Hospitalization for Toxicity in Patients Treated With Rituximab

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Objectives: To estimate the rates of hospitalizations in patients within 12 months after the first rituximab administration.

Methods: Patients who received rituximab between 2001 and 2008 for either benign or malignant conditions were identified from Texas Medicare files. The hospitalization rates for these patients with any diagnoses that might represent toxicity were then compared in the 12 months before and after the first infusion of rituximab. Dose-response analyses were performed on the basis of the number of doses received in the 8 weeks after initiating rituximab and also using the cumulative number of doses as a time-dependent covariate.

Results: In all, 2623 patients received rituximab as a single agent for malignant indications and 1124 received it for benign indications. Overall inpatient admission rates did not differ significantly between the 12 months before and after rituximab initiation in patients with benign or malignant conditions. Those with malignant conditions had higher rates of hospitalizations for cardiovascular, infectious, pulmonary, and neurological diagnoses after rituximab initiation. In those with nonmalignant conditions, the only increase was in hospitalizations for infections. Neither group of patients showed any clear dose-response relationships with any toxicity.

Conclusions: The increased hospitalizations for potential toxicities seen in patients with malignant disease were presumably because of the underlying disease process and not rituximab. Rituximab does not appear to be associated with hospitalizations for serious toxicity within 12 months after the first infusion, with the possible exception of infection.

Key Words: rituximab, Medicare, Texas

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Rituximab was approved in 1997[1,2] for the treatment of B-cell neoplasms. Subsequent studies have shown excellent responses in both indolent and aggressive B-cell neoplasms.[3,4] The drug has also been shown to be efficacious in autoimmune disorders and is used widely to treat nonmalignant conditions like rheumatoid arthritis,[5] immune thrombocytopenia,[6,7] thrombotic thrombocytopenic purpura,[8] granulomatosis with polyangitis,[9] and many other related disorders.[10,11]

Rituximab depletes the CD20-positive B cells within 24 to 48 hours after the first infusion.[2] Recovery of these cells occurs at 6 to 9 months after the last infusion, with attainment of normal levels at 9 to 12 months.[2] A number of clinical trials have shown rituximab to be a safe and well-tolerated drug with limited toxicity,[12–14] and major toxicities are usually limited to infusion reactions and transient cytopenias. However, post-marketing surveillance and case reports have identified some serious adverse effects in patients receiving this agent, including increased incidence of infections,[15] pulmonary toxicity,[16,17] and rare disorders such as progressive multifocal leucoencephalopathy.[18] It is unclear how many of those were serious enough to result in hospitalizations, and the true incidence of these toxicities in a large cohort of patients is unknown.

Patients in randomized controlled trials tend to be younger and healthier than those in the community practice. Some rituximab trials included patients older than age 80, but they were selected carefully and received therapy within the controlled setting of the clinical trial.[19] Most of the clinical trials also included patients who received other chemotherapy agents and hence the serious toxicities may not be attributable to rituximab alone.

We designed this study to assess the rates of serious toxicity related to cardiac, neurological, infectious, gastrointestinal (GI), and pulmonary diagnoses that lead to hospitalizations in Texas Medicare patients who received rituximab. We used several methods to explain the association of rituximab and potential toxicities in observational data. First, we compared the hospitalization rates for the 12 months before and after initiation of rituximab. It was not possible to identify a simultaneous matched population who did not receive rituximab during the study period because of the fact that it is used nearly universally in all B-cell neoplasms. Moreover, it is likely that the disease process for which rituximab was given may itself lead to increased hospitalizations. To control for this possibility, we also looked at toxicity in patients who received rituximab for nonmalignant conditions. Finally, we looked for a dose-response relationship of rituximab with potential toxicities in each group of patients.

PATIENTS AND METHODS

Data Sources

We used the Texas Medicare data for this analysis. The Medicare claims data used in this study include Medicare Provider Analysis and Review (MEDPAR) files, Outpatient Standard Analytic File (OUTSAF), and Medicare Carrier files

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from 2000 through 2009. The majority of the patients covered by Texas Medicare are 65 years of age or older but the data set also includes patients with disability and end-stage renal disease.

