Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphoma

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Abstract
Rituximab is widely used for CD20⁺ non-Hodgkin lymphoma (NHL). The use of rituximab has been uncommonly associated with pulmonary toxicity. We report here a single institution experience on the clinical characteristics, diagnosis, treatment and outcome of rituximab-induced interstitial lung disease. From May 2007 to February 2008, 107 patients with NHL received rituximab-containing chemotherapy. Among them, nine patients were identified who developed interstitial pneumonitis during rituximab-containing chemotherapy. The median cycles of rituximab prior to presentation was two. Most of the patients manifested with high fever, while some had dyspnea or non-productive cough. Pulmonary diffuse interstitial infiltrations were seen on computed tomography scans of all the patients. Treatment consisted of glucocorticoids with a slow taper and antibiotics against atypical pulmonary pathogens. Eight patients responded to glucocorticoid therapy and recovered, whereas one died of secondary infection. Two of the four patients who were retreated with rituximab had recurrence of interstitial pneumonitis. In conclusion, clinicians should be highly alerted of the possibility of interstitial pneumonitis in NHL patients treated with rituximab-containing regimen. Early recognition, timely establishment of diagnosis and prompt treatment with glucocorticoids in combination with empirical antibiotics are essential for a favourable clinical outcome. Retreatment with rituximab and other cytotoxic agents known to cause pulmonary toxicity should be carefully considered for risk benefit ratio.

Keywords: Interstitial pneumonitis, non-Hodgkin lymphoma, rituximab

Introduction
Rituximab, a chimeric (murine/human) anti-CD20 antibody, has been used widely as a single agent or in combination with chemotherapy regimens in the standard care for the treatment of CD20⁺ non-Hodgkin lymphoma (NHL) [1–3]. Rituximab therapy has been associated with an infusion-related symptom complex consisting of fever, chills and rigors that is usually self-limited [4]. Overt bronchospasm occurs in about 2% of patients. These complications are transitory and usually do not have long-term sequel. Recently, rituximab-induced interstitial lung disease (R-ILD) has also been recognised as a rare side effect, a series of cases have been reported in the literature as case reports [5,6], and the manufacturer reported rate of incidence is less than 0.03% [7]. These reports have alerted our awareness and early detection to this complication.

We report nine cases of rituximab-related interstitial pneumonitis diagnosed and treated in our institution. We show here the clinical details, the durations of steroid treatment and the outcomes on rituximab re-challenge.

Patients and methods
Chart reviews were done focussing on patients with NHL treated with rituximab-containing...
chemotherapy regimens between May 2007 and February 2008. One hundred and seven patients were identified who received rituximab-containing chemotherapy during this period, among them, nine patients were identified for the diagnosis of acute interstitial pneumonitis during the treatment. Medical records and radiographic documents were reviewed. Data on patient characteristics, clinical presentations, diagnostic procedures, chemotherapy regimens received including rituximab exposures, treatments, outcomes and retreatments with rituximab were extracted and analysed in the present study.

Results

The clinical characteristics of the nine cases are summarised in Table I. Five patients were diagnosed with diffuse large B cell lymphoma (DLBCL), two patients were treated for mantle cell lymphoma (MCL), one for follicular lymphoma (FL), and one for small B cell lymphoma. Eight patients were treated with rituximab, cyclophosphamide, epirubicin, vincristine and prednisone regimen (R-CEOP), only the patient with small B cell lymphoma was treated with rituximab, cyclophosphamide, vincristine and prednisone (R-CVP). The median age of the patients was 54 (range from 49 to 81 years old). All patients responded to chemotherapy by clinical and radiological image studies. All patients had pretreatment CT scans, none of the patients had interstitial lung abnormalities. After 1–5 treatment cycles of rituximab (median two cycles), eight (89%) patients presented with fever for 1–9 days, three (33%) patients also complained of dyspnea, and three patients complained of dry cough. Four patients were found to have inspiratory crepitations at presentation while other five patients had normal physical examinations. These symptoms and signs appeared at 9–19 days after the previous infusion of rituximab (median 14 days). At the onset of pulmonary symptoms and/or fever, four patients had normal blood count without signs of myelosuppression, among them, one patient received prophylactic G-CSF; five patients demonstrated grade I–III neutropenia. The durations of neutropenia in these patients were all transient, and the leukocyte counts returned to normal in all patients at the diagnosis of interstitial pneumonitis by CT scan. Blood culture for the detection of cytomegalovirus and fungus was performed for one patient but showed no evidence of pathogens. Chest X-ray exams were done in two patients with no obvious abnormalities. All the above eight patients underwent helical computed tomography (CT) scans for further diagnosis of fever or dyspnea within a range of 1–9 days (median 4 days).

