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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.

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Disclosure

The remaining authors have stated that they have no conflicts of interest.

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}

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 (2P), 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.

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% (2/69) of patients. Hypogammaglobulinemia was exacerbated in 72% (23/32) of patients who had baseline hypogammaglobulinemia (progressive hypogammaglobulinemia [PH]). In this cohort, the majority of patients (65% [15/23]) developed moderate hypogammaglobulinemia. Of the remaining 9 patients with baseline

hypogammaglobulinemia, after rituximab administration, 5 remained low but did not decrease further, whereas, in 4 patients, the IgG concentrations normalized.

Other immunoglobulin isotypes were also impacted by rituximab exposure. Among the 211 patients, IgA deficiency was seen in 33.5% and IgM deficiency was seen in 61.5% of cases with complete data (Table 3). Of the patients with DH, 80% (55/69) had more than 1 isotype decreased (IgG and IgA in 8; IgG and IgM in 20), and, in 49% (27/55) of these, all 3 isotypes were reduced. Of the patients with PH, 74% (17/23) had more than 1 isotype decreased (IgG and IgA in 3; IgG and IgM in 3); however, in 65% (11/17) of these, IgG, IgA, and IgM were all reduced.

Among patients with DH (n = 69), the median time from the initial exposure to rituximab to the development of hypogammaglobulinemia was 1.4 years. Among patients with PH (n = 23), the median time from initial exposure to rituximab to further worsening of hypogammaglobulinemia was 0.8 years. When both cohorts were combined (DH and PH, N = 92), the median time to either new or worsening hypogammaglobulinemia was 1.2 years. Of 179 patients with normal SIgG concentrations before rituximab, 26.8% (48/179) of patients received rituximab maintenance, whereas 73.2% (131/179) received rituximab as immunotherapy or chemoimmunotherapy alone. Hypogammaglobulinemia developed in 54.2% (26/48) of patients who received rituximab maintenance compared with 32.8% (43/131) who received chemoimmunotherapy or immunotherapy ($2P = .015$) (Table 4).

The possible risk factors associated with the development of hypogammaglobulinemia were examined by univariate analysis. The factors examined included prior chemotherapy (Table 1), exposure to purine analogues; courses of rituximab; sex; age; and histology. In this data set, 31.8% (67/211) of patients had exposure to purine analogues, whereas 68.2% (144/211) did not. Among patients with DH, 37.7% (26/69) had purine analogue exposure, compared with 47.8% (11/23) in patients with PH. Exposure to purine analogues was associated with a risk of hypogammaglobulinemia ($2P = .025$). Courses of rituximab received also influenced the development of hypogammaglobulinemia. Patients who received more than 1 course of rituximab were significantly more likely to have hypogammaglobulinemia, $2P = .002$. (We found that 65% of patients in the DH and PH cohorts had received more than 1 course of rituximab). Lastly, neither sex, age (< 65 years vs. >65 years), or histologic subtype were correlated with the development of hypogammaglobulinemia.

Symptomatic Hypogammaglobulinemia

Overall, symptomatic hypogammaglobulinemia was defined as recurrent (> 2) non-neutropenic infections within a 6-month period of time after exposure to rituximab and treatment with IVIG. Symptomatic hypogammaglobulinemia developed in a total of 6.6% (14/211) of the entire patient population. In patients with DH, 14.5% (10/69) experienced symptomatic hypogammaglobulinemia after rituximab use compared with 13.04% (3/23) of patients with baseline hypogammaglobulinemia ($P =$ not significant), which demonstrates that the DH and PH had the same risk in requiring IVIG. The severity of hypogammaglobulinemia also did not differ between the DH and PH cohorts ($P = .47$, χ^2 test). The 14th patient was symptomatic but was in either the DH or PH group.

