Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) decreases the incidence of interstitial pneumonia (IP) in B cell non-Hodgkin lymphoma (NHL) patients receiving chemotherapy with rituximab.

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B-cell lymphoma, Chemotherapy, Interstitial Pneumonia, TMP-SMX, Rituximab
Abstract
Background Several studies have reported on the incidence of interstitial pneumonia (IP) among patients with non-Hodgkin lymphoma (NHL) that have been treated with chemotherapy plus rituximab, however, the best means of prophylactically preventing IP remains unclear. This retrospective study was designed to explore the prophylactic effect of trimethoprim-sulfamethoxazole (TMP-SMX) on IP and to identify IP-associated risk factors in NHL patients. Methods Between March 2013 and April 2018, 498 patients (264 male, 53%) with B cell NHL undergoing first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP)-like chemotherapy treatment were enrolled in this study. Results These patients had a median age of 56 years, and 311 of these patients (62.4%) were administered prophylactic TMP-SMX. IP occurred in 65 patients (13.1%), with once daily prophylactic TMP-SMX treatment leading to a significant reduced IP rate (21.4% vs. 8.0%; p<0.001). Among patients treated with TMP-SMX, 2 (1.2%) exhibited rashes, 38 (12.2%) suffered from nausea and vomiting, 52 (16.7%) showed signs of neutropenia, and 18 (5.8%) suffered kidney dysfunction. Being male, having a history of diabetes, and not having undergone prophylactic TMP-SMX treatment were all found to be significantly associated with IP risk in both univariate and multivariate analysis. Disease progression was observed in 55/311 (17.7%) patients that underwent prophylactic TMP-SMX treatment and in 63/187 (33.7%) patients that did not (p<0.001). Conclusions Overall, these results reveal that IP is common in B cell NHL patients undergoing chemotherapy plus rituximab treatment, with the prophylactic administration of once daily oral TMP-SMX significantly reduces the IP incidence.

Background
The combination of CHOP chemotherapy plus rituximab has been widely employed for treatment of CD20+ non-Hodgkin lymphoma (NHL)\textsuperscript{1-3}. Previous studies have reported that 1.3 - 14\% of patients treated with chemotherapy regimens including rituximab develop interstitial pneumonia (IP)\textsuperscript{4-7}. IP is a heterogeneous group of disorders that are classified together owing to their similar clinical, radiographic, physiologic, or pathologic manifestations\textsuperscript{8}. IP can be caused by many reasons and can ultimately lead to dyspnea, respiratory failure, and even death. Individuals diagnosed with IP are
more likely to stop undergoing further chemotherapeutic treatment, thereby reducing the efficiency of chemotherapy and shortening patient survival\textsuperscript{9}. Therefore, active treatment and effective prevention of IP is essential in patients undergoing immunochemotherapeutic treatment. Combination treatment with chemotherapy plus rituximab has the potential to inhibit patient immune functionality, thereby increasing the risk of opportunistic infection. Several studies have concluded that the occurrence of IP is at least partially associated with a rising risk of pneumocystis carinii pneumonia (PCP) infection \textsuperscript{4-6,10,11}. However, the most effective prophylactic drugs and methods for preventing IP remain controversial. Trimethoprim-sulfamethoxazole (TMP-SMX), an oral broad-spectrum antibiotic, is a specific therapeutic and prophylactic agent that is used for the treatment of PCP infections\textsuperscript{5,6,11}. At our hospital, we have routinely administered prophylactic TMP-SMX to hundreds of lymphoma patients since 2013. In this study, we present a retrospective analysis of the impact of TMP-SMX prophylaxis on IP incidence among B cell NHL patients undergoing treatment with a combination of chemotherapy plus rituximab.

Methods

Participants and data collection

Study inclusion criteria were as follows: patients were diagnosed with CD20+ B cell non-Hodgkin lymphoma by a local pathologist according to WHO criteria\textsuperscript{12}. All patients had undergone treatment with rituximab plus CHOP-like chemotherapy for at least two cycles. Patients with T cell lymphomas were excluded from this study. Chemotherapy regimens other than RCHOP-like regimens were also excluded. Patients for whom full treatment data were not available were excluded from this analysis. As a control group, we included patients that had not undergone prophylactic TMP-SMX treatment. All of these randomly selected control patients had been diagnosed with untreated B-cell NHL and had been treated with first-line RCHOP-like chemotherapy for at least two cycles. For patients undergoing prophylactic TMP-SMX treatment, TMP-SMX was taken once daily from the time of treatment initiation until completion of chemotherapy. Each tablet contained 0.08 g TMP and 0.4 g SMX. TMP-SMX was not administered to patients with allergies to the drug, megaloblastic anemia, or severe liver or kidney
damage. Prophylactic granulocyte colony-stimulating factor (G-CSF) and antiemetic administration was allowed. Radiographic documents and data regarding patient clinical characteristics, histological diagnoses, chemotherapy regimens, and survival outcomes were retrospectively collected from the original computerized medical files. This trial was approved by the research ethics boards of Zhejiang cancer hospital, with all patients having giving written informed consent.