Bilateral pulmonary diffuse interstitial infiltrations were seen on CT scans in seven patients and unilateral pulmonary flaky interstitial infiltration in one patient. One patient also had a pulmonary-function test which demonstrated a restrictive pattern as well as diffusion deficit consistent with interstitial pneumonitis. In contrast to the above, one patient was found to have bilateral diffuse interstitial infiltrates on a routine mid-treatment CT scan.

The diagnosis of probable R-ILD for the above nine patients were made based on the CT scan findings and no clear evidence of infection was found. All patients were treated with 5 mg of dexamethasone or 40 mg of methyl-prednisolone intravenously daily for three consecutive days, followed by prednisone orally with slow taper. CT scans were repeated every week until complete absorption of interstitial infiltrates on CT scans. The median duration of steroid treatment needed to control the symptoms and have evidence of recovery on CT scans was 6 days. The median duration of steroid treatment was 21 days (10–35 days). Eight patients were also treated with azithromycin simultaneously to cover atypical pneumonia. Eight patients showed complete recovery and successful discontinuation of steroids, whereas one patient who responded to glucocorticoid therapy initially developed secondary pulmonary infection and pleural effusion with severe hypoxemia later. This patient died of respiratory failure 41 days after the occurrence of interstitial pneumonitis.

Subsequent rituximab and chemotherapy was held immediately after the diagnosis. Further treatment with rituximab was withheld in four patients, while continued in another four patients. Two of the four patients manifested with recurrence of interstitial pneumonitis after retreated with rituximab. One relapsed patient responded again to glucocorticoid with slow taper more than 1 month (Figure 1). This patient did not receive chemotherapy thereafter. The recurrence of interstitial pneumonitis of the other patient was diagnosed on routine CT scan after one more cycle of treatment, and the patient was entirely asymptomatic. No steroid treatment was given to the patient and the patient was further continued on CEOP regimen without rituximab.