Study Cohort

The initial study cohort consisted of all Texas Medicare beneficiaries who received their initial dose of rituximab in 2001 through 2008 (N = 14,124). Patients were selected if they received the first injection of rituximab between 2001 and 2008 without any injections of rituximab in the 12 months before that date. Excluded were patients who were ever enrolled in a health maintenance organization (HMO) and those who did not have full coverage of both Medicare Part A and Part B during the 12 months before the initial injection of rituximab (N = 12,001). Among these 12,001 patients, we limited our analysis to those who received rituximab as the only chemotherapy agent within the 3 months before and 12 months after the date of initial rituximab treatment (N = 3747). This exclusion was done to rule out toxicity related to other chemotherapeutic agents. We determined the indication for the rituximab administration by examining the primary diagnosis in the claims for rituximab injection (Table 1). In 22 cases, the primary diagnosis was not an indication associated with rituximab use; in those cases, we examined the secondary diagnosis. The cohort studied included 2623 patients with malignant diseases and 1124 with benign conditions (Table 2). In the malignant group, the majority of the cases were documented as other lymphomas, which include all diagnoses of lymphoma not otherwise specified.

Chemotherapy

As described in previous studies,[20,21] rituximab use was identified by the Healthcare Common Procedure Coding System code J9310 in the OUTSAF and Carrier files. Patients who received other chemotherapy agents along with rituximab were defined as having a claim for chemotherapy if any of the following codes were made within the 3 months before and the 12 months after the date of initial rituximab: V codes of V58.1, V66.2, or V67.2; the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code of 9925; the Healthcare Common Procedure Coding System codes of 96400-96549, Q0083-Q0085, and J9000-J9999; revenue center codes of 0331,0332, and 0335; and G codes of G0355-G0363. The number of infusions within the 8 weeks after the initial rituximab infusion was calculated. The cutoff period of 8 weeks was chosen because it represents the maximum number of weekly infusions approved for clinical use in relapsed lymphoma.

Toxicity Effects of Rituximab

We used ICD-9-CM diagnosis codes from the hospital inpatient claims to define toxicity effects of rituximab as hospitalization for any of the following 5 groups of primary diagnosis made within the 8 weeks after initial rituximab treatment: infection, neurological, cardiac, pulmonary, and GI (see Supplemental Digital Content 1, Appendix, http://links.lww.com/AJCO/A59 for ICD codes used). The cause of hospitalization was determined from the ICD-9 code in the first position. The rates of hospitalization in the same group of patients were compared before and after the rituximab infusion because of the inability to identify a control population with similar characteristics who received another agent instead of rituximab. We also defined hospitalizations as the surrogate for serious toxicity. As the patients who received other chemotherapeutic agents were excluded, the toxicities were assumed to be related to rituximab alone. The cohort was specifically analyzed for progressive multifocal leucoencephalopathy using the diagnosis code 046.3.

TABLE 1. Primary Diagnosis for Patients Receiving Rituximab Treatment

Diagnosis	n (%)
Benign (n = 1124)	
Rheumatoid arthritis	550 (48.93)
Immune thrombocytopenic purpura	189 (16.82)
Primary thrombocytopenia	89 (7.92)
Thrombocytopenia unspecified	8 (0.71)
Evans syndrome	2 (0.18)
Secondary thrombocytopenia	2 (0.18)
Disorders of plasma protein metabolism, macroglobulinemia	146 (12.99)
Disorders of plasma protein metabolism	5 (0.44)
Autoimmune hemolytic anemia	66 (5.87)
Diffuse diseases of CT	47 (4.18)
Microtic thromboangiopathy	6 (0.53)
Myasthenic syndromes	5 (0.44)
Wegener granulomatosis	4 (0.36)
Neuromyelitis optica	4 (0.36)
Bullous dermatoses, pemphigus	1 (0.09)
Malignant (n = 2623)	
Burkitt tumor or lymphoma	7 (0.27)
Hodgkin disease, lymphocytic-histiocytic predominance	3 (0.11)
Hodgkin disease, unspecified	24 (0.92)
Large cell lymphoma	6 (0.23)
Mantle cell lymphoma	4 (0.15)
Marginal zone lymphoma	20 (0.76)
Nodular lymphoma	361 (13.77)
Other lymphomas	1381 (52.65)
Post transplant lymphoproliferative disorder	20 (0.76)
Peripheral T-cell lymphoma	4 (0.15)
Chronic lymphoid leukemia	557 (21.24)
Leukemic reticuloendotheliosis	10 (0.38)
Lymphoid leukemia	4 (0.15)
Lymphosarcoma	58 (2.21)
Lymphosarcoma and reticulosarcoma	68 (2.59)
Multiple myeloma	13 (0.50)
Neoplasm of uncertain behavior of other lymphatic	35 (1.33)
Reticulosarcoma	48 (1.83)

