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ORIGINAL ARTICLE

Characteristics of pulmonary complications in non-Hodgkin's lymphoma patients treated with rituximab-containing chemotherapy and impact on survival

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Abstract

Patients with non-Hodgkin's lymphoma (NHL) receiving rituximab-containing chemotherapy are at risk of developing respiratory complications, but comprehensive information on these complications and their impact on survival is lacking. We performed a retrospective cohort analysis on 123 NHL patients who received rituximab-containing chemotherapy between 2009 and 2016 in order to describe the incidence, etiologies and effect on survival of respiratory complications defined by new or worsening respiratory symptoms requiring diagnostic work-up or hospitalization. Thirty patients (24%) developed respiratory complications during a follow-up time of 825 (555–1338) days after chemotherapy. They had a higher prevalence of congestive heart failure and lung or pleural involvement at diagnosis as compared to patients who did not develop complications. Overall, 58 episodes of pulmonary complications were observed after median (interquartile) times from the first and last rituximab doses of 205 (75–580) days and 27 (14–163) days respectively. Infectious etiologies accounted for 75% of the respiratory complications, followed by heart failure exacerbation, lymphomatous involvement, and ARDS. Two *Pneumocystis jirovecii* pneumonias were observed, and no complication was ascribed to rituximab toxicity. Respiratory complications required ICU admission in 19 cases (33%) and invasive mechanical ventilation in 14 cases (24%). Using a time-dependent Cox regression analysis, we observed that the occurrence of respiratory complications was associated with a 170% increase in death hazard (hazard ratio 2.65, 95% CI 1.60–4.40, $p = 0.001$). In conclusion, respiratory complications in NHL patients receiving chemotherapy are relatively frequent, severe, and mostly infectious and are associated with increased mortality.

Keywords Lymphoma · Respiratory complications · Rituximab · Mortality

Introduction

Non-Hodgkin's lymphoma (NHL) is the most frequent lymphoma in adults with about 70,000 new cases per year in the USA [1]. Clinical trials have reported that pulmonary complications are frequently observed in NHL patients receiving chemotherapy [2–4]; for instance, about 40% of elderly patients treated with R-CHOP regimen experience pulmonary complications which can be severe in 10% of patients [2]. In lymphoma patients receiving autologous bone marrow transplant, respiratory complications were found to be a major source of morbidity and mortality (33 and 65% mortality rates for infectious and non-infectious complications respectively) [5]. However, similar information in patients outside of the bone marrow transplant setting is lacking, as respiratory complications described in clinical trials were only reported as adverse events and were not specifically investigated. Yet, in NHL patients, acute respiratory failure is a leading cause for ICU admission [6], which is associated with decreased survival [7]. Respiratory complications may result from infections developing after chemotherapy, including bacterial, viral, fungal, and *Pneumocystis jirovecii* pneumonias. However, various other complications may affect the lungs: rituximab-

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induced interstitial pneumonitis [8–21], CHOP-associated cardiotoxicity with pulmonary edema [22], or lung involvement by NHL [23].

Overall, NHL patients receiving chemotherapy are exposed to a variety of respiratory complications. Fragmentary studies restricted to specific etiologies have been published, and some reported unexpectedly high incidence of *Pneumocystis jirovecii* pneumonias (13% in the study by Kolstad [24]) or interstitial pneumonitis (8% in the study by Liu [14]). However, comprehensive data on respiratory complications following R-CHOP administration, including their impact on outcome, are lacking. The objective of this retrospective study was to describe the timing, etiologies, and effect on survival of respiratory complications in NHL patient treated with rituximab-containing chemotherapy.

Methods

This study was approved by the Pennsylvania State University Institutional Review Board (IRB number 5590), and informed consent was waived due to the retrospective design of the data collection. Patients > 18 years old who received rituximab-containing chemotherapy for NHL between 2009 and 2016 were screened and included in the study if they had complete clinical information and pre- and post-chemotherapy chest CT scans available.

