Physician Experience and Risk of Rituximab Discontinuation in Older Adults With Non-Hodgkin's Lymphoma

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ABSTRACT

Background: Provider experience, or clinical volume, is associated with improved outcomes in many complex healthcare settings. Despite increased complexity of anticancer therapies, studies evaluating physician-level experience and cancer treatment outcomes are lacking. **Methods:** A population-based study was conducted of older adults (aged ≥ 66 years) diagnosed with B-cell non-Hodgkin's lymphoma in 2004 through 2011 using SEER-Medicare data. Analysis focused on outcomes in patients receiving rituximab, the first approved monoclonal anticancer immunotherapy. We hypothesized that lower physician experience using rituximab and managing its infusion-related reactions would be associated with early treatment discontinuation. A 12-month look-back from each initiation of rituximab was used to categorize physician volume (0, 1–2, or ≥ 3 initiations per year). Modified Poisson regression was used to account for provider-level correlation and estimated relative risk (RR) of early rituximab discontinuation (< 3 cycles within 180 days of rituximab initiation). Cox proportional hazards were used to measure the impact of rituximab discontinuation on survival. **Results:** Among 15,110 patients who initiated rituximab with 2,684 physicians, 7.6% experienced early rituximab discontinuation. Approximately one-fourth of patients (26.1%) initiated rituximab with a physician who had no rituximab initiations during the preceding 12 months. Compared with patients treated by physicians who had ≥ 3 rituximab initiations in the prior year, those treated by physicians without initiations were 57% more likely to experience early discontinuation (adjusted RR [aRR], 1.57; 95% CI, 1.35–1.82; $P < .001$ for 0 vs ≥ 3 , and aRR, 1.19; 95% CI, 1.03–1.37; $P = .02$ for 1–2 vs ≥ 3). Additionally, rituximab discontinuation was associated with higher risk of death (adjusted hazard ratio, 1.39; 95% CI, 1.28–1.52; $P < .001$). **Conclusions:** Lower oncologist experience with rituximab was associated with increased risk of early rituximab discontinuation in Medicare beneficiaries with non-Hodgkin's lymphoma. Physician-level volume may be an important factor in providing high-quality cancer care in the modern era.

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Background

The modern-day armamentarium against cancer is increasingly using targeted small molecules and novel immunotherapies.¹ These therapeutic advancements can offer meaningful clinical responses,^{2–4} yet increased treatment complexity and adverse effects unlike those of traditional chemotherapies may impact their delivery in the real-world setting. The quality of cancer care for patients receiving complex surgeries has been well characterized, with a rich body of literature demonstrating an association between volume of care provided and clinical outcomes.^{5–9} Hence, it is plausible that the quality of cancer care could also be better for patients receiving complex systemic therapies at the hands of medical oncologists who have greater experience with those agents.

To measure the association of physician-level volume with outcomes after systemic therapy, we selected rituximab, the first FDA-approved targeted monoclonal antibody for cancer. As an immunotherapy targeting CD20 on B lymphocytes, rituximab has been shown to improve survival in numerous lymphoma settings.^{10–12} Rituximab's adverse effect profile differs from standard chemotherapies, with infusion-related reactions (IRRs) occurring in upwards of 50% of patients during the first 2 exposures,^{13–15} a rate significantly higher than for monoclonal antibodies subsequently approved for solid tumor malignancies.¹⁶ Although most rituximab IRRs can be managed with conservative measures, they can be life-threatening for a limited number of patients.¹⁷

A population-based analysis was conducted to assess the role of physician-level volume with early rituximab discontinuation in Medicare beneficiaries with non-Hodgkin's lymphoma (NHL). B-cell NHL occurs mostly in elderly patients, with median age at diagnosis of 67 years.^{18,19} Furthermore, rituximab has been shown to be both efficacious and tolerated in older patients treated on clinical trials.^{10,20} However, we hypothesized that physicians who prescribed rituximab infrequently would

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be less familiar with managing IRRs, and that patients with NHL under their care would be more likely to experience early rituximab discontinuation. We also expected patients who experienced early rituximab discontinuation to have inferior lymphoma-specific and overall survival.

Methods

Study Design, Setting, and Data Source

Data were obtained from the SEER-Medicare linked dataset, which includes demographic cancer characteristics and survival data from population-based cancer registries linked to comprehensive Medicare claims.^{21,22} In addition to patient-level characteristics derived from SEER-Medicare, physician-level variables were obtained from the American Medical Association (AMA) Physician Masterfile. This study did not directly involve human subjects and therefore was deemed exempt from Yale University Institutional Review Board approval.