**IP Diagnosis and treatment**

The observation period for IP in this study extended from the first day of immunochemotherapy to 8 months after completion of immunochemotherapy. Routine imaging evaluations were performed every two cycles during chemotherapy and every 3 months after chemotherapy within the observation period. Patients underwent thoracic computed tomography (CT) scans when they exhibited symptoms of pulmonary infection. IP was diagnosed via a multidisciplinary approach based upon clinical symptoms, laboratory tests, radiologic imaging, and pathologic findings. IP typically presented in the form of diffuse pulmonary interstitial infiltrates with reticular or ground-glass opacity, alveolitis, and the presence of diffuse infiltrates on CT scans.\(^{11,13}\) When IP was suspected, laboratory tests measuring blood cell counts, C-reactive protein (CRP), procalcitonin (PCT), 3-b-D glucan antigens, Gram-negative lipopolysaccharides, Galactomannan antigen detection (GM), and bacterial culture were conducted to facilitate an appropriate diagnosis. Once they had been diagnosed with IP, patients began undergoing empirical treatment with a combination of antibiotics, antifungal agents, and glucocorticoids. Ganciclovir was given when viral infection was suspected. When PCP was suspected, a therapeutic dose of TMP-SMX was administered. CT scans were conducted weekly until complete interstitial infiltrate absorbance was evident. After patients recovered from IP, retreatment with chemotherapy and/or rituximab was allowed. TMP-SMX was administered at prophylactic doses as described previously. Parameters relating to clinical presentation, diagnosis, causative pathogen, treatments, and outcomes were additionally summarized for all patients as appropriate.

**Statistical analysis**

For this study, overall survival (OS) and progression-free survival (PFS) were measured, with the former corresponding to the amount of time between starting chemotherapy and last follow-up or
death due to any cause, and the latter corresponding to the period of time between the start of chemotherapy and the last follow-up, cancer progression, or all-cause death. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.0 criteria were used for the gradation of all adverse events (AEs). χ2 tests were used to compare categorical variables between patient groups. A binary logistic regression was used to conduct univariate analyses with appropriate hazard ratios (HRs) and 95% confidence intervals (CIs). Each variable with a \( p < 0.05 \) in the initial univariate analysis was incorporated into a multivariable model. \( p < 0.05 \) was the significance threshold. SPSS 23.0 was used for all statistical testing.

Results

**Patient characteristics**

Between March 2013 and April 2018, a total of 498 patients were analyzed for this study of whom the majority (264/498; 53%) were male. The clinical characteristics of these patients are compiled in Table 1. These patients had a median age of 56 years (range: 18 - 82). Of these patients, 414 (83.1%) were diagnosed with diffuse large B cell lymphoma (DLBCL), 9 (1.8%) were diagnosed with mantle cell lymphoma (MCL), 36 (7.2%) were diagnosed with follicular lymphoma (FL), 7 (1.7%) were diagnosed with chronic lymphocytic leukemia/small B cell lymphoma (CLL/SLL), 25 (5%) were diagnosed with marginal zone lymphoma (MZL), and 7 (1.7%) were diagnosed with highly aggressive B cell lymphoma. The most common chemotherapy regimens used to treat this patients included RCHOP (n=428, 85.9%), rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (REPOCH) (n=57, 11.4%), and rituximab plus cyclophosphamide, vincristine, and prednisone (RCOP) (n=13, 2.6%). A total of 311 patients (62.4%) were prophylactically administered TMP-SMX, while the remaining 187 patients (37.6%) did not undergo any prophylactic treatment. With the exception of gender, baseline characteristics such as age, eastern cooperative oncology group (ECOG) score, baseline LDH level, smoking history, disease stage, bone marrow involvement, and International Prognostic Index (IPI) did not differ significantly between groups.