Discussion

In this study, we describe nine patients with NHL in whom interstitial pneumonitis developed after rituximab-containing chemotherapy. This disorder showed a sudden onset, high fever and radiographically evident diffuse pulmonary infiltrates, with a dramatic response to treatment with glucocorticoids.
Table I. Review of nine cases with rituximab-related interstitial pneumonitis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62</td>
<td>63</td>
<td>54</td>
<td>49</td>
<td>58</td>
<td>51</td>
<td>81</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>DLBCL</td>
<td>DLBCL</td>
<td>MCL</td>
<td>FL</td>
<td>DLBCL</td>
<td>MCL</td>
<td>Small-B NHL</td>
<td>DLBCL</td>
<td>DLBCL</td>
</tr>
<tr>
<td>Stage</td>
<td>IIA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIA</td>
<td>IVA</td>
<td>IIA</td>
<td>IIA</td>
<td>IIA</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CVP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
</tr>
<tr>
<td>No. of cycles</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever</td>
<td>Asymptomatic</td>
<td>Dyspnea</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Fever, dry cough</td>
<td>Fever</td>
<td>Fever</td>
<td>Fever, dry cough, dyspnea</td>
<td>Fever, dry cough, dyspnea</td>
<td>Fever</td>
<td>Fever, dry cough, dyspnea</td>
<td>Fever, dry cough, dyspnea</td>
<td>Fever, dry cough, dyspnea</td>
</tr>
<tr>
<td>Physical exam findings</td>
<td>Bibal inspiratory crepitations</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
<td>Unremarkable</td>
</tr>
<tr>
<td>Time from previous infusion of R to onset (day)</td>
<td>9</td>
<td>12</td>
<td>9</td>
<td>19</td>
<td>14</td>
<td>18</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Time from onset to CT scan (day)</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>–</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Treatment (all drugs were used simultaneously unless specified)</td>
<td>DXM, azithromycin</td>
<td>DXM, azithromycin</td>
<td>m-PDN, azithromycin</td>
<td>m-PDN, azithromycin</td>
<td>m-PDN</td>
<td>m-PDN, azithromycin, tienam and itraconazole were used because of aggravation</td>
<td>DXM, azithromycin</td>
<td>m-PDN, azithromycin</td>
<td></td>
</tr>
<tr>
<td>Duration of steroid to control the disease (day)</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>–</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Total steroid treatment (day)</td>
<td>33</td>
<td>21</td>
<td>21</td>
<td>14</td>
<td>10</td>
<td>20</td>
<td>–</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>Outcome</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Recovery</td>
<td>Death</td>
<td>Recovery</td>
</tr>
<tr>
<td>Retreatment</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>R-CEOP</td>
<td>Radiation</td>
<td>CHOP</td>
<td>No</td>
<td>–</td>
<td>Recovery</td>
</tr>
<tr>
<td>Recurrence of ILD</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>Recovery</td>
<td>CHOP</td>
</tr>
</tbody>
</table>

Fever was the most common presenting symptom (89%), whereas only 33% patients had complaints of dyspnea in our study. These are in contrast to what was reported in Wagner’s review [6], where the most common symptoms were dyspnea (81%), fever (72%) and cough (36%). Conceivably, it is due to the early diagnosis made in the present study so that the full spectrum of symptoms such as dyspnea did not have chance to occur. In fact, the median time from the onset of fever or dyspnea to CT scan was only 4 days. CT scans were essential in demonstrating subtle interstitial disease, while chest radiographs are unreliable.

When treatment is started at the early course of the disease, there is rapid response to steroid, and the outcome is favourable. Steroid slow taper with close monitoring of the symptoms and radiological images is also essential to prevent recurrence. The initial dose of steroid was relatively low for our patients, whereas higher dose is needed for severe patients as reported in literatures.

In the period of May 2007 to February 2008, the total number of patients who were treated with rituximab-containing chemotherapy in our institute was 107. Among them, nine patients were identified with interstitial pneumonitis. So the incidence of this phenomenon was 8.4% in this patient population. The incidence is relatively higher than previously reported. This could be partially due to high alert and early detection of this complication. Increased genetic susceptibility of drug-induced interstitial lung disease in Japanese patients has been reported [8]. Whether there is a similar relationship in Chinese patients awaits further evaluation. Similarly, the median cycles of rituximab-containing chemotherapy prior to presentation was two in our study versus four in previous study [6]; most likely due to the same reason of high alert among our physicians and early detection.

The diagnosis of rituximab-induced interstitial lung disease in our study was mainly made based on the characteristic diffuse interstitial infiltrations and the lack of obvious clinical evidence of other microbial infections. Some of the diagnostic procedures such as bronchoscopy for bronchoalveolar lavage (BAL) are critical to rule out infectious disease, however, BAL and blood cultures for opportunistic infections are not widely available in China. Azithromax, an antibiotic effective for atypical pneumonia, was empirically added to all the patients managed for presumable rituximab-induced interstitial lung disease in our institutional experience. In contrast, in a clinical study comparing CEOP with or without thalidomide for the treatment of diffuse large B cell lymphoma in our institute (manuscript at preparation), only two of 66 patients developed infectious lung events in all patients combined. Neither of these two patients showed interstitial pneumonitis. Therefore, we believe that the patients

![Figure 1](a) Helical computed tomographic scanning showing bilateral ground-glass shadowing. (b) A repeat CT scan after glucocorticoid and antibiotic therapy showing almost complete resolution of the interstitial infiltration. (c) Bilateral pulmonary ground-glass shadowing recurred after the patient was retreated with R-CEOP chemotherapy.
described in this series most likely suffered from interstitial pneumonitis instead of infectious complications, and rituximab played an important role in it.

