REVIEW

Rituximab-induced lung disease: a systematic literature review

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ABSTRACT: **The anti-CD20 antibody rituximab has been reported to induce a heterogeneous spectrum of lung disorders. The aim of the present study was to critically review data on the clinical presentations, causality assessments and management strategies of lung diseases possibly related to rituximab.**

A systematic literature review was performed on English-language reports in PubMed until September 2008.

Cases of lung diseases ascribed to rituximab (n=45) were identified, with three time-to-onset patterns. The most common presentation was acute/subacute hypoxaemic organising pneumonia (n=37), starting 2 weeks after the last infusion (often around the fourth cycle) and resolving, in most cases, provided glucocorticoid therapy was given early. Acute respiratory distress syndrome occurred in five patients, within a few hours and usually after the first infusion. In the remaining three patients, macronodular organising pneumonia developed insidiously long after rituximab therapy and responded to steroids. Eight patients died. Based on time to onset, symptoms, and responses to discontinuation and rechallenge with rituximab and other drugs, 13 cases were highly compatible and 32 compatible with rituximab-induced lung disease.

Knowledge of these presentations of rituximab-induced lung disease should prove helpful for diagnosis and causality assessment purposes. Time-to-onset data, suggesting different pathogenic mechanisms, support closer clinical and perhaps radiological monitoring between infusions, particularly in patients with a history of reversible respiratory symptoms.

KEYWORDS: Adverse effects, B-cell lymphoma, interstitial pneumonitis, organising pneumonia, rheumatoid arthritis, rituximab

Rituximab is a chimeric human–mouse immunoglobulin G1–κ monoclonal antibody with high affinity for CD20 surface antigens expressed by normal human pre-B- and B-lymphocytes but not by stem or plasma cells. Binding of the antibody to CD20 causes cell lysis *via* activation of the complement cascade and natural killer cells. Accelerated apoptosis and sensitivity to antineoplastic agents are also induced by the drug [1]. Rituximab may persist in the body for several months. Peripheral B-cell depletion lasts 6–9 months after treatment in most patients [2].

Rituximab is the major step forward in lymphoma treatment since the late 1990s. It was approved by the Food and Drug Administration in 1997 and by the European Agency for the Evaluation of Medicinal Products (EMEA) in 1998 for low-grade non-Hodgkin's lymphoma expressing CD20 and chronic lymphocytic leukaemia, and subsequently diffuse large B-cell non-Hodgkin's lymphoma [3]. In 2006, the EMEA approved rituximab for rheumatoid arthritis (RA) in adults [4]. Uses in idiopathic thrombocytopenic purpura (ITP) [5], autoimmune haemolytic anaemia, Sjögren's syndrome, systemic lupus and systemic vasculitis are undergoing evaluation. Patients with lymphoma are given one to six infusions of 375 $mg \cdot m^{-2}$ at intervals depending on the treatment protocol. In RA, 1,000 mg is given twice, with a 2-week interval, followed by retreatment 6 months later if needed.

From safety data on 960,000 patients treated worldwide up to 2007 [2, 6–8], rituximab was well tolerated. However, side-effects were recorded in phase III controlled trials and post-marketing

surveillance programmes, with less severity in RA than in lymphoma [2, 9]. Infusion-related reactions (IRRs) occurred in 9–15% of patients. IRRs consist of influenza-like symptoms, with respiratory manifestations in 30% of cases. Patients may experience anaphylactic shock or, more rarely, acute respiratory distress syndrome (ARDS), fatal in 0.04–0.07%. These serious side-effects have led the pharmaceutical companies that market rituximab to recommend a number of precautions (table 1) [10]. Although the rate of delayed neutropenia was slightly increased, the immediate risk of infection, namely pulmonary infection, was not increased, and data were incomplete regarding the risk of delayed infection [11]. Severe delayed lung injury was noted with a rate of occurrence of 0.03% in the review of KIMBY [2] and 0.01% in the Spanish pharmacovigilance database [9]. Of all side-effects of rituximab, lung disease may have by far the highest reporting odds ratio (ROR; 68.1; 95% confidence interval 23.8–194.9) [9].