Study Sample

We identified individuals diagnosed with the most common subtypes of B-cell NHL in 2004 through 2011 (Figure 1). Criteria for participation included patients who (1) were ≥ 66 years at lymphoma diagnosis, (2) had known month of diagnosis, (3) had continuous Medicare Parts A and B coverage during the study period, (4) had at least one outpatient claim for rituximab in or after the month of diagnosis recorded by SEER, and (5) had not received rituximab within 12 months before diagnosis. Finally, we excluded individuals who were unable to be assigned to an initiating physician, lacked provider volume information, died within 6 months of first rituximab claim, or whose assigned physician was not matched to the AMA Physician Masterfile.

Construction of Variables

Exposure and Outcome

The Healthcare Common Procedure Coding System (HCPCS) code J9310 was used to identify receipt of rituximab from Medicare claims. We identified the first outpatient rituximab claim after NHL diagnosis as the index date for rituximab initiation, and then used distinct dates of rituximab claims and counted the number of doses from the date of initiation through 180 days. Because a single rituximab dose is occasionally split over adjacent days,²³ we defined the start of the next rituximab cycle as a claim that occurred ≥ 6 days after the preceding rituximab claim. Rituximab is typically given for at least 4 to 6 doses during the induction period, administered as either a single-agent or alongside chemotherapy as immunochemotherapy.^{10–12,24} The primary outcome of early rituximab discontinuation was

Figure 1. Cohort selection diagram.

Abbreviations: AMA, American Medical Association; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; MZL, marginal zone lymphoma.

defined as receipt of only 1 or 2 doses during the 180-day period.

Claims for the first rituximab administration were also used to assign the physician who initiated rituximab therapy for each Medicare beneficiary. If a distinct provider could not be assigned for the first cycle, rituximab claims from the second cycle were used to assign the responsible provider. We then calculated rituximab initiation physician volume for each beneficiary, where each volume measure was equal to the number of rituximab initiations the physician was assigned to during the 12 months before initiation. Due to this 12-month look-back period, we were not able to assign physician volume to individuals who initiated therapy during the first year of available data, but we did use the 2004 claims to calculate physician volume after 2004. We evaluated the distribution of physician volume and categorized this variable as 0, 1–2, or ≥ 3 patients initiated on rituximab in the preceding year. The high-volume category (≥ 3 initiations/year) corresponded to the upper tertile, a cutoff commonly used to define high provider volume in surgical settings.^{25,26}

In addition to the primary outcome of early rituximab discontinuation, we also measured lymphoma-specific and overall survival in this cohort. Survival was calculated from date of rituximab initiation until death, with cause of death recorded by SEER and date of death provided by SEER and Medicare. Patients were censored if they did not have death recorded by date of last available follow-up (December 31, 2013).

Other Variables

For each patient, we recorded age, sex, race, marital status, year of diagnosis, geographic region, metropolitan status of residence, and Medicaid dual enrollment in the year before SEER diagnosis (Table 1). We also included median household income at the census tract level as a proxy for individual socioeconomic status. Clinical characteristics were derived from SEER, including disease staging for those without chronic lymphocytic leukemia (CLL) histology. For patients with CLL, a diagnosis of anemia or thrombocytopenia on Medicare claims was used to indicate advanced stage.²⁷ Claims were also used to adjust for baseline health status using the Elixhauser comorbidity score and a claims-based proxy for performance status.^{28,29}

In addition to patient characteristics, we recorded whether rituximab was initiated as monotherapy or immunochemotherapy within ± 7 days of chemotherapy. Location of rituximab initiation was characterized as community-based if claims were present only in the physician/supplier file,³⁰ whereas hospital outpatient-based treatment was categorized as being at an NCI-designated or non-NCI-designated site.³¹ We also assessed receipt of radiation therapy. Finally, the AMA

Masterfile was used to include the following physician-level variables in the analysis: degree (MD vs DO), sex, medical school location (US-based, non-US-based), medical school graduation year (<1980, 1980s, 1990s, 2000s), and hematology and/or oncology as a primary or secondary specialty (Table 2).

