Original Study

Incidence of Hypogammaglobulinemia in Patients Receiving Rituximab and the Use of Intravenous Immunoglobulin for Recurrent Infections

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Abstract

Rituximab targets normal B cells and tumor B cells. We used a unique data-mining tool to identify patients with lymphoma who were treated with rituximab and who had serial pre and post rituximab immunoglobulin concentrations evaluated. After treatment, 39% (69/179) of patients had low levels of immunoglobulin G. Recurrent sinopulmonary infections were seen in 6.6% (14/211). Intravenous immune globulin appeared to reduce the frequency of infection.

Background: Rituximab has altered the treatment approach to B-cell malignancies and other diseases. Reports consider that rituximab had limited impact on serum immunoglobulins. However, anecdotes suggest that rituximab can cause symptomatic hypogammaglobulinemia. This retrospective study examined the relationship among rituximab, hypogammaglobulinemia, and treatment of symptomatic hypogammaglobulinemia with intravenous immune globulin (IVIG). **Methods:** Patients with serial quantitative serum immunoglobulin (SIgG) concentrations before and subsequent to rituximab administration at Memorial Sloan-Kettering Cancer Center were identified. Information regarding rituximab administration, SIgG concentrations, frequency of infection, and administration of IVIG were recorded. **Results:** Between December 1998 and April 2009, 211 patients with B-cell lymphoma treated with rituximab and with serial SIgG concentrations were identified. One hundred seventy-nine (85%) patients had normal SIgG before rituximab, 32 (15%) had low SIgG. After rituximab use, hypogammaglobulinemia was identified in 38.54% of patients with initially normal SIgG. The risk was greater in patients who received maintenance rituximab. Symptomatic hypogammaglobulinemia that prompted IVIG administration developed in 6.6% of patients. **Conclusions:** In this data set, rituximab administration was associated with a high frequency of hypogammaglobulinemia, particularly symptomatic hypogammaglobulinemia, among patients who received multiple courses of rituximab. Baseline and periodic monitoring of SIgGs is appropriate in patients who receive rituximab.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 13, No. 2, 106-11
Keywords: Gamma globulin, Hypogammaglobulinemia, Infections, Lymphoma, Rituximab

Introduction

Rituximab is a chimeric monoclonal antibody that binds to the CD20 antigen present on all peripheral B cells. In 1997, it became the first antibody approved for treatment of relapsed or refractory low-grade or follicular CD20$^+$ B-cell non-Hodgkin lymphoma (NHL), based on clinical trials that evaluated its safety and efficacy in the early 1990s.[1-3] Its use has subsequently widened to include treatment of all B-cell malignancies, including aggressive NHL and chronic lymphocytic leukemia.[4-9] The use of rituximab has also extended to nonmalignant indications, including rheumatoid arthritis.[9]

The efficacy of rituximab in these conditions as well as rituximab's favorable toxicity profile have led to several studies that evaluated rituximab as maintenance therapy after treatment for newly diagnosed or relapsed NHL. In addition, maintenance rituximab has been evaluated after high-dose therapy and autologous stem cell rescue in both indolent and aggressive lymphoma.[10-17]

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Submitted: Jul 23, 2012; Revised: Nov 20, 2012; Accepted: Nov 20, 2012; Epub: Dec 29, 2012

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2012.11.011

To date, 6 randomized trials have published results on the role of maintenance rituximab in indolent NHL and have noted improvements in progression-free survival. Maintenance therapy should ideally sustain prolonged remission, be well tolerated, and have minimal toxicities. Although rituximab meets these criteria and has contributed to extending periods of remission duration, the long-term impact of rituximab on B-cell depletion is not well understood. Long-term use may be associated with an increased incidence of grade 3 and 4 infections, neutropenia, hepatitis B reactivation, squamous cell skin carcinoma, and progressive multifocal leukoencephalopathy.[18-21] Furthermore, hypogammaglobulinemia associated with rituximab use has been documented in several settings: rituximab after high-dose therapy and autologous stem cell rescue, rituximab for autoimmune disorders in children with immunosuppression, and rituximab in patients with T-cell abnormalities.[22-27]

To understand the relationship between the use of rituximab and the development of hypogammaglobulinemia, we undertook a retrospective study to evaluate serum immunoglobulins (SIgG) and rituximab. In addition, we examined if patients receiving rituximab developed symptomatic hypogammaglobulinemia that required treatment with intravenous immunoglobulin (IVIG).