Further analysis of the symptomatic group revealed that 13 of 14 patients had more than 1 isotype decreased. Among the patients who were symptomatic in the DH group, 90% (9/10) had more than 1 isotype decreased (IgG and IgA in 2 patients), and, in 78% (7/9) of these, IgG, IgA, and IgM were all reduced. Of patients with symptomatic hypogammaglobulinemia in the PH cohort, all (3/3) the patients had more than 1 isotype decreased (IgG and IgM in 1 patient), and, in 67% (2/3) of these patients, IgG, IgA, and IgM were all reduced. The patient who was symptomatic and who was hypogammaglobulinemic at baseline without further decrease after rituximab had 2 decreased isotypes (IgM and IgG).

The non-neutropenic infections identified were predominantly sinopulmonary and upper respiratory (Table 5). The median time to the development of the first infection after rituximab use was 12.3 months (range, 0.3–68.4 months). The median time to requirement of IVIG from first use of rituximab was 30 months (range, 11.3–70.8 months). Nearly 79% (11/14) of patients who required IVIG received it after 2 or more courses of rituximab, whereas 21.4% (3/14) of patients received IVIG after only 1 course of rituximab. IVIG was administered for symptomatic hypogammaglobulinemia after a median of 2 courses of rituximab (range, 1–5; or a median of 12.5 doses [range, 4–28]).

Furthermore, we sought to analyze the relationship between symptomatic hypogammaglobulinemia and the number of doses of rituximab received. For this analysis, the patients were placed into 3 bins based on the total number of doses of rituximab received (defined as bin 1, bin 2, and bin 3). This was done to create nearly equal size cohorts of patients based on doses of rituximab received. Histogram bin analysis is a statistical approach to provide a guideline for how common or rare an event is in a population.²⁸ In this case, the bin sizes were determined based on the natural frequencies of rituximab administered among all patients ($n = 211$) to analyze the correlation between doses of rituximab and the development of symptomatic hypogammaglobulinemia. Bin 1 included 61 patients who received from 1 to 5 doses. Bin 2 included 72 patients who received 6 to 9 doses. Bin 3 consisted of 78 patients who received 10 doses. The numbers of patients with symptomatic hypogammaglobulinemia in bins 1, 2, and 3, were 1, 3, and 10, respectively. Bin analysis by the χ^2 test suggests that the number of doses of rituximab is significantly correlated to developing symptomatic hypogammaglobulinemia ($P = .018$).

Although hypogammaglobulinemia was more frequent in patients who received rituximab maintenance compared with those who received chemoimmunotherapy or immunotherapy, maintenance rituximab was not a risk factor for the development of symptomatic hypogammaglobulinemia that required IVIG. In addition, exposure to purine analogues was not associated with symptomatic hypogammaglobulinemia in either the DH or PH cohorts.

Impact of IVIG

To determine the clinical impact of IVIG, we examined the frequency of recurrent non-neutropenic infections in the 6 months before and subsequent to the initiation of IVIG (Table 6). Infectious episodes were determined by chart review of each patient who received IVIG. The median number of infectious episodes in the 6 months before and subsequent to starting IVIG was 2 and 1, respectively (range, 1–4; 0–3). This difference in infectious complications was significant ($2P = .004$ [95%CI, 0.211–1.45]), and we suspect that the

benefit might be greater, because it can take 3 to 6 months for the immunoglobulin concentrations to normalize.

Discussion

In this data set, we observed that rituximab administration was associated with a high frequency of hypogammaglobulinemia. This occurred in concert with a moderate risk of symptomatic hypogammaglobulinemia that required use of IVIG, particularly among patients who received multiple courses of rituximab. In addition, we found that the number of doses of rituximab significantly correlated to the development of symptomatic hypogammaglobulinemia.

In this study, we examined the impact of rituximab on patients whose pre- and postrituximab quantitative immunoglobulins were measured. We found that hypogammaglobulinemia was common in patients who received rituximab and that this risk increased significantly in patients who received maintenance rituximab. Rituximab maintenance had a significantly higher risk of causing hypogammaglobulinemia: 54% of patients who received rituximab maintenance developed hypogammaglobulinemia compared with 32.8% of patients who received immunotherapy or chemoimmunotherapy alone ($2P = .015$). Patients who were heavily pretreated were also found to be more susceptible to hypogammaglobulinemia. We found that 65.2% of patients who developed hypogammaglobulinemia received more than 1 dose, whereas only 43.7% of patients with normal IgG concentrations received more than 1 course of rituximab ($2P = .002$).

