Hindawi Publishing Corporation
Lymphoma
Volume 2014, Article ID 160421, 6 pages
http://dx.doi.org/10.1155/2014/160421

Clinical Study

Rituximab Induced Interstitial Lung Disease in Patients with Non-Hodgkin's Lymphoma: A Clinical Study of Six Cases and Review of the Literature

Uma Maheswari Krishnaswamy,[1] Vinayak V. Maka,[2] Murali Subramanian,[2] Rohith Chitrapur,[2] and Nalini Kilara[2]

[1] *Department of Respiratory Medicine, M. S. Ramaiah Medical College and Hospitals, MSRIT Post, Bangalore 560054, India*
[2] *Department of Medical Oncology, M. S. Ramaiah Medical College and Hospitals, MSRIT Post, Bangalore 560054, India*

Correspondence should be addressed to Uma Maheswari Krishnaswamy; umamohan99@gmail.com

Received 7 July 2014; Revised 21 August 2014; Accepted 7 September 2014; Published 15 September 2014

Academic Editor: Valli De Re

Background. Rituximab-induced lung disease (R-ILD) is a rare entity that should be considered in patients treated with rituximab who present with dyspnea, fever, and cough but no clear evidence of infection. *Aim.* The aim of this prospective longitudinal study is to describe the clinical presentation, management, and response to rechallenge in patients diagnosed with rituximab induced ILD over a period of one year. *Results.* Out of sixteen patients with CD20 positive non-Hodgkin's lymphoma who received rituximab along with standard chemotherapy, six patients developed features suggestive of R-ILD. Four (66.6%) of these patients had diffuse large B cell lymphoma. The median time of presentation of R-ILD was after the 3rd cycle of chemotherapy. Three patients (50%) presented with acute onset of high fever, dyspnea, and dry cough while the remaining three presented with insidious onset of dyspnea and dry cough. An infectious etiology for the respiratory illness was ruled out in all patients with an exhaustive work-up. Four patients (66.6%) responded to corticosteroid treatment and supplemental oxygen. One patient required mechanical ventilation and succumbed to ILD while another required prolonged supplemental oxygen. Two (33.3%) of patients were successfully rechallenged with rituximab under cover of corticosteroids. *Conclusions.* Rituximab induced lung disease is a rare but potentially fatal pulmonary toxicity which requires a high index of suspicion for early diagnosis and treatment.

1. Introduction

One of the recent advances in cancer therapy has been the addition of monoclonal antibodies to standard chemotherapeutic regimens. Rituximab is one such chimeric (human-mouse) anti-CD20 antibody which was first approved by the US-FDA in 1997 as a single agent for the treatment of relapsed or refractory, low grade or follicular CD20 positive B cell non-Hodgkin's lymphoma (NHL). It is presently part of the standard immune-chemotherapeutic regimen for CD20 positive B cell lymphomas [1]. In these patients, rituximab binds specifically to the CD20 antigen containing pre-B and B lymphocytes, which results in activation of the complement cascade as well as natural killer cells and subsequent cell lysis. It also accelerates apoptosis and increases sensitivity to chemotherapeutic agents [2]. Rituximab has also been approved for use as an immunotherapeutic agent in nonhaematological-like connective tissue disorders and ANCA associated vasculitis [3].

The most commonly reported adverse effect (AE) of rituximab is infusion related reaction (IRR), which typically occurs immediately after the infusion of rituximab [4]. IRR presents with influenza-like symptoms with respiratory manifestations in 30% of cases. Patients may have anaphylactic shock or, more rarely, acute respiratory distress syndrome (ARDS), with a reported fatality rate of 0.04–0.07%. The other reported AEs include lymphopenia, infections, cardiac arrhythmias, elevated liver enzymes, syncope, and urticaria

[4, 5]. Apart from these AEs, respiratory adverse effects were also documented in a postmarketing survey conducted by González et al. [6]. The spectrum of reported respiratory adverse effects reported include transient respiratory symptoms as part of an infusion related reaction, hypersensitivity pneumonitis, interstitial pneumonitis, organizing pneumonia, pulmonary fibrosis, and alveolar hemorrhage. These adverse effects have mostly been described in case reports [7–13], in small case series [14–16], and more recently in a systematic review [17].