**Diagnosis and treatment of IP**

IP occurred in 65 patients (13.1%), of whom 25 (38.5%) were in the TMP-SMX prophylaxis group. IP
patients had a median age of 60 years (range: 18 - 78), and exhibited the following pathological diagnoses: 57 cases of DLBCL, 1 of FL, 1 of MCL, 1 of CLL/SLL, 3 of MZL, and 2 of highly aggressive B cell lymphoma. IP incidence was significantly greater among patients that had not undergone prophylactic TMP-SMX treatment relative to those who did (21.4% vs 8.0%, \( p < 0.001 \)). The median time between the first day of immunochemotherapy and the date of IP diagnosis was 74 days, (range: 7 - 158 days). Prior to IP diagnosis, patients had been treated with a median of 3 cycles (range: 1 - 8 cycles). The median cumulative dose of rituximab upon IP diagnosis was 2100 mg (range: 600 – 4800 mg). A review of these 65 cases is shown in Table 2.

A total of 15 (23.1%) patients exhibited no IP-associated symptoms when a routine radiological examination detected IP in these individuals. Common clinical presentations included cough (n=24), fever (n=31), chest distress (n=20), expectoration (n=17), and shortness of breath (n=11). All patients diagnosed with IP were assessed in order to quantify the levels of inflammatory factors. Elevated CRP (> 10mg/L) was evident in 54 patients. Elevated PCT (>0.5ng/mL) was evident in 5 patients. A positive G test for 3-b-D glucan fungal antigens (> 60 pg/mL) was detected in 18 patients. Elevated levels of Gram-negative lipopolysaccharides (>10pg/mL) were detected in 36 cases. Type I respiratory failure was confirmed in 5 patients based upon arterial blood gas measurements. Sputum cultures were performed in patients following expectoration, and positive pathogenic bacteria included Candida albicans (n=3), Staphylococcus aureus (n=1), Klebsiella aeruginosa (n=2), Klebsiella pneumonia (n=2), hemolytic Steptotoccus (n=1), and Staphylococcus haemolyticus (n=1). Blood culture was performed in pyrexic patients with temperatures higher than 38.5 °C, but the results were negative for all 8 tested patients. 7 patients received bronchoalveolar lavage (BAL) but no Pneumocystis carinii was detected. Other common suspected pathogens included haemophilus, stenotrophomonas, tropheryma, exophiala, human gammaherpesvirus 4.

Further chemotherapy and rituximab treatments were withheld immediately following IP diagnosis. The average time to IP remission was 12 days (range: 7 day to 58 days). No patients died as a consequence of their infection. After remission from IP, 21 patients completed further chemotherapy combined with rituximab, 35 patients received subsequent chemotherapy without rituximab, and 9
patients did not receive chemotherapy or rituximab. No patients suffered from the recurrence of IP following continued immunochemotherapy treatments.

**Complications of prophylaxis**

Of the 311 patients receiving prophylactic TMP-SMX, 2 (1.2%) had rashes, 38 (12.2%) suffered nausea and vomiting, 52 (16.7%) exhibited neutropenia, and 18 (5.8%) suffered kidney dysfunction. No patients discontinued TMP-SMX prophylaxis as a result of these adverse reactions. As these patients were undergoing concomitant chemotherapy, it is difficult to determine whether these adverse reactions were specifically associated with TMP-SMX prophylaxis in most cases.

**IP Risk factors**

We next sought to identify clinical parameters that were associated with IP risk in this patient population (Table 3). In a univariate analysis, we found that being male, having a history of diabetes, and not receiving TMP-SMX prophylactic therapy were all associated with elevated IP risk, and in a subsequent multivariate analysis all these three variables were found to independently predict a higher risk of IP.

**Impact of IP on survival**

After a median 26 months follow-up period, median PFS and OS were 23.1 and 26.7 months, respectively, in all patients. Among the 311 patients receiving prophylactic TMP-SMX, 55 exhibited disease progression, while a significant larger proportion of those patients that did not undergo prophylactic treatment (63/187) suffered from progressive disease (17.7% vs 33.7%, \( p < 0.001 \)).