The following data were collected: demographics, type and stage (Ann Arbor classification [25]) of NHL, comorbidities and baseline echocardiographic findings, rituximab dosage and immediate adverse reactions, steroids administration, and chest CT and FDG-PET CT (if applicable) findings before and after chemotherapy. Clinical notes were screened for the development of respiratory complications; diagnostic work-up (blood and sputum cultures, respiratory virus panel, legionella urinary antigen, bronchoalveolar lavage if applicable, brain natriuretic peptide) was reviewed and presumed etiologies and treatment were collected. Respiratory complications were defined as any new or worsening respiratory symptom requiring hospitalization or diagnostic tests (chest imaging, echocardiogram, infectious work-up). Survival and cause of death, if applicable, were also recorded. All charts and chest CT scans were reviewed by a pulmonary and critical care physician with experience in the management of critically ill immunocompromised patients (AV).

Statistical analysis

Results were analyzed with SPSS version 24 and R package (https://www.R-project.org/). Data were reported as median (interquartile range) unless otherwise specified. Continuous and categorical variables were compared between groups with Wilcoxon rank sum test and Fisher's exact test respectively. Cumulative incidence of the first episode of respiratory complication was plotted considering death without respiratory complication as a competing risk. For patients developing respiratory complications, overall survival after the first complication was plotted using a Kaplan-Meier curve. To analyze the impact of respiratory complications on mortality, we used Cox models with time-dependent covariates as recommended by Therneau et al. (https://cran.rproject.org/web/packages/survival/vignettes/timedep.pdf). For this, a time-dependent predictor was created, which denoted, at any time t, the number of respiratory complications that occurred before time t for any subject. This predictor was always zero if the subject had no respiratory complications. If the subject had one respiratory complication at day d, this predictor was then zero for $t < d$ and one for $t >= d$. A standard Cox proportional hazards model was then fitted on this time-dependent predictor and on other static covariates selected based on univariate analysis (age, history of congestive heart failure (CHF), NHL stage, and lung/pleural involvement at diagnosis). All tests were two sided and $p < 0.05$ was considered for statistical significance.

Data availability All data generated or analyzed during this study are included in this published article.

Results

Patients' characteristics

We included 123 patients and 30 (24%) developed at least one respiratory complication during a follow-up of 825 (555–1338) days after chemotherapy. The curve displaying the cumulative incidence of the first respiratory complication is presented in Fig. 1; cumulative incidence of respiratory complications was 25.8% at 990 days (95% CI 18–34%). Main characteristics of the 123 patients and comparison of groups according to the development of respiratory complications are presented in Table 1. On univariate analysis, patients developing respiratory complications had a higher prevalence of lung or pleural involvement at diagnosis (32% versus 15%, $p = 0.04$) and a higher prevalence of pre-existing CHF (17% versus 0%, $p = 0.0007$) which persisted after exclusion of respiratory complications related to CHF exacerbation. None of the collected variables was significantly predictive of respiratory complications in multivariate logistic regression analysis. The number of distinct episodes of respiratory complications was 1 ($n = 19$ patients), 2 ($n = 7$), 3 ($n = 1$), 4 ($n = 1$), 7 ($n = 1$), and 11 ($n = 1$). About half of the first episodes of respiratory complications occurred within 90 days of chemotherapy, as depicted in Fig. 2. Fifteen and 9 patients required ICU admission and mechanical ventilation as a consequence of the complications respectively.