After the addition of rituximab to the standard chemotherapeutic regime for CD 20 positive B cell NHL in our institution, we had reported a case of rituximab induced ILD in 2009 [11]. In the present case series we have made an attempt to identify the risk factors, time of presentation, response to treatment, and relapse on rechallenge in 6 subsequent cases of rituximab induced acute ILD.

2. Methods

This was a prospective longitudinal study conducted over a period of one year in a tertiary care hospital. All patients receiving rituximab for CD20 positive NHL who were diagnosed with rituximab induced ILD (R-ILD) were included in the study. The following parameters were compiled in all patients for statistical analysis: demographic data, smoking status, presence of underlying lung disease, clinical presentation, relevant laboratory test results, treatment instituted, response to treatment, and final outcome.

2.1. Treatment Regimen for NHL. All patients included in the study had received the R-CHOP regime which consisted of rituximab (375 mg/sq.m), cyclophosphamide (750 mg/sq.m), doxorubicin (50 mg/sq.m), vincristine (1.4 mg/sq.m), and prednisolone (100 mg on days 1 to 5) at 3 weekly intervals for six to eight cycles depending on the response. All patients receiving the above regimen received the following parenteral premedication 45 min to one hour prior to chemotherapy: paracetamol, hydrocortisone, ranitidine, and chlorpheniramine.

2.2. Diagnosis of R-ILD. R-ILD was suspected when patients presented with one or more of the following symptoms: acute or insidious onset of dyspnea, dry cough, and/or fever. An infectious cause for fever was ruled out in all cases by extensive work-up (complete blood counts, blood and urine cultures, sputum and/or bronchoalveolar lavage (BAL) fluid for Gram stain and culture, stain for AFB, fungal elements, and PCP). In addition, all patients underwent an arterial blood gas analysis, chest radiogram, and echocardiogram. The diagnosis of R-ILD was confirmed in all patients with high resolution computed tomography (HRCT) of the lungs and bronchoscopy was performed in clinically stable patients.

2.3. Severe R-ILD. A patient was diagnosed as severe R-ILD if the clinical presentation was acute, rapidly progressing respiratory failure requiring supplemental oxygen, invasive or noninvasive ventilation, and parenteral corticosteroids.

2.4. Treatment of R-ILD. All patients in whom R-ILD was diagnosed were started on corticosteroids (dosing regimen described below), which were continued for a total duration of six to eight weeks depending on response to treatment.

In patients who were hypoxemic at rest or had features of impending or frank respiratory failure, intravenous methylprednisolone was given at a dose of 125 mg fourth to sixth hourly. Switchover to oral steroids was done after clinical stabilization. Oxygen inhalation was instituted in hypoxemic patients and mechanical ventilation was initiated in patients with rapidly progressive respiratory failure despite oxygen inhalation and high dose parenteral corticosteroids.

Oral prednisolone was given in nonhypoxemic patients at a dose of 0.75–1 mg/kg body weight for the first two weeks and tapered by 0.25 mg/kg every two weeks if there was clinical and radiological resolution.

2.5. Follow-Up Visits and Rechallenge with Rituximab. All patients were followed up on a weekly basis after discharge from hospital after stabilization and fortnightly until complete radiological resolution and normalization of oxygen saturation. At every follow-up visit, thorough clinical examination was done. Six-minute walk test was performed in patients with normal resting saturation on room air to look for desaturation on exertion. Chest radiograms were performed after two and six weeks of treatment.

If rechallenge with rituximab was planned, complete resolution of R-ILD was confirmed with a repeat HRCT and corticosteroids were continued at a dose of 0.5 mg/kg for at least four weeks after the last dose of rituximab infusion and tapered thereafter.

2.6. Statistical Analysis. Statistical analysis was carried out using SPSS (Version 18). Quantitative variables were expressed as mean ± standard deviation and qualitative variables as proportions.