**Discussion**

As the combination of chemotherapy plus rituximab has been employed with increasing frequency for the treatment of NHL, reports of treatment-associated IP have similarly become increasingly common. However, the exact incidence of IP among lymphoma patients remains uncertain owing to high variability among previous studies. In one retrospective analysis of 2212 consecutive Chinese lymphoma patients, overall IP incidence was determined to be 3.75%, with rates of 3.9% (7/287) and 2.4% (76/925) in patients with Hodgkin and non-Hodgkin lymphoma, respectively\(^9\). However, in other studies the reported incidence of IP among NHL patients undergoing CHOP-based chemotherapy with
or without rituximab has ranged from 1.3% in a study by Giselle Salmasi et al⁷. to 14.8% in a study by Wang qian et al¹⁴. Other groups have reported values within this range, including reports of 4.4% (5/114 patients) by Toshiro Kurokawa et al¹⁵, 6.2% (8/129 patients) by Katsuya Hiroo et al¹³, 7% (5/71 patients) by Lim KH et al¹⁶, and 4.9% (26/529 patients) by Huang et al¹⁷. These studies have also suggested that the addition of rituximab to therapeutic regimens may increase IP incidence. In the present study, we observed an IP incidence of 21.4% in patients not receiving any preventive treatment, with this rate being higher than that in previous reports. There are several possible reasons for this difference. As an anti-CD20 antibody with an extended in vivo half-life, rituximab possesses broad immunomodulatory activity. It can induce B cell apoptosis, alter complement activation, and induce cytokine release, thereby potentially interfering with normal cytotoxic T cell responses and immune functionality so as to elevate the risk of opportunistic infection¹⁸. In this study, all patients received rituximab and chemotherapeutic treatments simultaneously, which may have also contributed to our overall findings. As patients in this study were being actively monitored for IP, this too may have increased the overall IP incidence rate given that it led to disease detection in otherwise asymptomatic patients. Other possible causes for elevated IP rates include differences in the baseline characteristics of patient populations, the chemotherapy regimens administered, chemotherapeutic dose intensity, diagnostic techniques, the small size of previous studies, or the fact that we employed a longer observation period. Therefore, our results suggest that there is clear value in administering prophylactic IP treatment to NHL patients undergoing RCHOP therapy.

A number of pathological changes occur in the context of IP including the inflammation of the interstitial tissue surrounding the alveolar epithelium, leading to significant adverse alterations in local lymphatic and vascular systems¹⁹. A number of different factors can give rise to IP, including pathogens, environmental/chemical damage, or immune-mediated inflammation. Among patients undergoing immunochemotherapeutic treatment, however, opportunistic infections remain the leading cause of IP. While viruses, bacteria, and fungi all have the potential to cause IP, PCP is one of the most prominent and deadly pathogens responsible for this condition. As such it is vital that at-risk
patients be administered prophylactic medicines that can reduce the risk of PCP infection in a safe, convenient, and cost-effective manner. TMP-SMX, which is composed of sulfamethoxazole (SMX) and trimethoprim (TMP), is a sulfa antibiotic that offers good antibacterial efficacy against a range of bacteria while having a low frequency of adverse reactions. TMP-SMX is the first-line agent used for PCP prophylaxis in HIV-infected individuals. Even among immunocompromised individuals not infected by HIV, the preventive use of TMP-SMX during chemotherapy may decrease the incidence of PCP. Toshiro et al. found that the prophylactic administration of TMP-SMX to NHL patients undergoing RCHOP-based treatment led to no patients developing PCP infections. With adequate drug adherence and tolerance, TMP-SMX prophylaxis has been shown to protect against 89% of PCP cases. Moreover, TMP-SMX is widely available and inexpensive, at a price of just 2 dollars per 100 tablets in China. As such, TMP-SMX was selected as a prophylactic agent for use in this study.

To the best of our knowledge, no previous studies have examined the use of prophylactic TMP-SMX as a means of preventing IP infections in patients with lymphoma. Extant data regarding the efficiency of prophylactic TMP-SMX treatment is thus mainly derived from studies pertaining to PCP infections. Hughes et al. first demonstrated the successful use of TMP-SMX to treat pediatric oncology patients in 1977, with untreated patients suffering a 21% PCP incidence and treated patients suffering a 0% incidence rate when TMP-SMX was administered either daily or 3 days per week. More recently, many studies have confirmed the efficiency of TMP-SMX prophylaxis as a means of decreasing the incidence of PCP in adult patients with lymphoma and in pediatric oncology patients. A meta-analysis of twelve randomized trials found that TMP-SMX administration was linked to a 91% drop in the incidence of PCP, with a significant reduction in PCP-related mortality. Consistent with these findings, in the present study we found that prophylactic TMP-SMX treatment significantly decreased the incidence of IP in B cell lymphoma patients undergoing R-CHOP-like chemotherapy from 21.4% to 8.0% (p<0.001).