CT indicates computed tomography.

Covariates

Data on patient age (< 65, 65 to 69, 70 to 74, 75 to 79, 80 + years), sex, race/ethnicity (White, Black, Hispanic, Other), and Medicaid eligibility were obtained from the Medicare enrollment files. Comorbidity was assessed using an adaptation of the Charlson Comorbidity Index for use with inpatient and outpatient claims in the 12 months before the initial dose of rituximab.[22] The number of hospitalizations in the 12 months before receiving the initial rituximab treatment for each patient was calculated from the hospital inpatient claims data.

Statistical Analyses

The χ^2 statistic was used to test for differences in patient characteristics between study subjects with benign diseases and those with malignant diseases. We examined the number and percent of hospitalizations for toxicity effects of interest (cardiac, neurology, infection, pulmonary, or GI) possibly

TABLE 2. Characteristics of the Study Population

Characteristics	Category	All Patients (n [%])	Benign (n [%])*	Malignant (n [%])*
Number		3747 (100)	1124 (30)	2623 (70)
Age (y)	<65	469 (12.52)	308 (27.40)	161 (6.14)
	65-69	563 (15.03)	229 (20.37)	334 (12.73)
	70-74	568 (15.16)	189 (16.81)	379 (14.45)
	75-79	712 (19.00)	188 (16.73)	524 (19.98)
	≥80	1435 (38.30)	210 (18.68)	1225 (46.70)
Sex	Male	1483 (39.58)	326 (29.00)	1157 (44.11)
	Female	2264 (60.42)	798 (71.00)	1466 (55.89)
Ethnicity	White	3301 (88.10)	945 (84.07)	2356 (89.82)
	Black	218 (5.82)	92 (8.19)	126 (4.80)
	Hispanic	160 (4.27)	57 (5.07)	103 (3.93)
	Others	68 (1.81)	30 (2.67)	38 (1.45)
Medicaid eligible	Yes	523 (13.96)	217 (19.31)	306 (11.67)
	No	3224 (86.04)	907 (80.69)	2317 (88.33)
Year of initial rituximab treatment	2001	276 (7.37)	14 (1.25)	262 (9.99)
	2002	321 (8.57)	24 (2.14)	297 (11.32)
	2003	415 (11.08)	54 (4.80)	361 (13.76)
	2004	448 (11.96)	101 (8.99)	347 (13.23)
	2005	438 (11.69)	96 (8.54)	342 (13.04)
	2006	616 (16.44)	250 (22.24)	366 (13.95)
	2007	618 (16.49)	287 (25.53)	331 (12.62)
	2008	615 (16.41)	298 (26.51)	317 (12.09)
Comorbidity	0	1412 (37.68)	203 (18.06)	1209 (46.09)
	1	1114 (29.73)	432 (38.43)	682 (26.00)
	2	591 (15.77)	242 (21.53)	349 (13.31)
	≥3	630 (16.81)	247 (21.98)	383 (14.60)
Hospitalizations 12 mo before receiving initial rituximab treatment	0	1911 (51.00)	596 (53.02)	1315 (50.13)
	1	904 (24.13)	257 (22.86)	647 (24.67)
	2	470 (12.54)	143 (12.72)	327 (12.47)
	3	217 (5.79)	55 (4.89)	162 (6.18)
	≥4	245 (6.54)	73 (6.5)	172 (6.57)
Hospitalizations 12 mo after receiving initial rituximab treatment	0	1976 (52.74)	639 (56.85)	1337 (50.97)
	1	865 (23.09)	258 (22.95)	607 (23.14)
	2	414 (11.05)	93 (8.27)	321 (12.23)
	3	226 (6.03)	59 (5.25)	167 (6.37)
	≥4	266 (7.1)	75 (6.67)	191 (7.27)

related to receiving rituximab by comparing those with the number and percent of hospitalizations for the 12 months before receiving the initial dose of rituximab. McNemar tests were conducted to compare the rates of hospitalization before and after receiving rituximab within the same patient group (benign or malignant).