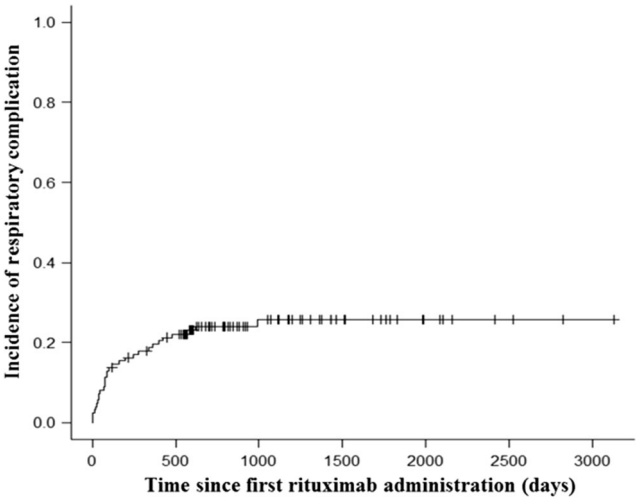

Fig. 1 Cumulative incidence of the first respiratory complication among 123 NHL patients treated with rituximab-containing chemotherapy. Follow-up started at the first rituximab administration and deaths without respiratory complication were treated as competing events. The cumulative incidence of respiratory complications was 25.8% at 990 days (95% CI 18–34%)

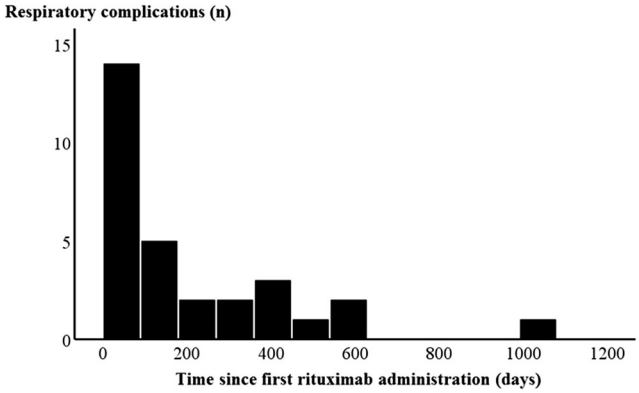

Fig. 2 Timeline of the occurrence of the first respiratory complication in the 30 NHL patients who developed respiratory complications after receiving chemotherapy. X-axis represents the time since first rituximab administration; whereas, y-axis represents the number of patients developing a first respiratory complication

Among the 30 patients who developed respiratory complications, 9 never completed the planned chemotherapy, 1 completed it before the respiratory complication and 20 afterwards, and 7 patients received radiation therapy. The chemotherapy was delayed due to respiratory complications for 18 patients. A majority of the 30 patients received granulocyte colony-stimulating factor ($n = 25$), and during the week preceding the respiratory complication 13 patients were receiving antibacterial prophylaxis, 9 antifungal prophylaxis, 14 antiviral prophylaxis, and 6 prophylaxis against *Pneumocystis jirovecii*.

Characteristics of pulmonary complications

A total of 58 episodes of pulmonary complications were observed. The time elapsed from the first rituximab dose was 205 (75–580) days, and the time from the last rituximab dose was 27 (14–163) days. Several causes were simultaneously present for some of the respiratory complications, and overall etiologies were presumed bacterial pneumonias ($n = 33$), viral

Table 1 Main characteristics at diagnosis of the whole population and according to the subsequent development of respiratory complications

	Overall population ($n = 123$)	No respiratory complication ($n = 93$)	Respiratory complications ($n = 30$)	p
Age (years)	65 (56–73)	66 (56–75)	65 (51–71)	0.21
Gender (M/F)	73/50	52/41	21/9	0.20
Tobacco use (n, %)	54 (44)	39 (42)	15 (50)	0.49
Significant comorbidities (n)	11	4	7	
COPD	6	4	2	0.60
CHF	5	0	5	0.0007
BMI (kg/m^2)	28.7 (24.0–32.4)	28.7 (23.8–31.9)	29.3 (25.1–33.5)	0.59
NHL type (n)				0.74
DLBC lymphoma	56	39	17	
Follicular lymphoma	21	20	1	
Mantle cell lymphoma	16	14	2	
Mediastinal lymphoma	6	4	2	
Other	24	16	8	
NHL stage 1/2/3/4 (n)	10/28/21/62	5/24/18/45	5/4/3/17	0.08
Lung/pleural involvement (n, %)	23 (19)	14 (15)	9 (32)	0.04
Ejection fraction (%)	65 (60–65)	65 (60–65)	65 (65–65)	0.15
Total rituximab doses (n)	8 (6–14)	8 (6–14)	7 (6–11)	0.21