Statistical Analysis

Bivariate comparisons between the distributions of patient and physician-level characteristics using our 3-category volume variable were evaluated using chi-square tests. Modified marginal Poisson regression models with a log-link function were created to estimate the relative risk of early rituximab discontinuation (<3 cycles within 180 days). Generalized estimating equations with exchangeable correlation were used to account for clustering of patients within physicians.^{32,33}

Cox proportional hazard models were used to investigate the relationship between early rituximab discontinuation and survival. To minimize the likelihood of rituximab discontinuation being solely related to poor health status or a serious non-lymphoma-related health event, patients were required to be alive at least 6 months after rituximab initiation. No significant deviation from proportional hazards assumptions was found.³⁴

Several sensitivity analyses were also used to minimize the impact of unmeasured confounders on the association between early rituximab discontinuation and survival. First, we generated 2 landmark survival models requiring patients to be alive 9 and 12 months, respectively, after rituximab initiation. We then generated a survival model for beneficiaries who initiated immunochemotherapy; this survival analysis excluded patients who discontinued both rituximab and chemotherapy, in order to compare survival of beneficiaries without early rituximab discontinuation, versus those who continued chemotherapy alone after rituximab discontinuation. By requiring patients to continue chemotherapy, this model attempted to isolate rituximab discontinuation caused by an early rituximab-specific toxicity (ie, IRR) rather than comorbidities or other serious health events. Lastly, we performed separate survival analyses by NHL subtype to evaluate whether early-rituximab discontinuation was associated with survival across histologies. All statistical analyses were completed using SAS 9.4 (SAS Institute Inc.) and 2-sided statistical tests with a significance level of $\alpha = 0.05$.

Results

Study Population

A total of 18,570 Medicare beneficiaries were diagnosed with B-cell NHL in 2004 through 2011 and

Table 1. Patient Characteristics

Characteristic	Full Cohort n (%)	Physician Volume (Rituximab Initiations During Prior Year)			P Value
		0 n (%)	1–2 n (%)	≥3 n (%)	
Total	15,110 (100)	3,943 (26.1)	6,365 (42.1)	4,802 (31.8)	
Sociodemographic					
Age group, y					.26
66–69	2,897 (19.2)	806 (20.4)	1,215 (19.9)	876 (18.2)	
70–74	3,900 (25.8)	1,007 (25.5)	1,604 (25.2)	1,289 (26.8)	
75–79	3,713 (24.6)	958 (24.3)	1,582 (24.9)	1,173 (24.2)	
80–84	2,856 (18.9)	729 (18.5)	1,224 (19.2)	903 (18.8)	
≥85	1,744 (11.5)	443 (11.2)	740 (11.6)	561 (11.7)	
Sex (male)	7,649 (50.6)	2,003 (50.8)	3,211 (50.5)	2,435 (50.7)	.93
Race					<.001
White	13,924 (92.1)	3,557 (90.2)	5,844 (91.8)	4,523 (94.2)	
Black	528 (3.5)	167 (4.2)	234 (3.7)	127 (2.6)	
Other	658 (4.4)	219 (5.6)	287 (4.5)	152 (3.2)	
Marital status					.27
Married	9,068 (60.0)	2,317 (58.8)	3,819 (60.0)	2,932 (61.1)	
Unmarried	5,006 (33.1)	1,350 (34.2)	2,100 (33.0)	1,556 (32.4)	
Other	1,036 (6.9)	276 (7.0)	446 (7.0)	314 (6.5)	
Year of diagnosis					<.001
2004	1,232 (8.2)	182 (4.6)	751 (11.8)	299 (6.2)	
2005	2,017 (13.3)	519 (13.2)	780 (12.3)	718 (15.0)	
2006	1,769 (11.7)	442 (11.2)	744 (11.7)	583 (12.1)	
2007	1,986 (13.1)	603 (15.3)	772 (12.1)	611 (12.7)	
2008	2,119 (14.0)	544 (13.8)	911 (14.3)	664 (13.8)	
2009	2,100 (13.9)	570 (14.5)	851 (13.4)	679 (14.1)	
2010	2,027 (13.4)	538 (13.6)	814 (12.8)	675 (14.1)	
2011	1,860 (12.3)	545 (13.8)	742 (11.7)	573 (11.9)	
Geographic region					<.001
Northeast	3,147 (20.8)	988 (25.1)	1,332 (20.9)	827 (17.2)	
Midwest	2,207 (14.6)	498 (12.6)	814 (12.8)	895 (18.6)	
South	3,515 (23.3)	834 (21.2)	1,593 (25.0)	1,088 (22.7)	
West	6,241 (41.3)	1,623 (41.2)	2,626 (41.3)	1,992 (41.5)	
Median household income (\$USD)					<.001
≥\$63,000	4,041 (26.7)	1,132 (28.7)	1,733 (27.2)	1,176 (24.5)	
\$50,000–\$62,999	3,042 (20.1)	789 (20.0)	1,305 (20.5)	948 (19.7)	
\$40,000–\$49,999	3,024 (20.0)	740 (18.8)	1,311 (20.6)	973 (20.3)	
\$33,000–\$39,999	2,247 (14.9)	579 (14.7)	864 (13.6)	804 (16.7)	
<\$33,000	2,756 (18.2)	703 (17.8)	1,152 (18.1)	901 (18.8)	
Metropolitan status of residence					<.001
Metropolitan	12,515 (82.8)	3,289 (83.4)	5,367 (84.3)	3,859 (80.4)	
Nonmetropolitan	2,595 (17.2)	654 (16.6)	998 (15.7)	943 (19.6)	
Medicaid dual coverage	1,468 (9.7)	448 (11.4)	633 (9.9)	387 (8.1)	<.001

(continued on next page)

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma.