The optimal administration schedule for prophylactic TMP-SMX is not well defined. Most previous
studies have concluded that intermittent dosing with TMP-SMX is an effective alternative prophylactic regimen. TMP-SMX is thus variously administered twice daily two times per week\textsuperscript{30}, two consecutive days per week\textsuperscript{28,32,33}, twice weekly\textsuperscript{31}, or three days per week\textsuperscript{27}. Intermittent TMP/SMZ is an effective means of preventing PCP and can lower associated costs and rate of fungal infections. However, this dosing is not universal, as in one study by Toshiro et al. patients were instead administered one TMP-SMX tablet daily throughout the course chemotherapy\textsuperscript{15}. A meta-analysis concluded that lower doses of TMP-SMX were an effective means of improving tolerance without compromising primary prophylactic efficacy\textsuperscript{34}. No differences between once-daily and thrice-weekly administration schedules have been found\textsuperscript{23}. Patients in the present study were administered one tablet of TMP-SMX per day, and this approach was convenient and easy to implement.

According to previous reports, roughly 30% - 40% of patients stop TMP-SMX therapy as a result of poor drug tolerance when receiving intermittent prophylactic treatment\textsuperscript{35}. The most common adverse events linked with such discontinuation include skin rash, myelosuppression, nausea, fever, renal and liver toxicity, and hyperkalemia\textsuperscript{36-39}. The observed adverse events associated with TMP-SMX prophylaxis in the present study were consistent with these previous reports, however the overall tolerance for this daily TMP-SMX regimen was high, with no instances of discontinuation due to adverse reactions. Moreover, the incidence of leukopenia and nausea and vomiting was low, which may be explained by the fact that patients were allowed to receive prophylactic G-CSF injections after chemotherapy and antiemetic treatments in this study.

We found that a history of diabetes, being male, and not undergoing prophylactic TMP-SMX treatment were independent risk factors associated with IP incidence. In diabetic patients, hyperglycemia can affect the chemotaxis, adhesion, phagocytosis and intracellular bactericidal efficacy of immune cells. In addition, the thickening of the alveolar epithelium, vascular hyaline degeneration, and pulmonary microangiopathy that occurs in diabetic patients can affect lung function. These factors will damage immune function and thereby increase rates of opportunistic infections among patients with diabetes,
who experience 30% more pneumonia-related mortality than do non-diabetic patient populations\textsuperscript{40}. Males usually receive higher doses of rituximab, have a longer smoking history, and are more likely to have poorer basic lung function than females. Other IP-associated risk factors identified in previous studies have included the application of rituximab\textsuperscript{13-15,17,41}, pre-treatment absolute lymphocyte counts <1x10\textsuperscript{9}/L\textsuperscript{17}, B symptoms (fever, weight loss, night sweat), a drug allergy history\textsuperscript{9,14}, and increased intensity of corticosteroid exposure\textsuperscript{5,42,43}.

This study has several limitations, and as such caution is warranted when interpreting our results. For one, BAL, as an important auxiliary examination procedure, was not widely used in this study. Only 7 patients received BAL and PCP infections were not detected in any of these patients. As such, we lack sufficient evidence regarding the specific cause of IP in this patient population. Secondly, 8% of patients in this study developed IP even after prophylactic TMP/SMX treatment, suggesting that there can be other causes for this condition. As such, further prospective studies are needed in order to explore other prophylactic drugs and their optimal administration in NHL patients. In addition, the retrospective nature of this study increases the risk of unintentional bias, potentially explaining the observed discrepancies regarding the rates of side effects associated with TMP-SMX.

Conclusions
These results clearly demonstrate that IP occurs relatively frequently among B-cell NHL patients undergoing chemotherapy plus rituximab treatment. Based on the findings of this retrospective analysis, we conclude that once daily prophylactic TMP-SMX administration beginning at the time of immunochemotherapy initiation significantly reduces IP incidence in these patients.

Abbreviations
TMP: trimethoprim
SMX: sulfamethoxazole
IP: interstitial pneumonia
NHL: non-Hodgkin lymphoma
RCHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
PCP: pneumocystis carinii pneumonia
Declarations

**Ethics approval and consent to participate**

The study protocol was approved by the Ethic Committee of Zhejiang Cancer hospital, Hangzhou, China. The subjects have given their informed consent.

**Consent for publication**

All authors read and approved the final manuscript.

**Availability of data and material**
All data generated during this study are included in this published article. The datasets used 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**

(I) Conception and design and administrative support: H Yang. (II): Provision of study materials or patients: CL. (III) Confirmation of image data: FL. (IV) Collection and assembly of data: CL, TL, H Yu, XC, SP, SH. (V) Data analysis and interpretation: CL. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

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**References**

1. Hainsworth JD, Burris HA, Morrissey LH, et al. Rituximab monoclonal antibody as initial systemic therapy for patients with low-grade non-Hodgkin lymphoma. Blood. 2000;95(10):3052-3056.