In the dose-response analyses, we first excluded those who died or had an interruption in the continuous enrollment of Medicare Parts A and B or who were ever enrolled in an HMO within 8 weeks after initial rituximab treatment (N = 3562). Kaplan-Meier curves for each patient group (benign or malignant) were plotted to indicate the risk for hospitalization due to the potential toxicity effect of each dosage of rituximab in the follow-up period. The log rank test was used to compare specific toxicity in patients receiving different dosages. Patients were censored at loss of Medicare coverage, switch to HMO, death, or end of study (December 31, 2009). A Cox proportional hazard model was also built to adjust for patient characteristics in the dose-response analyses based on the dosage within 8 weeks after initial rituximab treatment. As a sensitivity analysis, we examined the dose-response relationships by estimating the cumulative rituximab dose over time as a time-dependent covariate in the Cox proportional hazard model for the entire study cohort. We used the cumulative sum of Martingale Residuals to examine the proportionality of Cox models. All programming and analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

We identified 2623 (70%) patients who received at least 1 infusion of rituximab for lymphoma, leukemia, or other malignancies and who were not on other chemotherapy agents. We also identified 1124 (30%) patients who received rituximab and had nonmalignant conditions such as rheumatoid arthritis, immune thrombocytopenia, or other connective tissue disorders (Table 1). The benign and malignant groups differed by characteristics in that the malignant group was older, male predominant, less likely to be Medicaid eligible, and had fewer comorbidities. The patients were also grouped on the basis of the year of receiving the first infusion. An increase in the number of patients who received rituximab for benign disorders was noted after 2005 (Table 2).

Table 3 describes the hospitalizations in the 12 months before and 12 months after the initial rituximab infusion for the 2 types of patients: those with benign and those with malignant disease. The causes for hospitalizations are grouped by potential toxicity. The rates of hospitalizations for any cause did not increase in the 12-month period after infusion in either group of patients. However, when the causes of the hospitalizations were stratified by diagnoses, patients with malignant

TABLE 3. Hospitalization Rates for the 12 Months Before and After the First Rituximab Infusion

Primary Diagnosis for Hospitalizations	Diagnosis	12 mo Before Initial Rituximab (n [%])	12 mo After Initial Rituximab (n [%])	*P**
Any cause	Benign	528 (46.98)	485 (43.15)	0.03
	Malignant	1308 (49.87)	1286 (49.03)	0.48
Cardiac	Benign	49 (4.36)	56 (4.98)	0.44
	Malignant	148 (5.64)	184 (7.01)	0.02
Neurological	Benign	11 (0.98)	15 (1.33)	0.41
	Malignant	38 (1.45)	61 (2.33)	0.02
Infection	Benign	81 (7.21)	108 (9.61)	0.03
	Malignant	198 (7.55)	311 (11.86)	<0.001
Pulmonary	Benign	18 (1.60)	26 (2.31)	0.21
	Malignant	27 (1.03)	64 (2.44)	<0.001
GI	Benign	5 (0.44)	6 (0.53)	0.76
	Malignant	8 (0.30)	12 (0.46)	0.37

Benign conditions: n = 1124; Malignant diseases: n = 2623.

**P*-value indicates the results of comparison of 12 months hospitalization rates before and after receiving initial rituximab treatment in the same patient group (benign or malignant). McNemar tests are conducted to compare within same patient groups. The number of hospitalizations is compared for the 12 months before and after initial rituximab treatment.

GI indicates gastrointestinal.

disorders had an increase in admissions from cardiac, infectious, pulmonary, and neurological diagnoses. This increase was not observed after rituximab infusion in patients with benign conditions except for infectious causes, for which the hospitalization rate rose from 7.21% in the year before to 9.61% in the year after initial rituximab infusion ($P = 0.03$).