3. Results

Twenty-five patients were diagnosed to have non-Hodgkin's lymphoma over a period of one year out of which 16 (64%) patients were CD20 positive on immunohistochemistry and hence received rituximab along with standard chemotherapy. Age of patients receiving rituximab ranged from 27 to 82 years (mean ± SD = 57 ± 17.4 years). The male to female ratio was 9 : 7. Six patients developed features of R-ILD and were included for further statistical analysis. Demographic and histopathological features of patients with and without R-ILD are compared in Table 1.

3.1. Patient Profile (Table 1). Out of the six patients who developed R-ILD, there were five males and one female patient. All patients were nonsmokers and did not have any underlying chronic lung disease or exposure to occupational hazards. Four (66.6%) patients had diffuse large B cell lymphoma while one each had marginal zone and follicular type lymphoma. At the time of diagnosis of NHL, three (50%) patients were Stage IV, two (33.3%) were Stage IIIA, and one (16.6%) patient was Stage IIIB disease according to Ann

Table 1: Demographic and histological profile of patients receiving rituximab ($n = 16$).

Parameter	Patients without R-ILD ($n = 10$)	Patients with R-ILD ($n = 6$)
Age (mean ± SD) years	52.5 ± 19.3	63.5 ± 11.95
Age > 45 years	5	5
Age < 45 years	5	1
Male : female	4 : 6	5 : 1
Histopathology		
(1) DLBCL*	10	4
(2) Others**	0	2

*Diffuse large B cell lymphoma, **mantle zone lymphoma, and follicular lymphoma.

Table 2: Patients with severe and nonsevere ILD: clinical features.

Parameter	Severe R-ILD ($n = 4$)	Nonsevere ILD ($n = 2$)
Age > 45 years	3 (75%)	2 (100%)
Male gender	3 (75%)	2 (100%)
Histopathology (DLBCL)	4 (100%)	0
Stage III	2	1
Stage IV	2	1
Acute onset of dyspnea	3	0
High grade fever	4 (100%)	0

Arbor staging system. Five (83.3%) patients had developed neutropenia after chemotherapy but had no neutropenia at the time of diagnosis of R-ILD.

3.2. Clinical Presentation and Radiological Features of Patients with R-ILD. The median time of presentation of R-ILD was after the 3rd cycle of chemotherapy; 3 (50%) patients presented after third cycle of rituximab while one each presented after the 2nd, 4th, and 6th cycle, respectively. The mean time of onset of symptoms after the last rituximab infusion was 19 days (range: 15 to 27 days). The time of presentation with respect to the first and last dose of rituximab has been detailed in Table 3.

Three (50%) patients presented with acute onset of symptoms which included isolated high grade fever, high grade fever with dyspnea, and high grade fever with dry cough in one patient each. The remaining 3 patients had an insidious onset of symptoms and presented with dyspnea, dry cough, fever, and fatigue.

Clinical signs in all patients with R-ILD included tachypnea and significant desaturation on minimal exertion. Respiratory system examination was normal in two (33.3%) patients; one (16.6%) patient had bilateral rhonchi while three (50%) patients had end-inspiratory and early expiratory "velcro" crackles bilaterally. Chest radiogram revealed bilateral alveolar opacities in four (66.6%) patients while one (16.6%) patient each had localized opacities (right para-cardiac) and a normal chest radiogram respectively. High resolution computed tomography (HRCT) of the lung showed extensive bilateral ground glass opacities in all patients; one patient each had emphysema and minimal pleural effusion in addition to features of interstitial lung disease. Echocardiogram was normal in five (83.3%) patients; one (16.6%) patient had underlying left ventricular dysfunction.

All patients were nonneutropenic at presentation and underwent extensive work-up for infection including sputum and blood cultures and relevant serology. None of them had any identifiable focus of infection. Only one patient was clinically stable enough to undergo bronchoscopy. A BAL was performed which was negative for infectious etiology (bacteria, mycobacteria, and fungi) and showed neutrophilia on cytology. Transbronchial lung biopsy had been planned but could not be performed as the patient developed refractory desaturation during the procedure.