The present study was performed for several reasons: lung disease was not documented in the clinical trials, the drug is being used increasingly as mentioned before [4], and case reports of possible rituximab-induced lung disease are accumulating at a fast pace. The primary objective of this systematic literature review was to obtain a comprehensive picture of the pulmonary side-effects of rituximab and to provide a diagnostic standard (for drug causality assessment) [12, 13]. Time to onset was also evaluated for features that might help in the development of protective measures for clinical practice.

METHODS

Data sources and searches
According to Cochrane Reviews methodology, a systematic literature review was conducted for case reports in English or French indexed in PubMed between 1997 (the year of licensure of rituximab) and September 2008.

Study selection
The following Medical Subject Heading (MeSH) terms were used: ''rituximab'' AND ''adverse effects'' AND ''interstitial pneumonitis'' OR ''idiopathic interstitial pneumonitis'' OR ''organizing pneumonia''. Subsequently, a search was conducted using ''rituximab'' combined with ''respiratory side effect'', ''drug reaction'' or ''pulmonary toxicity''. The references of the articles retrieved by the PubMed search were searched manually. Abstracts from meetings with no corresponding full-length publication were not considered. For each reported case, the country and city were recorded in order to eliminate redundancies.

Data extraction and quality assessment
When available, seven categories of data were extracted from each case report: 1) patient characteristics (age, sex, geographic origin and reason for rituximab therapy); 2) treatment modalities (dosage, number of cycles and cumulative dose); 3) time to onset (time between the last rituximab infusions and respiratory symptoms) and whether symptoms had occurred following previous cycles; 4) tempo of onset (hyperacute: development of pneumonitis within hours after the first symptom; acute or subacute: development over a few days; and chronic: development over several weeks or months); 5) respiratory and extra-respiratory manifestations (clinical and radiological features, computed tomographic findings, cytological studies of bronchoalveolar lavage fluid (BALF), and histological findings from transbronchial and/or open lung biopsy specimens); 6) therapeutic management (discontinuation of rituximab alone or of all chemotherapy agents, and steroid therapy) and course; and 7) whether subsequent treatment involved the use of rituximab (alone or with other chemotherapy agents) or other chemotherapy agents without rituximab, and whether re-exposure to rituximab of patients with respiratory symptoms at one or more earlier cycles was intentional or unintentional (e.g. in patients with self-limited symptoms identified retrospectively).

Study quality was assessed independently by two reviewers, one with expertise in drug-induced lung diseases and one with expertise in research methods. The following key design features were evaluated: presence of valuable data, especially for time to onset; exclusion of other causes; and re-introduction conditions. Disagreements were resolved by independent adjudication.

Data synthesis and analysis
Numerical data are expressed as mean, range and percentage. A Chi-squared test for independence was used to compare the two distributions, namely, time since the last infusion and tempo of onset since the first symptom.

TABLE 1	Recommended precautions for prevention of infusion-related reactions when using rituximab

Pharmaceutical company recommendations#

Give 1 g acetaminophen (paracetamol), an antihistamine and 100 mg methylprednisolone 60 min before the rituximab infusion, which should be started 30 min after the end of the methylprednisolone infusion

Mild side-effects

Decrease the infusion rate

Serious side-effects

Stop the infusion immediately

Symptomatic treatment

Look for laboratory features of tumour lysis syndrome

Restart on a case-by-case basis, at a lower dosage and at a slower rate, under close monitoring

In the event of recurrence, definitive treatment discontinuation is recommended

Present authors' recommendations

Prevent hyperacute lung disease by increasing the glucocorticoid dose given before the rituximab infusion

Acute and subacute lung disease

Inform the patients of the risk of respiratory disease, which is greatest on day 15 and around cycle 4

Routinely monitor respiratory symptoms between infusions

Obtain a radiograph immediately if any symptom occurs, however mild

Diagnostic evaluation and prompt glucocorticoid therapy if suspicion of rituximab-induced lung disease

#: modified from SMOLEN et al. [10].