Figure 1 shows the distribution of total doses of rituximab in the first 8 weeks for those with benign and malignant disorders. Patient with malignant disorders received a median 4 doses in the first 8 weeks compared with 2 doses for those with nonmalignant indications. This is similar to the approved dosages of rituximab in clinical practice wherein the malignant B-cell disorders are typically treated with 375 mg/m^2 weekly for 4 to 8 weeks and the rheumatologic conditions are treated with 1000 mg every 2 weeks for 2 doses. The difference in dosing may have contributed to the difference in toxicity between the 2 groups. To explore this possibility further, we looked for any dose-response relationship in rates of hospitalization for patient with malignant diseases, using 2 methods. One was to assess the number of doses given in the first 8 weeks and cumulatively assess the number of rituximab doses as a time-dependent covariate in a Cox survival analysis. There was no clear relationship between rituximab doses and hospitalizations for neurological, infectious, pulmonary, cardiac, or GI etiologies (Table 3). There was no violation of assumption on proportional hazard in any of the dose-response models (Table 4). No differences in rates of hospitalizations were noted in the common benign and malignant disorders either, as detailed in Table 5.

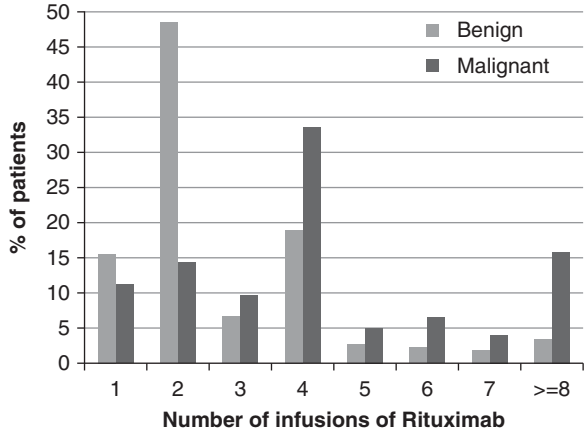

FIGURE 1. Total number of doses of rituximab in the first 8 weeks.

Finally, we looked for the diagnosis of progressive multifocal leucoencephalopathy in patients with either malignant or nonmalignant conditions treated with rituximab, but found none.

DISCUSSION

Our overall approach in this study was to assess the rates of hospitalizations for specific potential toxicities from cardiac, pulmonary, infectious, GI, and neurological diagnoses in the 12 months before and 12 months after the initial infusion of rituximab. We also specifically analyzed the data set for the incidence of progressive multifocal leucoencephalopathy. The study included patients with both benign and malignant conditions and only accounted for toxicities serious enough to lead to hospitalizations. A dose-response analysis was also performed. Our study did not show an increase in the rates of hospitalizations for cardiac, pulmonary, neurological, or GI diagnoses in patients with benign disorders. The rates of admissions for infections were higher in the year after initial rituximab infusion in both the benign and malignant groups. Patients with malignant conditions had increased hospitalizations for several other potential toxicities. However, the lack of increase in patients with benign conditions and the lack of a dose-response relationship led us to conclude that the most likely explanation for the increase in hospitalizations in the malignant group was secondary to the underlying disease.

We tried to limit the influence of other medications by limiting our analysis to patients who did not receive any other chemotherapy. The nature of the study does not allow us to determine whether the reason for hospitalizations was purely from rituximab-related toxicity. In patients with benign diseases, the overall rates of hospitalizations decreased in the year after initiation of rituximab and this drop likely reflects the improvement in their systemic disease.

