5(2)	5(2)	3(1)	5(2)	< 0.001

patients had ECOG 0–1 ( $p = 0.252$ ). DLBCL was the most common diagnosis in our patients, and other common existing subtypes of lymphoma included FL, MALT, and MCL ( $p = 0.065$ ). About half of the patients were in advanced stage ( $p = 0.581$ ), and approximately 40% of patients were in low risk with international prognostic index (IPI) 0–1 ( $p = 0.306$ ). The mean cycles of chemotherapy were 5, 5, 3, and 5 in the four groups ( $p < 0.001$ ), respectively.

Among 207 patients, symptomatic interstitial pneumonitis occurred in 13 patients, and details of these patients were listed in Table 2. The median age of these patients was 49 years with a range of 20 to 72 years, and more than three quarters of patients were male patients. The most common subtype of lymphoma was DLBCL in our patients, and more than 60% of patients were in advanced stage (stage III/IV). The mean cycle of chemotherapy before pneumonitis was 4 in these patients, and they had a median grade 4 of neutropenia during chemotherapy cycles.

As shown in Fig. 1, 21.1, 17.4, and 1.8% of patients suffered symptomatic interstitial pneumonitis in RCDOP, CDOP, and RCHOP groups, respectively, and no patients experienced

pneumonitis in CHOP group. Incidence rates of pneumonitis in RCDOP and CDOP groups were apparently higher than RCHOP and CHOP groups, and the difference was statistically significant ( $p < 0.001$ ). The mean grades of pneumonitis were 0, 2, 2.5, and 3 in patients with pneumonitis in CHOP, RCHOP, CDOP, and RCDOP groups, respectively (Fig. 2). Interstitial pneumonitis was severe in RCDOP group than in CDOP group or RCHOP group, and the difference was statistically significant among the four groups ( $p < 0.001$ ). Among the 13 patients with pneumonitis, chemotherapy was not interrupted in four patients with grade 2 pneumonitis; in other two patients with grade 2 pneumonitis and two patients with grade 3 pneumonitis, rituximab was given up in the following chemotherapy cycles; chemotherapy was discontinued in other two patients with grade 3 pneumonitis and three patients with grade 4 pneumonitis.

As summarized in Table 3, chemotherapy regimens (OR 3.491, 95% CI 1.527–7.981,  $p = 0.003$ ) and neutropenia in previous cycles (OR 2.186, 95% CI 1.281–3.731,  $p = 0.004$ ) were independently associated with the incidence of pneumonitis, while patients' gender, age, ECOG, lymphoma types,

**Table 2** Summary data of cases of pneumonitis (*n* = 13)

Cases	Age (years)	Gender	Lymphoma type	Stages	Chest radiation (Y/N)	Chemotherapy	Cycles before pneumonitis	Grade of pneumonitis	Grade of neutropenia
1	30	Male	DLBCL	III	N	RCHOP	4	2	1
2	20	Male	DLBCL	II	N	RCDOP	5	2	3
3	44	Male	DLBCL	I	N	RCDOP	4	3	4
4	24	Female	DLBCL	IV	N	RCDOP	4	4	4
5	49	Female	DLBCL	II	N	RCDOP	4	4	4
6	46	Male	DLBCL	I	N	RCDOP	6	4	4
7	67	Male	DLBCL	IV	N	RCDOP	3	2	2
8	69	Male	DLBCL	III	N	RCDOP	3	2	4
9	72	Female	DLBCL	I	N	RCDOP	2	3	4
10	58	Male	DLBCL	IV	N	CDOP	2	2	4
11	70	Male	FL	IV	N	CDOP	5	2	2
12	49	Male	SLL	IV	N	CDOP	4	3	4
13	27	Male	MALT	III	N	CDOP	4	3	0

stages, IPI, and chemotherapy cycles were not associated with incidence of pneumonitis (all *p* > 0.05).

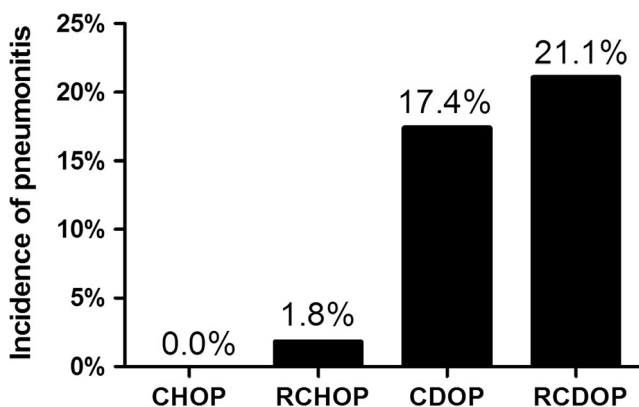
**Discussion**

To our knowledge, this study is among very rare studies that focused on interstitial pneumonitis in NHL patients receiving immunochemotherapy with rituximab and pegylated liposomal doxorubicin. In this study, we found that NHL patients receiving RCDOP regimen experienced highest prevalence and most severity of interstitial pneumonitis. Moreover, chemotherapy regimens and neutropenia in previous cycles were independently associated with the incidence of pneumonitis.