2. Bertrand C, Eric L, Josette B, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. New England Journal of Medicine. 2002;346(4):235.

3. Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncology. 2006;7(5):379-391.
4. Xin L, Xiao-Nan H, Ya-Jia G, Bi-Yun W, Zhi-Guo L, Junning C. Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphoma. Leukemia & Lymphoma. 2008;49(9):1778-1783.

5. Arne K, Harald H, Alexander F, Grete Fossum L, Peter G, Dag T. Pneumocystis jirovecii pneumonia in B-cell lymphoma patients treated with the rituximab-CHOEP-14 regimen. Haematologica. 2007;92(1):139-140.

6. Sarah K, Shaun OC, Newton L, Robin F, Harshal N, Tam CS. High incidence of Pneumocystis jirovecii pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. Leuk Lymphoma. 2010;51(5):797-801.

7. Giselle S, Michael L, Vithika S, et al. Incidence of pneumonitis in patients with non-Hodgkin lymphoma receiving chemoimmunotherapy with rituximab. Leukemia & Lymphoma. 2015;56(6):1659-1664.

8. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63 Suppl 5:v1-58.

9. Liu WP, Wang XP, Zheng W, et al. Incidence, clinical characteristics, and outcome of interstitial pneumonia in patients with lymphoma. Annals of Hematology. 2017;8(3):1-7.

10. Lin PC, Hsiao LT, Poh SB, et al. Higher fungal infection rate in elderly patients (more than 80 years old) suffering from diffuse large B cell lymphoma and treated with rituximab plus CHOP. Ann Hematol. 2007;86(2):95-100.

11. Daisuke E, Yasuhito T, Masahiro Y, et al. Increased incidence of interstitial pneumonia by CHOP combined with rituximab. International Journal of Hematology. 2008;87(4):393-397.
12. Diebold J. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. Journal of Clinical Oncology Official Journal of the American Society of Clinical Oncology. 1999;17(12):3835.

13. Katsuya H, Suzumiya J, Sasaki H, et al. Addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy has a high risk of developing interstitial pneumonia in patients with non-Hodgkin lymphoma. Leuk Lymphoma. 2009;50(11):1818-1823.

14. Wang Q, Zhu YF, Jia RF, Jiang L, Yang XY, Oncology DO. The risk factors and clinical features of interstitial pneumonia in B-cell non-Hodgkin's lymphoma patients who were treated with rituximab-CHOP regimen. China Oncology. 2014.

15. Toshiro K, Hiroyasu K, Takashi Y. Two cases of Pneumocystis jiroveci pneumonia with non-Hodgkin's lymphoma after CHOP-based chemotherapy containing rituximab. J Clin Exp Hematop. 2010;50(2):159-162.

16. Lim KH, Yoon HI, Kang YA, et al. Severe Pulmonary Adverse Effects in Lymphoma Patients Treated with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) Regimen Plus Rituximab. Korean Journal of Internal Medicine. 2010;25(1):86-92.

17. Huang YC, Liu CJ, Liu CY, et al. Low absolute lymphocyte count and addition of rituximab confer high risk for interstitial pneumonia in patients with diffuse large B-cell lymphoma. Annals of Hematology. 2011;90(10):1145.

18. Kolk LE, Van Der, Grillo-López AJ, Baars JW, Hack CE, Oers MH, Van. Complement activation plays a key role in the side-effects of rituximab treatment. British Journal of Haematology. 2015;115(4):807-811.

19. Berezowska S, Pöllinger A. [Interstitial pneumonias--Histopathological and
radiological correlation]. Therapeutische Umschau Revue Thérapeutique. 2016;73(1):11.

20. Wagner SA, Mehta AC, Laber DA. Rituximab-induced interstitial lung disease. American Journal of Hematology. 2010;82(10):916-919.

21. Mofenson LM, Oleske J, Serchuck L, Dyke RV, Wilfert C. Treating Opportunistic Infections among HIV-Exposed and Infected Children: Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. Clinical Infectious Diseases. 2005;40 Suppl 1(Supplement 1):S1.

22. Herishanu Y, Polliack A, Leider-Trejo L, Grieff Y, Metser U, Naparstek E. Fatal Interstitial Pneumonitis Related to Rituximab-Containing Regimen. Clin Lymphoma Myeloma. 2006;6(5):407-409.