The decision to administer IVIG to patients who exhibited 2 non-neutropenic infections in a 6-month period of time was consistent with the guidelines suggested by the position paper of the American Academy of Allergy, Asthma, and Immunology that proposed IVIG administration when appropriate, to patients who exhibited a clinical history of infections.²⁹ Because there are no consensus guidelines that define degrees of hypogammaglobulinemia, we chose these definitions based on data that demonstrated benefit to maintaining IgG concentrations over 599 mg/dL in other immunodeficient states.^{30–32} Our decision to maintain a nadir of 550 mg/dL to 600 mg/dL is in line with National Comprehensive Cancer Network guidelines on the management of symptomatic hypogammaglobulinemia.³³ The infectious complications observed in this data set were mainly upper respiratory and sinopulmonary (Table 3). We noted that infections occurred shortly after rituximab use, within a median time to first infection of 12.3 months.

In addition, patients were more likely to require IVIG after multiple courses of rituximab. Seventy-nine percent of patients received IVIG after 2 or more courses of rituximab compared with 21% of patients who received IVIG after only 1 course of rituximab. IVIG was administered for symptomatic hypogammaglobulinemia after a median of 2 courses of rituximab (range, 1–5; or median of 12.5 doses [range 4–28]). In addition, the administration of IVIG for patients with symptomatic hypogammaglobulinemia led to a significant reduction in recurrence of infections ($2P = .007$), a benefit that may be underestimated given that serum immunoglobulins may rise over several months.

An increased risk of infections and of hypogammaglobulinemia is a recognized risk with rituximab treatment. Asystematic review and meta-analysis by Aksoy et al³⁴ that evaluated the infectious complications of rituximab in patients with lymphoma during maintenance therapy found significantly increased rates of infection in patients who received maintenance vs. those who did not, 8.1% vs. 3.9%, respectively ($P = .004$). Other studies confirmed the risk of hypogammaglobulinemia with rituximab treatment, including in other autoimmune diseases such as autoimmune cytopenias, and anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitides.^{16,24–27,35} Prolonged hypogammaglobulinemia after rituximab has been observed in the posttransplantation setting and was described in 1 study, but infections were not seen among this small population of patients ($n = 29$).¹⁶ However, there have been numerous case reports of hypogammaglobulinemia associated with infection, and the incidence of sinopulmonary and other infections is purported to be increased in patients with deficiencies of an IgG subclass,^{24–27,35} which is consistent with our findings that demonstrate a heightened risk of hypogammaglobulinemia in patients after rituximab use.

In this series, we also observed an increased risk of hypogammaglobulinemia among patients with prior purine exposure. The impaired cellular immunity caused by exposure to drugs such as fludarabine and other purine analogues may be exacerbated by the B-cell depletion caused by rituximab. Consequently, combined use of these regimens in induction therapy and maintenance may increase infections.^{36,37} In this context, the influence of purine exposure on the development of hypogammaglobulinemia after rituximab use in this data set was anticipated and may be a confounding factor in delineating the exact contribution of each agent to reduced serum immunoglobulins. Despite these findings, symptomatic hypogammaglobulinemia was seen equally in both cohorts of patients with DH or PH who received purine analogues as part of prior therapy.

As in any retrospective study, we were concerned about the potential for biased patient selection. To address the risk of selection of patients with symptomatic hypogammaglobulinemia, we required that patients had quantitative immunoglobulins before the initiation of rituximab. By using this selection criterion, we could evaluate the impact of therapy on the quantitative immunoglobulins. We found that extent of prior therapy as well as the extent of prior rituximab are predictive factors in developing hypogammaglobulinemia. Therefore, symptomatic hypogammaglobulinemia may develop in patients with an exposure to rituximab and extensive prior therapy. In addition, due to the retrospective nature of this study, we were unable to examine the impact of rituximab-associated hypogammaglobulinemia in response to vaccination. However, we believe that this would be a valuable addition to a prospective evaluation.