RESULTS

Number of articles retrieved and numbers of included and excluded cases

A total of 52 cases were identified (fig. 1) [3, 14–41], described in anecdotal case reports and in nine case series reporting two cases [16, 21, 29, 34, 35], three cases [19, 33], four cases [38] or nine cases [39]. A few adequately documented cases occurred during clinical trials. Seven out of these 52 cases were excluded due to insufficient detail about cases that occurred in clinical trials (n=2) [15], the time to onset being too long to be compatible with causality of rituximab (n=2, one case each of fluctuant macronodular organised pneumonia 9 months after the last infusion in a patient with Castleman disease [16] and constrictive bronchiolitis 10 months after the last infusion [14]) and manifestations unrelated to rituximab-induced lung disease (one case each of heart failure ascribed to direct myocardial toxicity of rituximab [3], fludarabine-induced lung disease confirmed by a positive rechallenge test result [3] and fatal haemoptysis complicating necrotising lymphomatoid granulomatosis of the lung [41]). This left 45 cases of possible rituximab-induced lung disease for the present study.

Characteristics of the patients

The mean (range) age of the patients was 65 (43–80) yrs, and the male:female ratio was 2:1. Of the 45 patients, 17 (38%) were in Asia, 12 were in the Americas (and their ethnic origin was not reported) and 16 were in Europe. The rate of occurrence was 8.4% (nine out of 107) in the Korean case series [39] and 11% (four out of 36) in the Dutch case series [38]. The reason for rituximab therapy was diffuse large B-cell lymphoma in 30 patients, indolent lymphoma in 10 (mantle cell lymphoma (n=2) [20, 21, 39], marginal zone lymphoma or mucosa-associated lymphoid tissue (MALT) (n=3) [22, 32, 33], follicular lymphoma (n=4) [24, 32, 39] and Waldenström's macroglobulinaemia (n=1) [38]), chronic lymphocytic leukaemia in two [3, 37], ITP in two [18, 26] and RA in one [16].
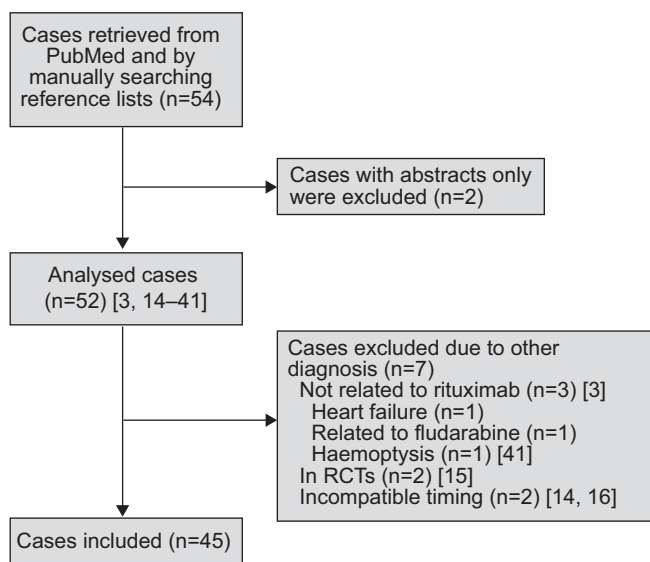

FIGURE 1. Flow chart showing the total number of cases retrieved by the literature search and the numbers of excluded and included cases. RCT: randomised controlled trial.

Modalities of rituximab administration

Overall, rituximab was given at a mean dosage of 375 mg·m^{-2} per intravenous cycle on 1 or 2 days consecutively. The interval between cycles was 8, 15 or 21 days. Rituximab alone was used in seven patients [20, 21, 24, 26, 33, 37, 40], and with stable-dosage methotrexate for maintenance therapy of RA in one [16]. The other 37 patients received rituximab in combination with multiple chemotherapy regimens (COP, CHOP, CEOP, CVP, ACVBP, VNCOP, fludarabine, cladribine and growth factors (where C is cyclophosphamide, O vinblastine, P prednisone, H doxorubicin, E epirubicin, V etoposide, A Adriamycin, B bleomycin and N mitoxantrone)).