Our study also showed that most patients should have rapid response to the steroid treatment; therefore, if such response is not observed, further invasive work up should be immediately done to look for alternative diagnosis. On the other hand, it is questionable whether there is a role of BAL or lung biopsy in elucidating the pathophysiology of the underlying etiology of interstitial lung disease. The histological findings in two studies [5,6] showed nonspecific interstitial inflammation or fibrosis. Likewise, the role of positron emission tomography/computed tomography (PET/CT) in the diagnosis of interstitial pneumonitis is also uncertain, some studies described diffusely increased uptake in the lungs [5,9].

Interstitial pneumonitis recurred in two of four cases retreated with R-CEOP. Similarly, retreatment of rituximab with or without CHOP resulted in pulmonary deterioration in two reported cases [10,11], one of which was fatal [10]. On the other hand, our study and others both observed that some patients can be rechallenged uneventfully [12]. It poses a complex clinical dilemma regarding the continuation of rituximab containing therapy. The decision should be made based on a balance between the curative intention for the malignant tumor versus the potential impact of the pulmonary toxicity. Although one study suggested an associated risk of chemotherapy-induced pulmonary fibrosis [13] with the presence of polymorphic tumor necrosis factor z(TNFz) microsatellite, there is still no effective predictor for rituximab-induced interstitial pneumonitis.

The pathogenesis of R-ILD is largely unknown and cytokine release is postulated to be the mechanism. Several studies demonstrated that rapid lymphocyte lysis, complement activation, and TNFz release occur after rituximab infusion [4,14,15]. TNFz has been implicated as a key cytokine in many inflammatory lung diseases, including chronic obstructive pulmonary disease [16] and pulmonary fibrosis [17]. Interestingly, rituximab-induced acute pulmonary fibrosis [18] and bronchiolitis obliterans [9] had also been reported. On the basis of the proposed pathophysiology of the lung injury, some authors propose to use anti-TNFz directed therapy in patients whose clinical condition worsen despite corticosteroids [6].

Many cytotoxic agents are known to cause lung injury. Cyclophosphamide, which all of our patients were treated with, has also been shown to cause drug-induced lung disease. Cyclophosphamide-induced lung injury includes two patterns [19]. Early-onset pneumonitis appears 1–6 months after exposure, which is reversible and may respond to corticosteroid therapy. Late-onset pneumonitis can even appear years after drug discontinuation, which has a chronically progressive course and appears unresponsive to corticosteroid therapy. Endogenous production of reactive oxygen species was suggested as an important mechanism of cyclophosphamide-induced lung injury [20].

In conclusion, clinicians should be aware of interstitial pneumonitis in NHL patients receiving rituximab-containing regimen. Once a patient has fever of unknown reason, CT scan should be performed immediately to make an early diagnosis of the disease. Bronchoscopy with bronchoalveolar lavage should be done to rule out infectious disease. Discontinuation of rituximab-containing chemotherapy and treatment with glucocorticoids immediately is critical to prevent severe sequel. According to our experience, we suggest empirical use of antibiotics against atypical pulmonary pathogens until cultures of pathogens demonstrate negative results. Retreatment with rituximab and other cytotoxic drugs known to cause pulmonary toxicity should be carefully considered based on benefit and risk ratio. Further basic and clinical researches are needed to elucidate the mechanisms of rituximab-induced lung injury.

References