3.3. Treatment of R-ILD. Five (83.3%) patients were acutely ill at presentation and were started on intravenous methyl prednisolone (in doses described in Section 2) and supplemental oxygen. One patient had prolonged hospitalisation for hypoxemia and respiratory failure; this patient required invasive mechanical ventilation for worsening respiratory failure and succumbed to the illness. One patient was clinically stable and responded to oral corticosteroids alone.

3.4. Outcome. One patient succumbed to ILD while one other patient required domiciliary oxygen and a gradually tapering course of oral corticosteroids for 6 weeks. The remaining 4 patients responded to standard treatment and were discharged on oral corticosteroids alone. All patients were followed up in the respiratory medicine out-patient clinic as described in Section 2.

3.5. Determinants of Severe R-ILD (Table 2). Demographic, clinical, and laboratory parameters of patients who presented with acute onset, rapidly progressing symptoms were analysed. It was found that three out of the four patients presenting with severe ILD were more than 45 years old. The other determinants of severe ILD were the histopathological type of lymphoma (DLBCL) and presentation with high grade fever. The other parameters analyzed have been depicted in Table 2.

3.6. Rechallenge with Rituximab. Two patients who did not have severe ILD were rechallenged with rituximab under steroid cover after complete clinical and radiological resolution. The patients were rechallenged with rituximab after complete clinical and radiological resolution and corticosteroids were continued for at least 4 weeks after the last dose of rituximab. Both patients received rituximab for three cycles along with the other chemotherapeutic agents and did not develop features of ILD during therapy and on follow-up.

4. Discussion

Although the indications for the use of rituximab have expanded to include nonhematological disorders, the

Table 3: Clinical and radiological profile of patients with rituximab-induced interstitial lung disease.

Age and gender	Histology	Stage	Protocol	Cycle at onset	Onset after 1st rituximab infusion (days)	Onset after preceding rituximab infusion (days)	Clinical features	Thoracic high resolution computed tomography findings	Outcome	Rituximab rechallenge
69, M	MZL	IV	R-CHOP	6	150	16	Dyspnea	Bilateral ground glass opacities	Remission	Yes, no recurrence
76, F	DLBCL	IV	R-CHOP	2	30	15	Dyspnea, fever, and rhonchi	Bilateral ground glass opacities bilateral minimal pleural effusion	Remission	No
62, M	FL	IIIB	R-CHOP	3	43	17	Dyspnea, dry cough, fatigue, and crackles	Bilateral ground glass opacities emphysema	Remission	Yes, no recurrence
71, M	DLBCL	IV	R-CHOP	4	72	17	Fever and fatigue	Bilateral ground glass opacities	Remission	No
42, M	DLBCL	IIIA	R-CHOP	3	54	22	Fever	Bilateral ground glass opacities	Remission	No
61, M	DLBCL	IIIA	R-CHOP	3	58	27	Fever, productive cough, and crackles	Bilateral ground glass opacities	Death	No

M: male, F: female, MZL: marginal zone lymphoma, DLBCL: diffuse large B cell lymphoma, FL: follicular lymphoma, R-CHOP: rituximab (375 mg/sq.m), cyclophosphamide (750 mg/sq.m), hydroxy daunorubicin (50 mg/sq.m), oncovin (1.4 mg/sq.m), and prednisolone (100 mg on days 1 to 5).

reported rate of possible drug-induced lung injury is currently <0.03% in more than 540,000 patients treated with this drug worldwide [5]. Among the other chemotherapeutic agents used for the treatment on NHL, cyclophosphamide has also been reported to cause lung toxicity, albeit at much higher doses than that used for the treatment of NHL. Liu et al. reported that among 107 patients treated with R-CHOP regimen, 9 patients developed interstitial pneumonitis when compared to none out of the 66 patients treated with CHOP alone [18]. In a retrospective analysis, 13 of the 90 patients treated with R-CHOP developed interstitial pneumonitis when compared to none out of the 105 patients treated with CHOP alone [19]. Thus, it is evident that pulmonary complications have been reported more frequently in rituximab containing chemotherapy regimens.