Time-to-onset data

The mean time from the first rituximab infusion to onset of the respiratory manifestations (n=21) was 3 months (12 weeks), with a peak at the fourth cycle (fig. 2a) and a mean cumulative dosage of 1,600 mg·m^{-2}. The histogram of time to onset from the last rituximab infusion clearly shows three peaks (fig. 2b). The first peak, with five patients [17–19], occurred a few hours after the infusion (day 1), i.e. reflected early-onset forms. The second peak, with 29 patients, occurred exactly on day 15, and eight additional cases occurred a few days before (days 8–15) or after (days 15–21) this second peak. Thus 37 patients experienced delayed-onset forms [3, 20–39]. Finally, the third peak reflected late-onset forms, occurring 1–3 months after the last infusion in three patients [16, 33, 40].

Tempo of onset

The tempo of onset (table 2) was usually acute or subacute (36 patients) [3, 20, 21, 23–39]. In six patients, the onset was hyperacute [17–19], and, in three patients, it was chronic [16, 33, 40]. The distributions of tempo of onset and time to onset from the last rituximab infusion showed a nearly perfect match (table 2) and were significantly linked ($p < 1 \times 10^{-16}$): the five early-onset cases were hyperacute; 36 out of the 37 delayed-onset cases were acute or subacute; and the three late-onset cases were chronic.

Symptoms and course

Early-onset hyperacute forms

All five patients in this group had ARDS with arterial oxygen tensions (Pa,O$_2$) of <50 mmHg. A single patient underwent lung biopsy, which showed diffuse alveolar damage and intra-alveolar haemorrhage [19]. All five patients required mechanical ventilation and received a bolus of steroids. Two patients died.

Of the five patients, four were receiving combination chemotherapy regimens and four experienced ARDS following the first rituximab cycle. The recommended pre-medication was given to four patients; for the remaining patient, this information was not available. Rechallenge was performed in two patients and gave negative results in both, despite the absence of additional precautions [19].

Delayed-onset acute forms

Of the 37 patients in this group, 34 had non-Hodgkin's lymphoma, two had chronic lymphocytic leukaemia and one had ITP. Rituximab was used alone in four patients, and with combination chemotherapy in 33. Onset occurred after the third, fourth or fifth cycle in 18 of the 32 patients for whom this
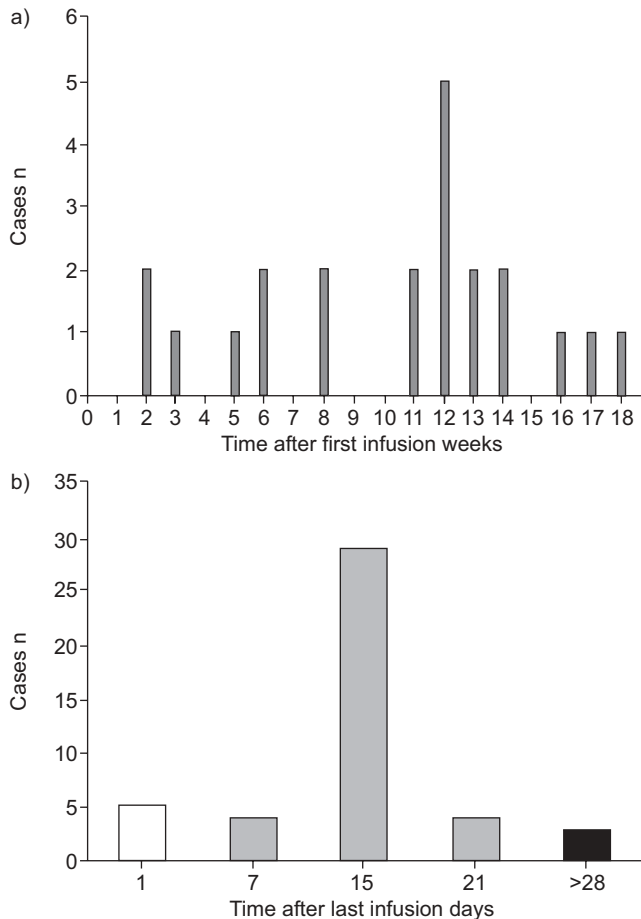
a)

b)