Given the findings observed in this data set, we believe that clinicians should be aware of the increased risk for symptomatic hypogammaglobulinemia in the setting of rituximab use, particularly with the increased frequency of rituximab use for maintenance. In the absence of an overall survival advantage, the 6.6% risk of symptomatic hypogammaglobulinemia and eventual requirement of IVIG should be considered when deciding whether to use maintenance rituximab.

Clinical Practice Points

- The use of rituximab has transformed the treatment of lymphomas and several other diseases. However, the development of hypogammaglobulinemia and an increased incidence of infections are accepted risks with rituximab treatment. Several reports suggest that rituximab can contribute to the development of hypogammaglobulinemia; however, the precise mechanisms by which this occurs, or its incidence, is unknown.
- We conducted a study to review the contributions of rituximab administration and the development of hypogammaglobulinemia in patients with lymphoma. We found that use of rituximab was associated with a high risk of hypogammaglobulinemia, especially symptomatic hypogammaglobulinemia.
- Our study supports that baseline and periodic monitoring of serum immunoglobulins levels should be considered in patients who receive rituximab.

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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.

Table 2

Change in IgG Concentrations Subsequent to Rituximab

n	Baseline Low IgG (PH)		Baseline Normal IgG (DH)	
	Total	Decrease, No. (%)	Total	Decrease, No. (%)
211	32	23/32 (72%)	179	69/179 (38.9%)

Abbreviations: DH = de novo hypogammaglobulinemia; Ig = immunoglobulin; PH = progressive hypogammaglobulinemia.

Table 3Impact of Rituximab on Immunoglobulin (Ig) Isotypes^a

Isotype	n	Baseline Hypogammaglobulinemia, No. (%)	New Onset Hypogammaglobulinemia After Rituximab, No. (%)
IgG	211	32/211 (15)	69/211 (33)
IgA	201	22/201 (11)	50/201 (25)
IgM	203	49/203 (24)	76/203 (37)

^aPercentages represent decreases in individual immunoglobulin isotypes; normal values: IgG, 600–1500 mg/dL; IgA, 50–400 mg/dL; IgM, 50–300 mg/dL.

IVIg Use in Patients With Symptomatic Hypogammaglobulinemia and Impact of Rituximab Maintenance

Table 4

All Patients			Initial Baseline Normal IgG, Rituximab Maintenance		
Initial Baseline Low IgG, No.		Initial Baseline Normal IgG, No.	Yes		No
n	IVIg Use	n	IVIg Use	n	IVIg Use, No.
32	4	179	10	48	131
				5	5

Abbreviations: Ig = immunoglobulin; IVIG = intravenous immune globulin.

Table 5

Non-Neutropenic Infections in Patients Who Received Intravenous Immune Globulin for Symptomatic Hypogammaglobulinemia^a

Type of Infection	No. Episodes
Upper respiratory infections	45
Sinopulmonary infections	10
Pneumonia	3
Urinary tract infection	1
Cellulitis	4
Ocular infection	1
Respiratory syncytial virus	1
Total	65

^aInfections observed in 14 patients.

Table 6Change in Infectious Complications With IVIG^a

Before IVIG Replacement					Subsequent to IVIG Replacement			
Patient No.	Sinopulmonary	Upper Respiratory	Pneumonia	Total	Sinopulmonary	Upper Respiratory	Pneumonia	Total
1	1	1	1	3		1		1
2		1	1	2	1		1	2
3	1	1	1	3				0
4		3	1	4		3		3
5		1		1			1	1
6	1			1		1		1
7	2	1		3				0
8	3			3	1			1
9		1	1	2		1		1
10		1		1		1		1
11	1			1	1			1
12		1	1	2				0
13	1	1	1	3	2	1		3
14	1			1		1		1
Total				30				16

Abbreviation: IVIG = intravenous immune globulin.

^aThe median number of infectious episodes in the 6 mo before and subsequent to starting IVIG was 2 and 1, respectively (range, 1–4 and 0–3, respectively); this difference in infectious complications was significant ($P = .004$ [95% CI, 0.211–1.45]).