The reported pulmonary complications of rituximab are hypersensitivity pneumonitis, ARDS, interstitial pneumonitis, organizing pneumonia, pulmonary fibrosis, and alveolar haemorrhage [17]. While ARDS has been reported to occur as part of a severe infusion related reaction [5], the other reported pulmonary complications occur weeks after the rituximab infusion.

In earlier studies, the time of onset of symptoms suggestive ILD has ranged from 1 day to several weeks after the first infusion, the mean duration being 3 months from the first infusion. Three patterns of presentation have been described in the systematic review by Liote et al. [17], acute (within few hours after the infusion), delayed (1 to 3 weeks after the infusion), and late onset (1–3 months after the last infusion). In our case series of 6 cases of R-ILD, it was observed that respiratory symptoms appeared after a mean of 19 days of the last rituximab infusion between the 3rd and 6th cycles of chemotherapy and that the presentation was acute in about 50% of patients.

The main symptoms of rituximab induced ILD that have been reported in the literature are dyspnea, fever, and hypoxemia. In our case series, half of the patients presented with acute onset while the other half presented with insidious onset of symptoms. All patients had significant hypoxemia at presentation. None of them had a hyperacute onset or ARDS-like picture.

The various radiological patterns reported on HRCT include focal alveolar densities (54%), ground glass opacities (34%), and alveolar opacification (8.5%) [15]. All our patients had bilateral ground glass opacities on HRCT. Bronchoscopic findings reported in various case reports and series are: lymphocytosis in the BAL fluid and the predominant histological pattern was organizing pneumonia [12, 15]. Other patterns that have been reported were nonspecific interstitial pneumonitis, usual interstitial pneumonitis, diffuse alveolar damage, and intra-alveolar hemorrhage [17]. Only one patient in our case series underwent a bronchoscopy; his BAL fluid showed neutrophilic leukocytosis. Lung biopsy could not be performed as the patient developed refractory desaturation during the procedure.

The treatment options mentioned in the reviewed literature include use of corticosteroids, oxygen supplementation, and mechanical ventilation. In the systematic review by Liote et al. [17], 27% of patients required mechanical ventilation and the mortality was 16%. Rituximab rechallenge was done on 15 out of the 37 patients included in this systematic review. Out of these 15 patients, 3 did not develop ILD on rechallenge. Among the remaining 12 patients who developed ILD, 4 patients received rituximab alone and 8 patients received rituximab as part of combination chemotherapy. The use of concomitant corticosteroids probably prevented the development of ILD in the 3 patients who did not develop ILD on rechallenge.

In the present case series, all patients except one responded to supplemental oxygen with high dose intravenous corticosteroids and one patient required invasive mechanical ventilation. One out of the six diagnosed patients succumbed to ILD. Rechallenge with rituximab was done in two patients under cover of corticosteroids and clinical monitoring. None of them developed features of ILD during the infusion or on follow-up.

The possible drawback of the present series is the non-availability of histopathological proof of ILD as all patients except one were unsuitable for bronchoscopy.

5. Conclusion

Interstitial lung disease is a rare but potentially fatal pulmonary toxicity due to rituximab. As the symptoms at presentation are nonspecific, physicians must maintain a high index of suspicion to recognize this complication early and initiate treatment in order to prevent severe morbidity and mortality.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

Thanks are due to Dr. Beena Hemanth for data collection and recording and Ms. Radhika (Biostatistics) and Dr. N. S. Murthy (Biostatistics) for statistical analysis of data.

References

[1] B. D. Cheson and J. P. Leonard, "Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma," *The New England Journal of Medicine*, vol. 359, no. 6, pp. 613–626, 2008.

[2] J. W. Friedberg, "Unique toxicities and resistance mechanisms associated with monoclonal antibody therapy," *Hematology/The Education Program of the American Society of Hematology*, vol. 2005, no. 1, pp. 329–334, 2005.

[3] V. McDonald and M. Leandro, "Rituximab in non-haematological disorders of adults and its mode of action," *The British Journal of Haematology*, vol. 146, no. 3, pp. 233–246, 2009.