FIGURE 2. Time to onset of the respiratory manifestations from a) the first rituximab infusion and b) the last rituximab infusion. □: hyperacute early-onset forms; ■ (grey): acute and subacute delayed-onset forms; ■: chronic late-onset forms.

information was available, and on day 15 after the infusion in 29 out of the 37 patients. Earlier infusions had been followed, in nine patients, by respiratory symptoms consisting of coughing, dyspnoea or reversible bronchospasm [3, 20, 21, 25, 26, 31, 33, 38]. These symptoms were not consistently present following the first cycle. They occurred repeatedly in eight patients (twice in three, three times in two, four times in two, and five times in one).

The clinical and radiological features are shown in table 3. The main manifestations were dyspnoea and fever. Hypoxaemia with P_{a,O_2} of <60 mmHg was the rule. Computed tomography of the chest showed focal alveolar densities in 54% of patients, usually at multiple sites and in combination with ground-glass attenuation (32%). Positron emission tomography was performed in seven patients and consistently showed an early increase in tracer uptake [31, 33, 38]. Findings from micro-biological studies were negative (n=40), including those on BALF. Failure of empirical antibiotic treatment was mentioned for 20 patients.

BALF cytology results were available for nine patients [22, 28–30, 34, 37, 38]. A consistent finding was lymphocytosis (13–90%), with a predominance of CD4+ T-cells. Histological data were obtained (table 3) by surgical lung biopsy in six patients

TABLE 2	Distribution of cases by time to onset from the last rituximab infusion and by tempo of respiratory symptom development after the first symptom

Tempo of onset	Time to onset			Total
	Early[#]	Delayed[¶]	Late[+]	
Hyperacute[§]	5	1		6
Acute/subacute[f]		36		36
Chronic[##]			3	3
Total	5	37	3	**45**

[#]: day 1; [¶]: days 7–21; [+]: day >30; [§]: over a few hours; [f]: over several days; [##]: over several weeks or months.

[3, 23–25, 32, 33] and by transbronchial lung biopsy in five [27, 31, 35–37]. According to the American Thoracic Society/European Respiratory Society classification [42], the predominant histological pattern was organising pneumonia (eight out of 11; 72%) [23–25, 27, 31–33, 37], isolated (n=5) or associated with nonspecific interstitial pneumonia or usual interstitial pneumonia. None of the patients exhibited nonspecific interstitial pneumonia or usual interstitial pneumonia as the only histological pattern.

Of the 37 patients in this group, 10 required mechanical ventilation [20, 23–25, 28, 29, 31–33, 35]. Six patients died, including

TABLE 3	Clinical, computed tomography (CT) and histological findings in patients with acute or subacute rituximab-induced lung disease

Clinical features[#]	
Cough	16 (43)
Dyspnoea	30 (85)
Fever	23 (62)
Crepitant rales	13 (35)
Hypoxia	15 (37)
P_{a,O_2} <60 mmHg	8 (53)[§]
Chest pain n	1
Rash and hypereosinophilia n	2
Predominant CT pattern[#]	
Focal alveolar pattern $\geqslant 1$[¶]	19 (54)
Ground-glass opacities	12 (34)
Diffuse alveolar pattern	3 (8.5)
Macronodules n	1
Histological pattern[+]	
Organising pneumonia	8 (5)
Nonspecific interstitial pneumonia	4 (0)
Usual interstitial pneumonia	2 (0)
Diffuse alveolar damage	2 (0)
Intra-alveolar haemorrhage	2 (0)

Unless otherwise indicated, data are presented as n (%), except for histological pattern, which is presented as n (number with isolated pattern). P_{a,O_2}: arterial oxygen tension. [#]: n=37 [3, 20–39]; [¶]: $\geqslant 1$ focal alveolar infiltrates; [+]: evaluated by lung biopsy (n=11) [3, 23–25, 27, 31–33, 35–37]; [§]: of n=15 with hypoxia.

two with a history of respiratory symptoms following previous cycles [25, 31]. Of the six patients who died, only one was receiving rituximab alone, for follicular lymphoma [24]. The 31 survivors made a full recovery, with clinical resolution within a few days and imaging resolution within a few weeks. In 27 patients, simultaneous steroid therapy was given.