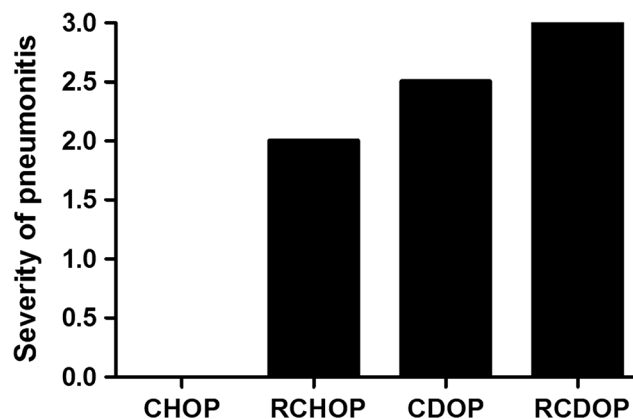
Several previous studies reported the incidence of interstitial pneumonitis in NHL patients receiving immunochemotherapy with rituximab. In the study of Liu X et al. [33], 8.4% of NHL patients receiving rituximab-containing chemotherapy

developed interstitial pneumonitis. In another study of Salmasi, G. et al. [34], incidence of interstitial pneumonitis was 3.95% in NHL patients receiving RCHOP or RCVP chemotherapy, and it was 1.3% in NHL patients receiving CHOP or CVP chemotherapy. In a study of interstitial pneumonitis in patients with diffuse large B cell lymphoma [35], interstitial pneumonitis was found in 4.9% of patients receiving first-line tri-weekly COP- or CHOP-based chemotherapy with or without rituximab. In another study of Katsuya, H. et al. [22], interstitial pneumonitis occurred in 1.7% of NHL patients receiving CHOP chemotherapy, and it occurred in 6.2% of NHL patients receiving RCHOP chemotherapy. In comparison with these studies, incidence of interstitial pneumonitis was lower in our patients with CHOP or RCHOP regimens, partly due to different populations and the different chemotherapy regimens included in these studies.

Interstitial pneumonitis of pegylated liposomal doxorubicin was reported in a few studies of patients with



**Fig. 1** Incidences of interstitial pneumonitis among non-Hodgkin's lymphoma patients receiving CHOP, RCHOP, CDOP, and RCDOP regimens



**Fig. 2** Severity of interstitial pneumonitis among non-Hodgkin's lymphoma patients receiving CHOP, RCHOP, CDOP, and RCDOP regimens

**Table 3** Logistic regression analysis for pneumonitis

Variables	OR	95%CI	<i>p</i> value
Chemotherapy regimens	3.491	1.527–7.981	0.003
Neutropenia in previous cycles	2.186	1.281–3.731	0.004
Gender	0.205	0.040–1.043	0.056
Age	0.990	0.945–1.038	0.691
ECOG	0.411	0.080–2.121	0.288
Lymphoma subtypes	1.115	0.613–2.025	0.722
Stages	1.611	0.556–4.669	0.380
IPI	0.944	0.365–2.442	0.906
Cycles of chemotherapy	0.952	0.665–1.361	0.787

hematological malignant tumors. In a phase II study of pegylated liposomal doxorubicin combination chemotherapy for patients with multiple myeloma [29], the incidence of pneumonitis was 15%. In another study of pegylated liposomal doxorubicin combination chemotherapy in Hodgkin's lymphoma patients [30], 5 of 30 patients experienced grades 3–5 pneumonitis. In comparison with these studies, incidence of interstitial pneumonitis of pegylated liposomal doxorubicin was higher in our results, and the reason could be the differences of chemotherapy regimens and diagnoses of patients in these studies.

Cardiotoxicity was always highlighted in studies of lymphoma patients receiving immunochemotherapy containing pegylated liposomal doxorubicin and rituximab [17–19, 36], but few studies reported the incidence of pneumonitis. In a phase II study of splenic marginal zone lymphoma [21], 51 patients received RCDOP immunochemotherapy; however, one patient died during treatment because of pneumonitis, which confirmed that pneumonitis was a severe and fatal adverse effect in patients receiving RCDOP regimen.

In our study, the mean cycle of chemotherapy before the onset of pneumonitis was four, which was consistent with the study of patients with DLBCL receiving rituximab-containing chemotherapy [35]. Apart from chemotherapy regimens, neutropenia was considered as another risk factor associated with the incidence of pneumonitis. Although no study has analyzed the association between neutropenia and pneumonitis in lymphoma patients, low lymphocyte count was reported as a risk factor for incidence of pneumonitis in previous studies [22, 35].

This study also had some limitations. Firstly, this study was a retrospective study and the respiratory symptoms of patients were reviewed from medical records, which may lead to information bias and influence the incidence and severity of interstitial pneumonitis in our patients. Secondly, a large number of patients were reviewed in our study, but many patients were excluded due to chemotherapy regimens other than CHOP/RCHOP/CDOP/RCDOP or use of less than 2 cycles of chemotherapy. The limited number of patients included in

each group, especially the low number of patients and low number of chemotherapy cycles in CDOP group, may affect the results of our study. Finally, this study was conducted in a single center, and the generalizability of our results may be limited.

In conclusion, incidences of interstitial pneumonitis were higher in NHL patients receiving RCDOP and CDOP regimens than RCHOP and CHOP regimens, and interstitial pneumonitis was severe in NHL patients receiving RCDOP chemotherapy than CDOP chemotherapy. Replacement of doxorubicin by pegylated liposomal doxorubicin in NHL patients receiving CHOP regimen with or without rituximab could increase the incidence of interstitial pneumonitis. Moreover, addition of rituximab in chemotherapy regimen of CDOP could aggravate the severity of interstitial pneumonitis. The mean cycle of chemotherapy before the onset of pneumonitis was four. Apart from chemotherapy regimens, neutropenia was also a risk factor that was independently associated with the incidence of pneumonitis. Therefore, interstitial pneumonitis should be highlighted in NHL patients who received more than 4 cycles of immunochemotherapy containing pegylated liposomal doxorubicin and rituximab, especially in those who had grade 4 neutropenia in the previous cycles of chemotherapy. Further prospective studies with large samples are needed for confirming our results.

**Acknowledgements** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflict of interest.

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