TABLE 4. Cox Proportional Hazard Ratios for Specific Toxicity

		Benign		Malignant	
Characteristic	**Category**	**HR**	**95% CI**	**HR**	**95% CI**
A: Cardiac					
Dose of rituximab within first 8 wk*	1	1.00		1.00	
	2	1.11	0.67-1.83	0.84	0.62-1.14
	3	2.59	1.49-4.51	1.09	0.80-1.48
Age		1.04	1.02-1.06	1.04	1.03-1.05
Sex	Male	1.00		1.00	
	Female	1.02	0.66-1.56	0.97	0.78-1.22
Ethnicity	White	1.00		1.00	
	Black	1.35	0.67-2.74	0.87	0.48-1.46
	Hispanic	0.74	0.24-2.29	1.12	0.52-2.35
	Others	1.34	0.41-4.52	0.94	0.31-2.91
Comorbidity	0	1.00		1.00	
	1	2.27	1.12-4.61	1.73	1.31-2.29
	2	3.61	1.71-7.59	2.00	1.41-2.84
	≥ 3	6.58	3.17-13.66	2.35	1.65-3.34
Year of initial rituximab treatment	2001	1.00		1.00	
	2002	0.37	0.08-1.70	1.27	0.77-2.09
	2003	0.38	0.11-1.34	1.47	0.92-2.34
	2004	0.28	0.08-0.92	1.40	0.87-2.25
	2005	0.49	0.15-1.58	0.90	0.55-1.50
	2006	0.41	0.13-1.31	0.95	0.57-1.59
	2007	0.50	0.16-1.59	1.35	0.81-2.25
	2008	0.48	0.15-1.59	1.05	0.59-1.90
Medicaid eligible	No	1.00		1.00	
	Yes	1.04	0.59-1.84	1.19	0.83-1.71
Count of hospitalization 12 mo before initial rituximab treatment		1.08	0.97-1.20	1.02	0.93-1.11
Any hospitalization due to specific conditions 12 mo before first rituximab treatment	No	1.00		1.00	
	Yes	2.54	1.37-4.72	3.92	2.82-5.44
B: Neurological					
Dose of rituximab within first 8 wk*	1	1.00		1.00	
	2	2.67	1.16-4.16	1.68	0.95-2.99
	3	0.18	0.02-1.55	1.31	0.69-2.49
Age		1.02	0.99-1.05	1.01	0.98-1.02
Sex	Male	1.00		1.00	
	Female	0.96	0.45-2.03	1.26	0.84-1.90
Ethnicity	White	1.00		1.00	
	Black	1.82	0.38-4.26	0.97	0.31-2.98
	Hispanic	3.01	0.44-5.69	1.39	0.31-6.37
	Others	1.27	0.66-2.06	1.42	0.10-2.97
Comorbidity	0	1.00		1.00	
	1	1.27	0.49-3.29	1.07	0.64-1.79
	2	1.42	0.48-4.22	1.72	0.96-3.08
	≥ 3	1.69	0.54-5.27	1.95	1.05-3.63
Year of initial rituximab treatment	2001	1.00		1.00	
	2002	0.76	0.05-6.57	0.65	0.31-1.36
	2003	0.63	0.05-7.41	0.69	0.35-1.35
	2004	1.54	0.18-9.85	0.72	0.37-1.42
	2005	0.74	0.08-7.03	0.36	0.16-0.82
	2006	0.56	0.06-4.99	0.41	0.18-0.91
	2007	0.33	0.03-3.16	0.62	0.28-1.37
	2008	0.55	0.06-5.49	0.45	0.17-1.17
Medicaid eligible	No	1.00		1.00	
	Yes	0.58	0.17-1.96	1.17	0.62-2.20
Count of hospitalization 12 mo before initial rituximab treatment		1.01	0.74-1.22	1.07	0.94-1.23
Any hospitalization due to specific conditions 12 mo before first rituximab treatment	No	1.00		1.00	
	Yes	40.59	9.02-80.58	3.85	1.01-8.12
C: Infections					
Dose of rituximab within first 8 wk*	1	1.00		1.00	
	2	0.94	0.66-1.32	0.74	0.60-0.92
	3	0.72	0.44-1.18	0.68	0.53-0.87

TABLE 4. (*continued*)