Rituximab was reintroduced in 15 patients with previous respiratory manifestations, either intentionally or unintentionally (table 4). The rechallenge gave positive results in four patients with rituximab alone [20, 31, 26, 38], and in eight patients with rituximab and combination chemotherapy [3, 25, 31, 34, 38, 39]. The rechallenge gave negative results in three patients who concomitantly received high-dose steroids (1 mg·kg body weight^{-1}) independent of the recommended prophylactic methylprednisolone therapy. Finally, nine patients experienced no further respiratory symptoms when their chemotherapy was restarted without rituximab [22, 25, 27, 29, 38, 39].

Late-onset chronic forms
The mean time to onset in these three patients was 8 weeks from the last rituximab infusion. The symptoms started after the second, third and fifth cycles. None of these patients were receiving anticancer chemotherapy. The diagnoses were RA [16], gastric MALT lymphoma [33] and Waldenström's macroglobulinaemia [40]. Clinically silent pulmonary macronodules and BALF lymphocytosis were the only manifestations. Lung biopsy was performed in all three patients and consistently showed organising pneumonia. Steroid therapy ensured a full recovery in all three patients. None of these patients were rechallenged with rituximab.

DISCUSSION

The present systematic review confirms that rituximab can cause pulmonary toxicity. Three clinical presentations were identified based on time to onset and symptoms. The most common presentation by far was acute or subacute organising pneumonia, occurring ~2 weeks after the last infusion and rapidly causing hypoxaemia but responding favourably to early steroid therapy. More rarely, the pulmonary toxicity of

rituximab manifested as early and potentially fatal ARDS or as chronic macronodular organising pneumonia.

Causality

Although there is no consensus regarding the best method of assessing causality [43], the criteria generally used to evaluate drug-induced lung disease (table 5) [12, 13, 44] support a causal link with rituximab in all 45 patients. The time to onset, clinical and radiological features, and cytohistological findings were consistent with drug-induced lung disease. Other causes of pneumonia were considered and ruled out in most patients. The histological data and course excluded pulmonary lymphoma relapse, lymphoma-related organising pneumonia [45], rheumatoid lung disease and other respiratory diseases. Doubtful cases were excluded [14–16]. Respiratory tract infection was ruled out by negative microbiological studies, including tests for opportunistic pathogens in BALF, and by a negative response to antibiotics. Exacerbation of a cardiac or previous respiratory disease was excluded [3]. The full recovery achieved by survivors of the acute–subacute episodes following rituximab discontinuation should be interpreted with caution. Five patients received steroid therapy, which is known to improve lung disease due to other causes. Only seven patients were taking rituximab alone. In the other patients, it is unclear which drug or drug combination was responsible for the respiratory manifestations. Indeed, similar times to onset and features of pneumonitis have been reported with the associated drugs [46]. The results of rechallenge with the drug (table 4), usually considered a major causality criterion for drug-induced hypersensitivity pneumonitis [13, 47], must be interpreted according to the circumstances, which varied across patients. In 13 patients, the data were highly compatible with drug causation. In the 32 remaining patients, the data remained compatible with drug causation. Five among these 32 patients gave negative rechallenge results but either received steroids at an unspecified dosage (n=3)

TABLE 4	Results of rechallenge with rituximab (RTX) and/or other drugs in patients with any clinical pattern of lung disease		
Drug causation		**Patients n**	**[Refs]**
Highly compatible			
Positive to RTX alone		4	[20, 21, 26, 38]
Negative to chemotherapy without RTX		9	[22, 25, 27, 29, 38, 39]
Total		**13**	
Compatible			
Positive to chemotherapy with RTX		8	[3, 25, 31, 33, 38, 39]
No rechallenge		19	
Negative to RTX[#]		5	[19, 30, 39]
Total		**32**	

[#]: RTX rechallenge with glucocorticoid therapy at an unspecified dosage (n=3) or following a hyperacute episode of lung disease (n=2).