COPD chronic obstructive pulmonary disease, *CHF* congestive heart failure, *BMI* body mass index, *DLBC* diffuse large B cell lymphoma

infections or co-infections ($n = 12$), *Pneumocystis jirovecii* pneumonias ($n = 2$), CHF exacerbations ($n = 9$), ARDS in the setting of septic shock ($n = 2$), diffuse alveolar hemorrhage ($n = 1$), and pleural or lung lymphomatous involvement ($n = 3$). Infectious complications were diagnosed based on chest imaging (mostly CT) associated with clinical signs ($n = 19$), positive blood cultures ($n = 12$), positive cultures of respiratory samples (sputum or bronchoalveolar lavage) ($n = 11$), or positive respiratory virus panel ($n = 13$). For the episodes with positive cultures, the bacteria involved were *Pseudomonas aeruginosa* ($n = 3$), *Staphylococcus aureus* ($n = 3$), *Enterobacter* ($n = 2$), *Enterococcus* ($n = 2$), *Escherichia coli* ($n = 2$), *Klebsiella* ($n = 1$), *Streptococcus pneumoniae* ($n = 1$), and *Rothia* ($n = 1$); fungi involved were *Candida* ($n = 5$), *Aspergillus* ($n = 1$), and *Pneumocystis jirovecii* ($n = 2$). Overall, 12 patients were found positive for respiratory viruses during an episode of respiratory complication (6 rhinoviruses, 2 influenza viruses, 2 human metapneumoviruses, and 2 parainfluenza viruses), whether it was isolated or associated with bacterial pneumonia. Infectious etiologies in general accounted for 44 (75%) of the episodes. None of the respiratory complication was ascribed to rituximab toxicity. These complications required ICU admission in 19 cases (33%) and invasive mechanical ventilation in 14 cases (24%).

Table 2 provides a description of the respiratory complications observed in 30 patients (for patients with multiple complications, only the last one is reported as the focus of this table is the impact on mortality). Seven patients died during their admission for respiratory complications; however, the death was directly related to acute respiratory failure for only one patient; another patient died from acute on chronic respiratory failure, two from sepsis with multiple organ failure, two from refractory lymphoma, and one from candidemia. For the other 11 patients who died during follow-up, causes of death were mostly relapsed/refractory NHL ($n = 5$) followed by sepsis ($n = 2$), intracranial bleeding ($n = 1$), progressive multifocal leukoencephalopathy ($n = 1$), or undetermined cause ($n = 2$).

Effect of pulmonary complications on mortality

A Cox proportional hazards analysis including respiratory complications as a time-dependent variable showed that the significant predictors for mortality were NHL stage at diagnosis and the development of respiratory complications (Table 3). The occurrence of a respiratory complication was associated with a 170% increase in death hazard (hazard ratio 2.65, 95% CI 1.60–4.40, $p = 0.001$).

Figure 3 displays the Kaplan-Meier overall and progression-free survival time after the first complication for the 30 patients developing respiratory complications.

Discussion

The main results of this study were that about 25% of NHL patients receiving rituximab-containing chemotherapy developed respiratory complications over time. First respiratory complications occurred within 3 months of chemotherapy initiation for half of the patients, and infectious etiologies accounted for most of them (75%), bacterial pneumonias but also frequently viral infections. The occurrence of respiratory complication was strongly associated with mortality.