23. Hefziba G, Mical P, Liat V, Leonard L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clinic Proceedings. 2007;82(9):1052-1059.

24. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. New England Journal of Medicine. 1995;332(11):693.

25. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;15(2):104-114.

26. Hughes WT, Kuhn S, Chaudhary S, , et al. Successful chemoprophylaxis for Pneumocystis carinii pneumonia. The New England journal of medicine. 1977;297(26):1419-1426.

27. Hughes WT, Rivera GK, Schell MJ, Thornton D, , Lott L, . Successful intermittent
28. Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for Pneumocystis carinii (jiroveci) pneumonia in pediatric oncology patients. Pediatrics. 2007;120(1):e47-51.

29. Halaas JL, Moskowitz CH, Steven H, et al. R-CHOP-14 in patients with diffuse large B-cell lymphoma: feasibility and preliminary efficacy. Leukemia & Lymphoma. 2009;46(4):541-547.

30. Isidori A, Merli F, Angrilli F, Ferrara F, Alesiani F, Visani G. The incidence of pneumonia is not higher in patients receiving dose-dense therapy with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine, and prednisolone and adequate pneumonia prophylaxis. 2011.

31. Hardak E, Oren I, Dann EJ, et al. The increased risk for pneumocystis pneumonia in patients receiving rituximab-CHOP-14 can be prevented by the administration of trimethoprim/sulfamethoxazole: a single-center experience. Acta haematologica. 2012;127(2):110-114.

32. Muñoz P., Muñoz RM, Palomo J., Rodríguez-Creixéms M., Muñoz R., Bouza E. Pneumocystis carinii infection in heart transplant recipients. Efficacy of a weekend prophylaxis schedule. Medicine. 1997;76(6):415-422.

33. Souza JP, Boeckh M, Gooley TA, Flowers MED, Crawford SW. High Rates of Pneumocystis carinii Pneumonia in Allogeneic Blood and Marrow Transplant Recipients Receiving Dapsone Prophylaxis. Clinical Infectious Diseases An Official Publication of the Infectious Diseases Society of America. 1999;29(6):1467-1471.

34. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. Archives
of Internal Medicine. 1996;156(2):177-188.

35. Medina I, ., Mills J, ., Leoung G, ., et al. Oral therapy for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. The New England journal of medicine. 1990;323(12):776-782.

36. Asmar BI, Maqbool S, Dajani AS. Hematologic abnormalities after oral trimethoprim-sulfamethoxazole therapy in children. American journal of diseases of children (1960). 1981;135(12):1100-1103.

37. Woods WG, Daigle AE, Hutchinson RJ, Robison LL. Myelosuppression associated with co-trimoxazole as a prophylactic antibiotic in the maintenance phase of childhood acute lymphocytic leukemia *. Journal of Pediatrics. 1984;105(4):639-644.

38. Hoyle C, Goldman JM. Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. Bone Marrow Transplant. 1994;14(2):247-252.

39. Colby C, ., Mcafee S, ., Sackstein R, ., Finkelstein D, ., Fishman J, ., Spitzer T, . A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplantation. 1999;24(8):897-902.

40. Ya-Juan LU, Guan FQ, Wang S, Zhou W, Hospital BC. Clinical Analysis of 108 Cases of Interstitial Pneumonia in Elderly with Diabetes. Diabetes New World. 2015.

41. Alexandrescu DT, Dutcher JP, Kevin OB, Mehmet A, Stanley O, Wiernik PH. Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. Leukemia & Lymphoma. 2015;45(11):5.

42. Brusamolino E, Rusconi C, Montalbetti L, et al. Dose-dense R-CHOP-14 supported by
Tamar T, Peter ML, Aaron P. A resurgence of Pneumocystis in aggressive lymphoma treated with R-CHOP-14: the price of a dose-dense regimen? Leuk Lymphoma. 2010;51(5):737-738.