TABLE 5	Modified criteria for assessing drug causation of lung disease
Intrinsic criteria from the clinical analysis	
Timing	
Clinical manifestations	
Exclusion	
Specific site of treated disease	
Infection	
Other condition or exacerbation of a previous condition (*e.g.* heart failure and pulmonary embolism)	
Favourable outcome following discontinuation of the suspected drug	
Positive results following accidental or intentional rechallenge	
Extrinsic criteria from the literature	
Same as the intrinsic criteria when the pattern of lung disease has been reported previously with the same drug	
Rate of occurrence, interpreted according to the time the drug has been on the market	
Confrontation of intrinsic and extrinsic criteria	
Similarity of the clinical presentation, time to onset and course	

Data from [13].

[30, 39] or had ARDS, *i.e.* a manifestation probably unrelated to hypersensitivity [19].

Pathogenic mechanisms and precautions for use

The three clinical presentations of rituximab-induced lung disease may differ regarding their underlying mechanism. Early-onset ARDS is probably unrelated to hypersensitivity. Indeed, immediate hypersensitivity would be expected to produce symptoms within a few minutes after the beginning of the infusion, in most cases after at least one previous cycle. Instead, ARDS symptoms started after a few hours, suggesting an IRR related to cytokine release and/or tumour lysis syndrome [10]. This mechanism is consistent with the occurrence of early-onset ARDS in patients receiving multiple cytotoxic agents and at the first cycle, *i.e.* when the tumour burden is greatest, or with circulating malignant B-cells. Similarly, early-onset ARDS is exceedingly rare in patients treated with rituximab alone for systemic diseases. Additionally supporting this mechanism is the negative response to rechallenge in two patients and the inconsistent efficacy of pre-medication, only 10% in clinical trials [4]. Therefore, close monitoring is in order at the first cycle, particularly in patients receiving combination chemotherapy for high-burden lymphoma. Recommendations concerning serious side-effects should be followed (table 1) [10]. Higher-dose steroid therapy may deserve consideration.

Acute or subacute rituximab-induced lung disease, most notably organising pneumonia, probably reflects a hypersensitivity reaction to the potentially immunogenic chimeric anti-CD20 antibody. Arguments that support a hypersensitivity reaction include the recurrence and increasing severity of the symptoms from one infusion to the next, occurrence during the third month on average, responsiveness to steroid therapy (delayed onset 15 days after the methylprednisolone infusion and favourable outcome with steroid therapy), rash and eosinophilia, BALF lymphocytosis and histological pattern of organising pneumonia in many patients [48]. The potential for severity lies in the risk of a delayed diagnosis, with the initial reversible symptoms being overlooked as a result of inadequate knowledge of this complication.

Given the potential severity of rituximab-induced lung disease and the strong suspicion of underlying hypersensitivity, we suggest a number of recommendations (table 1). First, patients should be told that respiratory disease may develop, with the risk being greatest ~15 days after the last infusion and around the fourth cycle. Secondly, respiratory symptoms should be routinely sought after each infusion. Thirdly, any clinical manifestation, however mild, should prompt chest radiography. Finally, when the findings support a diagnosis of rituximab-induced lung disease, steroid therapy should be started immediately, as it seems to improve the outcome. Furthermore, instead of the currently recommended methylprednisolone infusion at each rituximab administration, a longer period of steroid therapy, with tapering of the dose to avoid a rebound reaction, may be appropriate.

Late-onset organising pneumonia (which may occur up to several months after the last rituximab infusion) may be related either to toxicity of the drug, whose biological half-life is poorly known but probably long, or to immune system restoration [49]. Although not severe, these forms require histological confirmation as the nodules may suggest a malignancy or a chronic infection in these immunocompromised patients.

Conclusion

In conclusion, the present study confirms the pulmonary toxicity of rituximab. Our data should prove helpful to clinicians in assessing causality in patients with respiratory symptoms following rituximab therapy. Three distinct clinical presentations were identified according to time to onset, suggesting different underlying mechanisms. For each, we suggest specific recommendations. Pulmonologists must ensure the early diagnosis and treatment of rituximab-induced lung disease and inform other specialists of this complication and of the need for close monitoring of respiratory status.

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