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Risk Factors for Rituximab-Induced Interstitial Lung Diseases in Patients with Malignant Lymphoma

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Rituximab, a chimeric human-mouse immunoglobulin G1 monoclonal antibody with a high affinity for CD20 surface antigen expressed by normal human pre-B and B lymphocytes, has been approved for low-grade non-Hodgkin's lymphoma expressing CD20, chronic lymphocytic leukemia and diffuse large B cell lymphoma [1]. Currently, it is regarded as part of the standard therapy for treatment of CD20+ non-Hodgkin's lymphoma [2]. Although the incidence of rituximab-induced interstitial lung disease (ILD) was estimated to be very rare by the manufacturer (<0.03%) [3], it has been reported more frequently (8.4–11%) in a few studies [4, 5]. A systematic review has described the detailed clinical characteristics of rituximab-induced lung diseases [1]. However, data regarding the risk factors for rituximab-induced ILD in patients with malignant lymphoma are lacking.

To investigate the clinical features of and risk factors for rituximab-induced ILD in patients with non-Hodgkin's lymphoma who undergo treatment with rituximab-containing regimens, a retrospective study was conducted in a tertiary referral center in Korea. Of 264 patients with non-Hodgkin's lymphoma who were treated with rituximab-containing chemotherapy regimens, 9 (3.5%) were diagnosed as having rituximab-induced ILD, including clinically suspected cases (n = 5). Based on clinical and radiological findings, the most common pattern was organizing pneumonia [n = 7 (78%)], followed by a diffuse ground-glass opacity pattern [n = 2 (22%)]. Six patients (67%), including 1 who received no treatment, were cured or showed improvement and treatment failure was observed in 3 (33%), all of whom died from respiratory failure caused by rituximab-induced ILD. In a multivariate analysis, poor Eastern Cooperative Oncology Group (ECOG) performance status (odds ratio 10.8 and 95% confidence interval 1.6–74.8, p = 0.016) and age (odds ratio 1.1 and 95% confidence interval 0.0–1.2, p = 0.048) were significant risk factors for rituximab-induced ILD.

Hadjinicolaou et al. [6] suggested that the elderly are at the greatest risk of rituximab-associated ILD. However, no study regarding risk factors for rituximab-induced ILD has been conducted.

In the current study, results of multivariate analyses may indicate that poor ECOG performance status and age are significant predictors of rituximab-induced ILD. Previously, low serum albumin level was reported as a risk factor for adverse pulmonary reactions associated with the use of monoclonal antibodies in cancer patients [7]. However, in this study, no significant difference in the level of serum albumin was observed between the ILD and control groups, even in the univariate analysis. Early diagnosis and corticosteroid therapy are required for successful treatment of rituximab-induced ILD [5, 6]. For early diagnosis, we should be alert to elderly patients with poor performance status who have been treated with rituximab.

In conclusion, rituximab-induced ILD in patients with non-Hodgkin's lymphoma is a rare occurrence (3.5%), but with a high rate of mortality (33%). The most common form on CT scan is an organizing pneumonia pattern. In these patients, poor performance status before rituximab infusion and age are predicting factors for rituximab-induced ILD.

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None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this paper.

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