Tables

Table 1 Baseline characteristics of all the patients (n=498)

| Factor               | All patients (%) | Prophylaxis of TMP/SMX |
|----------------------|------------------|-------------------------|
|                      |                  | Yes (61.5%) | No (38.5%) |
| Age                  |                  |              |            |
| > 60 years           | 18236.5%         | 112 (61.5%) | 70 (38.5%) |
| ≤ 60 years           | 31663.5%         | 199 (63%)   | 117 (37%)  |
| Gender               |                  |              |            |
| Female               | 23447%           | 158 (67.5%) | 76 (32.5%) |
| Male                 | 26453%           | 153 (58%)   | 111 (42%)  |
| ECOG                 |                  |              |            |
| PS >1                | 5711.4%          | 4273.7%     | 152        |
| PS ≤1                | 44188.6%         | 26961%      | 172        |
| Elevated LDH         |                  |              |            |
| YES                  | 231 (46.4%)      | 145 (62.8%) | 86 (37.2%) |
| NO                   | 26753.6%         | 166 (62.2%) | 101 (37.8%)|
| Smoking history      |                  |              |            |
| YES                  | 131 (26.3%)      | 77 (58.8%)  | 54 (41.2%) |
| NO                   | 367 (73.7%)      | 234 (63.8%) | 133 (36.2%)|
| Ann Arbor stage      |                  |              |            |
| I                    | 88 (17.7%)       | 4551.1%     | 434        |
| II                   | 162 (32.5%)      | 10363.6%    | 593        |
| III                  | 97 (19.5%)       | 6061.9%     | 373        |
| IV                   | 151 (30.3%)      | 10368.2%    | 483        |
| BM involvement       |                  |              |            |
| YES                  | 27 (5.4%)        | 19 (70.4%)  | 8 (29.6%)  |
| NO                   | 471 (94.6%)      | 292 (62%)   | 179 (38%)  |
| IPI risk (score)     |                  |              |            |
| Low (0-1)            | 23647.4%         | 14059.3%    | 964        |
| Low-intermediate-2   | 12625.3%         | 8164.3%     | 453        |
| High-intermediate-3  | 8016.1%          | 5062.5%     | 303        |
| High (4-5)           | 56 (11.2%)       | 4071.4%     | 162        |

Table 2 Review of 65 cases with interstitial pneumonia

| Factor               | Number        |
|----------------------|---------------|
|                      |               |
| Age                  |               |
| > 60 years           | 30 (46.2%)    |
| ≤60 years            | 35 (35.8%)    |
| Sex                  |               |
| Female               | 23 (35.4%)    |
| Male                 | 42 (64.6%)    |
Table 3 Binary logistic regression analysis of risk factors for interstitial pneumonia

| Factor                  | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | Odds ratio          | P value               | Odds ratio | P value | 95%CI       | 95%CI       |
|                         |                     | Lower     | Upper     |          | Lower     | Upper     |
| Male vs female          | 1.736               | 0.046     | 1.009     | 2.985    | 1.779     | 0.048     | 1.066     |
| Age >60 vs <=60         | 1.585               | 0.086     | 0.936     | 2.682    |           |           |           |
| IPI score >2 vs <=2    | 1.587               | 0.159     | 0.835     | 3.018    |           |           |           |
| ECOG PS >1 vs <=1      | 2.945               | 0.076     | 0.893     | 9.71     |           |           |           |
| Smoking history YES vs | 3.042               | 0.003     | 1.468     | 6.3      | 3.625     | 0.001     | 1.675     |
| NO                     | 1.648               | 0.077     | 0.948     | 2.865    |           |           |           |
| Diabetes history YES   | 3.405               | 0.162     | 0.611     | 18.973   |           |           |           |
| NO                     | 0.321               | <0.001    | 0.188     | 0.55     | 0.33      | <0.001    | 0.19      |
| Elevated LDH YES vs no | 0.921               | 0.759     | 0.545     | 1.556    |           |           |           |
|                         |                     |           |           |          |           |           |           |

ECOG                     | >1 3 (4.6%)          | ≤1 62 (95.4%)         |
Elevated LDH              | YES 29 (44.6%)       | NO 36 (55.4%)         |
Smoking history           | YES 23 (35.4%)       | NO 42 (64.6%)         |
Ann Arbor stage           | I 12 (18.5%)         | II 24 (36.9%)         |
|                         | III 15 (23.1%)       | IV 14 (21.5%)         |
IPI risk (score)          | Low (0-1) 34 (52.3%) | Low-high (2-3) 26 (40.0%) |
|                         | High (4-5) 5 (7.7%)  |           |           |
Diabetes history          | YES 12 (18.5%)       | NO 53 (81.5%)         |
Ann Arbor stage           | I 12 (18.5%)         | II 24 (36.9%)         |
|                         | III 15 (23.1%)       | IV 14 (21.5%)         |
IPI risk (score)          | Low (0-1) 34 (52.3%) | Low-high (2-3) 26 (40.0%) |
|                         | High (4-5) 5 (7.7%)  |           |           |
Diabetes history          | YES 12 (18.5%)       | NO 53 (81.5%)         |