Characteristic	Category	Benign		Malignant	
		HR	95% CI	HR	95% CI
Age		1.01	0.99-1.03	1.03	1.01-1.06
Sex	Male	1.00		1.00	
	Female	0.88	0.65-1.20	0.78	0.65-0.94
Ethnicity	White	1.00		1.00	
	Black	0.79	0.45-1.53	1.34	1.09-2.06
	Hispanic	1.69	1.04-3.02	1.23	0.89-3.01
	Others	0.85	0.27-2.66	0.97	0.42-1.13
Comorbidity	0	1.00		1.00	
	1	0.87	0.56-1.35	1.40	1.12-1.75
	2	1.34	0.85-2.12	1.63	1.24-2.16
	≥ 3	1.91	1.20-3.03	1.78	1.35-2.33
Year of initial rituximab treatment	2001	1.00		1.00	
	2002	1.71	0.56-5.17	0.84	0.59-1.19
	2003	1.21	0.45-3.32	0.89	0.65-1.24
	2004	0.89	0.33-2.37	0.67	0.48-0.95
	2005	1.05	0.39-2.81	0.64	0.45-0.91
	2006	1.02	0.39-2.65	0.82	0.59-1.16
	2007	0.79	0.30-2.11	0.57	0.39-0.84
	2008	0.99	0.37-2.67	0.53	0.34-0.82
Medicaid eligible	No	1.00		1.00	
	Yes	1.09	0.73-1.61	1.15	0.86-1.52
Count of hospitalization 12 mo before initial rituximab treatment		1.14	1.05-1.23	1.13	1.07-1.19
Any hospitalization due to specific conditions 12 mo before first rituximab treatment	No	1.00		1.00	
	Yes	1.03	0.63-1.68	2.03	1.51-2.74
D: Pulmonary					
Dose of rituximab within first 8 wk*	1	1.00		1.00	
	2	0.85	0.40-1.81	0.97	0.57-1.65
	3	1.72	0.76-3.91	1.15	0.65-2.03
Age		1.02	0.99-1.05	1.05	1.02-1.07
Sex	Male	1.00		1.00	
	Female	0.55	0.29-1.01	0.55	0.37-0.82
Ethnicity	White	1.00		1.00	
	Black	0.86	0.45-2.01	1.25	0.29-2.96
	Hispanic	0.32	0.06-2.30	0.98	0.40-2.17
	Others	1.03	0.24-2.54	0.92	0.61-1.44
Comorbidity	0	1.00		1.00	
	1	0.61	0.23-1.65	1.11	0.67-1.83
	2	1.48	0.57-3.85	1.34	0.73-2.47
	≥ 3	2.98	1.19-4.42	1.31	1.02-2.40
Year of initial rituximab treatment	2001	1.00		1.00	
	2002	0.36	0.03-4.12	0.94	0.44-1.98
	2003	0.57	0.11-2.18	0.66	0.31-1.40
	2004	0.73	0.15-2.58	0.97	0.48-1.97
	2005	0.23	0.04-1.49	0.51	0.22-1.16
	2006	0.48	0.09-2.39	0.75	0.35-1.62
	2007	0.71	0.14-3.51	0.84	0.37-1.91
	2008	0.62	0.12-3.24	0.66	0.24-1.77
Medicaid eligible	No	1.00		1.00	
	Yes	2.53	1.22-5.24	1.57	0.85-2.89
Count of hospitalization 12 mo before initial rituximab treatment		1.06	0.92-1.21	1.23	1.10-1.37
Any hospitalization due to specific conditions 12 mo before first rituximab treatment	No	1.00		1.00	
	Yes	3.21	1.74-6.93	4.56	2.31-8.35

GI conditions not analyzed due to small number.
*Dose of rituximab within first 8 weeks: 1 (1 to 2 doses); 2 (3 to 4 doses); 3 (≥ 5 doses).
CI indicates confidence interval; GI, gastrointestinal; HR, hazard ratio.

The median number of doses received by malignant patients was higher than those received by patients with benign conditions. Hence, we were also concerned that the differences in doses received by these 2 groups of patients may have also contributed to differences in toxicity. The dose-response analysis in our study that included the total number of doses administered in the first 8 weeks of therapy failed to demonstrate any significant effect on subsequent serious toxicity.