[4] J. Bienvenu, R. Chvetzoff, G. Salles et al., "Tumor necrosis factor α release is a major biological event associated with rituximab treatment," *Hematology Journal*, vol. 2, no. 6, pp. 378–384, 2001.

[5] E. Kimby, "Tolerability and safety of rituximab (MabThera)," *Cancer Treatment Reviews*, vol. 31, no. 6, pp. 456–473, 2005.

[6] V. González, E. Salgueiro, F. J. Jimeno, A. Hidalgo, T. Rubio, and G. Manso, "Post-marketing safety of antineoplasic monoclonal antibodies: rituximab and trastuzumab," *Pharmacoepidemiology and Drug Safety*, vol. 17, no. 7, pp. 714–721, 2008.

[7] P. R. Bauer, C. S. Zent, M.-C. Aubry, and J. H. Ryu, "Recurrent fevers, cough, and pulmonary opacities in a middle-aged man," *Chest*, vol. 137, no. 6, pp. 1465–1469, 2010.

[8] A. R. Tonelli, R. Lottenberg, R. W. Allan, and P. S. Sriram, "Rituximab-induced hypersensitivity pneumonitis," *Respiration*, vol. 78, no. 2, pp. 225–229, 2009.

[9] M. Subramanian, R. Manjunath, N. Kilara, and M. K. N. Rao, "Rituximab-induced subacute interstitial pneumonitis: a case report and review of literature," *Journal of Cancer Research and Therapeutics*, vol. 6, no. 3, pp. 344–346, 2010.

[10] B. Saito, T. Nakamaki, D. Adachi, J. Suzuki, and S. Tomoyasu, "Acute respiratory distress syndrome during the third infusion of rituximab in a patient with follicular lymphoma," *International Journal of Hematology*, vol. 80, no. 2, pp. 164–167, 2004.

[11] R. J. Leon, A. Gonsalvo, R. Salas, and N. C. Hidalgo, "Rituximab-induced acute pulmonary fibrosis," *Mayo Clinic Proceedings*, vol. 79, no. 7, pp. 949–953, 2004.

[12] M. Mian, C. Rass, G. Hutarew, B. Kofler, M. Fiegl, and R. Greil, "Extensive organizing pneumonia during chemo-immunotherapy containing rituximab and G-CSF in a patient with diffuse large B-cell lymphoma: case report and review of the literature," *Leukemia and Lymphoma*, vol. 47, no. 8, pp. 1683–1685, 2006.

[13] D. T. Alexandrescu, J. P. Dutcher, K. O'Boyle, M. Albulak, S. Oiseth, and P. H. Wiernik, "Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma," *Leukemia & Lymphoma*, vol. 45, no. 11, pp. 2321–2325, 2004.

[14] C. Burton, R. Kaczmarski, R. Jan-Mohamed, M. C. Benyunes, P. S. Multani, and A. Saunders, "Interstitial pneumonitis related to rituximab therapy," *The New England Journal of Medicine*, vol. 348, no. 26, pp. 2690–2691, 2003.

[15] M. Soubrier, G. Jeannin, J. L. Kemeny et al., "Organizing pneumonia after rituximab therapy: two cases," *Joint Bone Spine*, vol. 75, no. 3, pp. 362–365, 2008.

[16] S. A. Wagner, A. C. Mehta, and D. A. Laber, "Rituximab-induced interstitial lung disease," *The American Journal of Hematology*, vol. 82, no. 10, pp. 916–919, 2007.

[17] H. Liote, F. Liote, B. Seroussi, C. Maynaud, and J. Cadranel, "Rituximab induced lung disease: a systematic literature review," *European Respiratory Journal*, vol. 35, pp. 681–687, 2010.

[18] X. Liu, X.-N. Hong, Y.-J. Gu, B.-Y. Wang, Z.-G. Luo, and J. Cao, "Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphoma," *Leukemia and Lymphoma*, vol. 49, no. 9, pp. 1778–1783, 2008.

[19] D. Ennishi, Y. Terui, M. Yokoyama et al., "Increased incidence of interstitial pneumonia by CHOP combined with rituximab," *International Journal of Hematology*, vol. 87, no. 4, pp. 393–397, 2008.