Pulmonary complications were reported to occur in 35 out of 77 non-Hodgkin and Hodgkin lymphoma patients after autologous bone marrow transplant with an associated mortality of 26% [5]; another series reported that 13 out of 35 NHL patients developed respiratory complications post-autologous transplant (8 pneumonitis, 4 community acquired pneumonias, 1 pleural effusion) [26]. However, similar information in patients receiving chemotherapy alone is scarce and mostly comes from clinical trials, which reported for instance pulmonary adverse events rates of about 30% (10% for grade 3 or 4) [2] or severe pneumonia rates of 4% [27] after R-CHOP. As these publications were clinical trials, respiratory complications were mostly reported as adverse events, without detail on timing, etiologies and impact on survival. The incidence of respiratory complications in NHL patients treated with rituximab-containing chemotherapy observed in the present study (24%), and the associated mortality (12%) are lower than reported after bone marrow transplant but consistent with these two clinical trials.

Infections were the most frequent cause of respiratory complications in our series, accounting for 75% of episodes and developing overall in 17% of patients. This incidence is higher than reported in clinical trials [27], one reason might be a longer follow-up in our study. This result, however, is consistent with the study by Coiffier et al. which reported that 65% of 202 NHL patient developed infections within 2 years follow-up after receiving R-CHOP, 12% being graded as severe (sources of infections were not reported though and may have included non-respiratory infections). Seymour et al. reported 4% of pneumonias classified as serious adverse events among 386 patients receiving R-CHOP for diffuse large B cell lymphoma [27]. Most of the infections that we observed were bacterial pneumonias, but viral infections or co-infections were also very frequent, and *Pneumocystis jirovecii* pneumonias developed in 2 patients. The spectrum of infectious complications was somewhat different than reported after autologous bone marrow transplant, as *Aspergillus*, CMV, and Herpes simplex virus infections were common in the study by Jules-Elysee [5] and not observed in our population. An association between rituximab administration and *Pneumocystis jirovecii* pneumonia has been suggested in two retrospective cohort studies [19, 20], and another series reported an incidence as high as 13% in NHL patients

Table 2 Characteristics of the respiratory complications for the 30 patients involved (for patients with multiple complications, only the last one was reported). Last column reports the ultimate cause of death, if applicable, including for patients who survived respiratory complications