TABLE 5. Any Hospitalization Rate 12 Months Before and After the First Rituximab Infusion

Diagnosis	12 mo Before Initial Rituximab (n [%])	12 mo After Initial Rituximab (n [%])	*P*
Rheumatoid arthritis	194 (35.27)	192 (34.91)	0.89
Thrombocytopenia	187 (64.48)	155 (53.45)	0.003
Disorders of plasma protein metabolism	49 (33.56)	64 (43.84)	0.03
Nodular lymphoma	165 (45.71)	152 (42.11)	0.26
Other lymphomas	674 (48.81)	643 (46.56)	0.17
Chronic lymphoid leukemia	271 (48.65)	297 (53.32)	0.08

We found an increase in hospitalizations for infection in patients with either malignant or nonmalignant conditions. Patients treated with rituximab tend to have low peripheral blood B-cell levels for about 2 to 6 months after the last infusion, followed by recovery to pretreatment levels by about 12 months.[2]

Rituximab has also been shown to cause late-onset neutropenia with an incidence of 3% to 27% that appears after a median range of 38 to 175 days from the last infusion.[23] Most of the infections described in these cases were mild without any serious consequences. The maintenance study by Swiss Group for Clinical Cancer Research (SAKK) demonstrated that the immunoglobulin IgM levels in patients who receive rituximab also tend to be lower for about 12 months and that patients on prolonged doses take longer to return to baseline levels.[24] However, this finding did not translate into an increase in clinically relevant immune-related complications in this study. In a meta-analysis of 9 trials that included 2586 follicular lymphoma patients who received maintenance rituximab, an increase in infections was noted in the patients treated with prolonged courses of rituximab (pooled relative risk = 1.67, 95% confidence interval = 1.40-2.00).[25] The authors report an even higher rate of infections when only grade 3 or 4 adverse events were included in the analysis (pooled relative risk = 3.55, 95% confidence interval = 1.88-6.69). The major clinical trials utilizing rituximab as a single agent or in combination with other chemotherapy agents do not report any significant increase in infections related to rituximab use. In a pivotal study in which patients aged 60 to 80 years were randomized to CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) or rituximab with CHOP, both groups of patients showed similar infection rates.[4,26] Low rates of infection have also been reported in studies of patients with rheumatoid arthritis and other autoimmune conditions who were treated with rituximab.[5,27] In a retrospective study of 370 rituximab patients with various autoimmune disorders, the incidence of serious infections was 3.7%, with the majority occurring within the first 7 months after initiation of rituximab.[28] A population-based analysis of the impact of adding rituximab to multiagent chemotherapy in diffuse large B-cell lymphoma did not show any significant increase in 1 year hospitalization rates for infections, cardiac, pulmonary, GI, or neurological diagnoses.[29] In our study, there was an increase in hospitalizations due to infections in both benign and malignant patients, but no correlation was noted with increasing doses in either group of patients.

Studying toxicity of medications in a population-based setting has several potential advantages.[30] A population-based analysis of toxicity can provide a more robust picture of potential toxicities in the community than other types of studies. As Medicare databases provide information on a large number of patients, it should help identify unique and rare toxicities, if any. Although some of these toxicities are available in the form of case reports, the small number of patients treated in randomized trials makes it difficult to assess the true incidence of such occurrences. Administrative databases also offer a cost-effective method of analyzing toxicity rates.

This study has limitations. It does not determine the overall toxicity of rituximab. The data only included patients who were admitted to the hospital with serious toxicity. It is possible that many of the side effects were less serious and were managed on an outpatient basis. Another limitation is that our study included toxicities within the first year of initiating rituximab; patients who received more doses need longer follow-up periods to determine the toxicities associated with prolonged exposures. Hence, our study does not provide an estimate of toxicity in patients who receive maintenance rituximab. We studied patients with fee-for-service Medicare who received rituximab in a single large state in the United States. It is possible that our results may not apply to a younger population, those with HMO coverage and those living in other states, but we have no reason to suspect that toxicity effect varies by state and payer. Even though we tried to look for the specific diagnosis of progressive multifocal leucoencephalopathy, we acknowledge that the patients who did not have a tissue diagnosis might not have been accurately reported in the database. We tried to capture those patients by utilizing the ICD-9 codes for neurological symptoms, but increase in neurological toxicity was also not demonstrated.

In conclusion, this study did not demonstrate any significant increase in hospitalizations for serious toxicity other than infections in the 12-month period after initiating rituximab infusion in Medicare patients.

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