Patients and Methods

This study was performed under a waiver of authorization from the institutional review board at Memorial Sloan-Kettering Cancer Center (MSKCC). We used DAVInCI (Data Analysis and Visualization for Integrated Cancer Information), a Web-based data mining tool, to identify patients with B-cell lymphoma who had been treated with rituximab either as a single agent for primary or maintenance therapy or in combination with chemotherapy as part of induction or salvage treatment at MSKCC between December 1998 and April 2009, and who had serial determination of SIgG before and subsequent to treatment with rituximab.

Hypogammaglobulinemia was defined as a deficiency in the serum immunoglobulin (Ig) G level below 600 mg/dL. We defined 3 categories of patients based on the severity of the hypogammaglobulinemia: mild, 400-599 mg/dL; moderate, 300-299 mg/dL; and severe, 0-199 mg/dL. Symptomatic hypogammaglobulinemia was defined as having 2 or more non-neutropenic infections in a 6-month period after rituximab use treated with IVIG. Patients with symptomatic hypogammaglobulinemia were treated with IVIG at a dose of 400 mg/kg monthly until the IgG level rose above 550 mg/dL. Thereafter, the interval between treatments was adjusted to maintain nadir, preinfusion concentrations of 550-600 mg/dL. Frequencies were compared by using the 2-sided Fisher exact test (2*P*), for all 2 × 2 comparisons, and the χ^2 test for all other frequency comparisons; the results were calculated with SPSS, version 18 (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

Two hundred eleven patients with NHL had serial quantitative immunoglobulin studies before and subsequent to therapy with rituximab, and were included in the analysis (Table 1). Eighty-two percent of patients (173/211) received rituximab as immunotherapy or chemoimmunotherapy for first-line treatment. Eighteen percent of patients (38/211) received rituximab for relapsed or refractory disease. The median age of patients was 58 years old (range, 9-90 years). The histologies included diffuse large B-cell lymphoma (n = 65), follicular lymphoma (FL) (n = 42), chronic lymphocytic leukemia–small lymphocytic lymphoma (n = 38), marginal zone lymphoma (n = 30), mantle cell lymphoma (MCL) (n = 19), and other subtypes (n = 17). Patients received a median of 7 doses of rituximab (range, 2-50). For the total population (211), the median follow-up of surviving patients was 2.95 years.

Table 1 Patient Characteristics

	All Patients	Baseline HypoIgG
Median (Range) Age, y	58 (9-90)	
Total No. Patients	211	32
Histology, No. (%)		
Diffuse large B cell lymphoma	65 (31)	10 (31.2)
Follicular lymphoma	42 (20)	5 (15.6)
Chronic lymphocytic leukemia–small lymphocytic lymphoma	38 (18)	6 (18.8)
Marginal zone lymphoma	30 (14)	4 (12.5)
Mantle cell lymphoma	19 (9)	1 (3.1)
Other subtypes	17 (8)	6 (18.8)
Rituximab as Part of Chemoimmunotherapy and/or Immunotherapy, No. (%)		
First-line treatment	173 (82)	27 (84)
Relapsed and/or refractory disease	38 (18)	5 (15.6)
Prior Chemotherapy, No. (%)		
Rituximab monotherapy	58 (27)	
Rituximab plus chemotherapy	177 (84)	
CHOP with or without rituximab	105 (50)	
CVP with or without rituximab	19 (9)	
Fludarabine with or without Cx with or without R	58 (27)	
Purine analogue	37 (18)	
Bendamustine with or without rituximab	16 (8)	

Abbreviations: CHOP = cyclophosphamide/doxorubicin/vincristine (Oncovin)/prednisone; CVP = cyclophosphamide; Cx = chemotherapy; HypoIgG = hypogammaglobulinemia; R = rituximab.

Before treatment with rituximab, 85% (179/211) had normal SIgG concentrations and 15% (32/211) had low concentrations. Baseline hypogammaglobulinemia observed in these 32 patients was distributed across all histologies: diffuse large B-cell lymphoma (10), chronic lymphocytic leukemia–small lymphocytic lymphoma (6), follicular lymphoma (5), marginal zone lymphoma (4), MCL (1), other, (6).

Development of Hypogammaglobulinemia

After rituximab use, IgG hypogammaglobulinemia was documented in 38.5% (69/179) of patients who had normal baseline SIgG concentrations (de novo hypogammaglobulinemia [DH]) (Table 2). The severity of hypogammaglobulinemia was mild (IgG, 400-599 mg/dL) in 77% (53/69) of patients, moderate (IgG, 200-399 mg/dL) in 20% (14/69) of patients, and severe (0-199 mg/dL) in 3%