N	Age (years)	Gender (1 M/ 2 F)	CHF (0/1)	NHL type	NHL stage	Lung/pleural involvement	Time since first R dose (days)	Time since last R dose (days)	Etiology 1	Etiology 2	ICU admission (0/1)	Invasive mechanical ventilation (0/1)	Survival to respiratory complication (0/1)	Ultimate cause of death if applicable
1	87	1	0	DLBCL	1	0	15	15	PNA	CPE	0	0	1	Intracerebral bleeding
2	61	2	0	DLBCL	4	1	90	12	PNA		0	0	1	Cerebral lymphoma
3	65	1	0	DLBCL	4	0	480	330	PNA		1	0	1	Refractory lymphoma
4	20	1	0	DLBCL	4	0	160	11	PNA		1	1	0	Sepsis with MOF
5	57	1	1	Other	4	0	580	18	PNA	CPE	1	1	0	Candidemia
6	72	2	1	DLBCL	4		1	1	DAH	PNA	1	1	1	Unknown
7	71	2	0	Other	4	0	75	19	PCP PNA		0	0	1	Unknown
8	46	2	0	Mediastinal	1	0	245	150	Malignant pleural effusion	Pericardial tamponade	0	0	1	NA
9	28	2	0	Other	4	0	990	270	PNA		1	0	1	NA
10	58	1	0	DLBCL	4	0	265	70	PNA		1	1	0	Cerebral lymphoma
11	71	1	0	DLBCL	3	0	68	18	Asthma		0	0	1	NA
12	51	1	0	Other	4	0	105	15	Lung lymphoma		0	0	1	NA
13	51	2	0	DLBCL	4	1	1	1	Malignant pleural effusion		0	0	1	Refractory lymphoma
14	34	1	0	Other	1	0	808	672	CPE		0	0	1	NA
15	72	1	0	DLBCL	4	0	425	21	Unknown		0	0	1	NA
16	63	1	0	Other		0	102	13	PCP PNA		1	1	1	NA
17	65	1	0	DLBCL	1		27	15	PNA		0	0	1	Refractory lymphoma
18	88	2	0	DLBCL	4	1	120	8	PNA	CPE	1	0	0	Acute on chronic respiratory failure
19	66	1	1	DLBCL	4	1	214	113	PNA		0	0	1	NA
20	22	1	0	Mediastinal	1	1	368	32	Septic cardiomyopathy		1	1	1	NA
21	71	2	0	Follicular	4	0	620	120	URI		0	0	1	NA
22	75	1	1	DLBCL	3	0	622	163	PNA		0	0	1	NA
23	65	1	0	DLBCL	2	1	1372	69	PNA		0	0	1	NA
24	66	1	0	DLBCL	4	0	1495	1354	PNA		1	1	0	Acute respiratory failure
25	50	1	0	DLBCL	4	1	551	12	PNA		1	1	0	Sepsis with MOF
26	60	1	0	Mantle cell	2	0	80	1	CPE		0	0	1	NA
27	70	1	0	Mantle cell	3	0	398	120	PNA	*E. coli* bacteremia	1	0	1	PML
28	64	1	0	Other	4	1	90	43	PNA		1	1	0	Refractory lymphoma
29	73	1	1	Other	2	0	1692	1570	PNA		0	0	1	Metastatic esophageal cancer
30	51	2	0	DLBCL	2	1	363	232	PNA		0	0	1	NA

CHF congestive heart failure, *R* rituximab, *DLBCL* diffuse large B cell lymphoma, *PNA* bacterial pneumonia, *DAH* diffuse alveolar hemorrhage, *PCP PNA Pneumocystis jirovecii* pneumonia, *CPE* cardiogenic pulmonary edema, *URI* upper respiratory tract infection, *MOF* multiple organ failure, *PML* progressive multifocal leukoencephalopathy, *NA* not applicable (patients alive)

Table 3 Time-dependent Cox proportional hazards analysis of survival in 123 NHL patients, including the development of respiratory complications as time-dependent variable and age, NHL stage, lung/pleural involvement at diagnosis, and history of CHF as covariates

Covariate	Hazard ratio	95% CI	*p*
Respiratory complications	2.65	1.60–4.40	0.001
Age	1.01	0.98–1.04	0.66
NHL stage	1.73	1.14–2.62	0.01
Lung or pleural involvement	1.03	0.43–2.48	0.95
History of CHF	0.79	0.19–3.39	0.75

receiving rituximab [24]. We observed a much lower incidence of less than 2%; however, clinicians should certainly consider *Pneumocystis jirovecii* pneumonia when evaluating a patient developing respiratory complications after chemotherapy for NHL.

Although numerous case reports or small series of rituximab-induced interstitial lung disease have been published [10, 14], none of the complication observed in our relatively small series of patients was ascribed to rituximab. We were particularly careful in our evaluation for potential rituximab toxicity, only including patients with pre- and post-chemotherapy chest CT scans available; this suggests that rituximab lung toxicity remains a rare event, as recently shown in a retrospective cohort study of 560 patients,

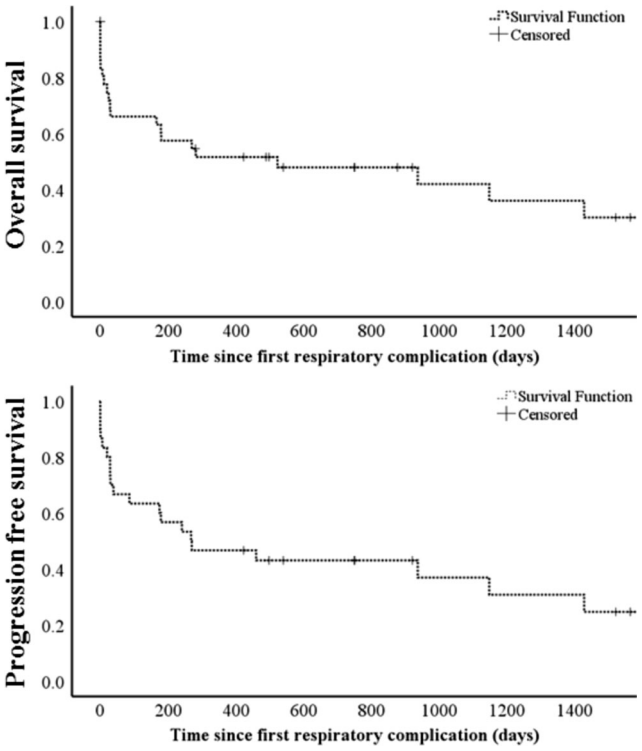

Fig. 3 Kaplan-Meier curves displaying the overall survival (top panel) and the progression-free survival (bottom panel) in days after the first respiratory complication in the 30 NHL patients who developed respiratory complications after chemotherapy

where the authors reported that computed tomographic abnormalities were frequent in NHL patients regardless of rituximab administration, and that rituximab only marginally increased the risk of developing interstitial pneumonitis (3.9% versus 1.3%, $p = 0.07$) [8].

None of the complications reported here was related to acute pulmonary embolism, which is likely due to the small population included; even though a higher incidence of thromboembolic events has been described in patients with lymphoma, these events were mainly deep vein thromboses and only 2% of patients developed acute pulmonary embolism in a large cohort study [28].

In addition to lung or pleural involvement at diagnosis, our study suggests that pre-existing CHF may be a risk factor for developing respiratory complications, even from non-cardiac origin, after chemotherapy, and that CHF exacerbations account for a significant part of respiratory complications. Among the 5 patients developing CHF exacerbations in our cohort, only one had pre-existing CHF, highlighting the potential for chemotherapy to induce left ventricular dysfunction, which has been recently reported to develop in 15% of NHL patients after chemotherapy [29].

The occurrence of a respiratory complication after chemotherapy was associated with a 170% increase in hazard ratio for death in our population. To our knowledge, this is the first demonstration of the impact of respiratory complications on survival. Interestingly, acute respiratory failure was the immediate cause of death for only one of the 18 patients who died during follow-up after developing respiratory complications. For most patients, respiratory complications were either associated with or preceded a progression of the NHL, which ultimately led to death. The other variable significantly associated with survival in our time-dependent Cox analysis was the NHL stage at diagnosis, which seems intuitive.

A limitation of our study is its limited sample size, which especially prevented us from investigating the predictive factors for the development of respiratory complications. Larger studies would be warranted to address this important question. However, this does not affect the validity of our results regarding the impact of respiratory complications on survival as we used a time-dependent, valid statistical approach, and observed a strong statistical association. Although our population was relatively homogeneous in terms of chemotherapy received (all patients received rituximab, known to cause interstitial pneumonitis), we included different types of NHL, and this may also have affected our results.

Conclusions

In our cohort of 123 NHL patients receiving rituximab-containing chemotherapy, respiratory complications developed in about 25% of patients, 75% were infectious (bacterial

and viral), and 25% required mechanical ventilation. Only two *Pneumocystis jirovecii* pneumonias and no rituximab-induced interstitial lung disease were observed. Occurrence of respiratory complication was associated with a 170% increase in death hazard.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval 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 with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This study was approved by the Pennsylvania State University Institutional Review Board (IRB number 5590), and informed consent was waived due to the retrospective design of the data collection.

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