^aFor individuals with CLL, a diagnosis of anemia or thrombocytopenia on Medicare claims was used to indicate advanced stage.

Table 1. Patient Characteristics (cont.)

Characteristic	Full Cohort n (%)	Physician Volume (Rituximab Initiations During Prior Year)			P Value
		0 n (%)	1–2 n (%)	≥3 n (%)	
Clinical					
Histology					.040
CLL/SLL	2,894 (19.2)	773 (19.7)	1,230 (19.3)	891 (18.6)	
Mantle cell lymphoma	872 (5.8)	255 (6.5)	328 (5.2)	289 (6.0)	
Lymphoplasmacytic/MZL	1,721 (11.4)	468 (11.9)	697 (11)	556 (11.6)	
DLBCL	6,312 (41.8)	1,635 (41.5)	2,685 (42.2)	1,992 (41.5)	
Follicular lymphoma	3,311 (21.9)	812 (20.6)	1,425 (22.4)	1,074 (22.4)	
Advanced stage ^{27,a}	7,585 (50.2)	1,995 (50.6)	3,157 (49.6)	2,433 (50.7)	.47
Elixhauser comorbidity score					.63
0	6,252 (41.2)	1,641 (41.6)	2,590 (40.7)	2,021 (42.1)	
1–2	6,169 (40.8)	1,605 (40.7)	2,637 (41.4)	1,927 (40.1)	
>3	2,689 (17.8)	697 (17.7)	1,138 (17.9)	854 (17.8)	
Disabled ²⁹	721 (4.8)	208 (5.3)	297 (4.7)	216 (4.5)	.21
Treatment					
Type of therapy					.47
Rituximab monotherapy	4,477 (29.6)	1,196 (30.3)	1,882 (29.6)	1,399 (29.1)	
Rituximab + chemotherapy	10,633 (70.4)	2,747 (69.7)	4,483 (70.4)	3,403 (70.9)	
Received radiation	2,141 (14.2)	565 (14.3)	945 (14.9)	631 (13.1)	.036
Location of treatment					<.001
Community-based	10,172 (67.3)	2,339 (59.3)	4,431 (69.6)	3,402 (70.9)	
Non–NCI-designated outpatient hospital	4,216 (27.9)	1,285 (32.6)	1,705 (26.8)	1,226 (25.5)	
NCI-designated outpatient hospital	722 (4.8)	319 (8.1)	229 (3.6)	174 (3.6)	

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma.

^aFor individuals with CLL, a diagnosis of anemia or thrombocytopenia on Medicare claims was used to indicate advanced stage.

initiated rituximab through 2013. After creating our volume variable with a 12-month look-back period and linking providers to the AMA Physician Masterfile, the analyzed cohort contained 15,110 beneficiaries initiating rituximab under the care of 2,684 physicians (Figure 1). Median patient age was 75 years (interquartile range, 71–81 years) and the most common histology was diffuse large B-cell lymphoma (DLBCL) (41.8%) (Table 1). Approximately half of the cohort had advanced-stage disease at diagnosis and most initiated rituximab alongside chemotherapy (70.4%). Patients initiating therapy with high-volume physicians were more likely to be white, receive treatment in the community setting, and live in a nonmetropolitan setting (all with $P < .001$).

Early Rituximab Discontinuation

Of the 15,110 individuals in the study cohort, 1,146 (7.6%) experienced early rituximab discontinuation, defined as ≤ 2 doses within 180 days of initiation. In multivariable

Poisson regression, lower physician volume was associated with increased risk of early rituximab discontinuation (Table 3); a significant dose-dependent relationship was observed between physician volume and rituximab discontinuation (Cochran-Armitage trend test, $P < .001$). Compared with beneficiaries treated by a physician with ≥ 3 rituximab initiations during the previous 12 months, those treated by a physician with no initiations had a 57% increased likelihood of discontinuing rituximab (95% CI, 1.35–1.82; $P < .001$), and those treated by a physician with 1–2 initiations had a 19% increased likelihood of discontinuing rituximab (95% CI, 1.03–1.37; $P = .02$).

In addition to the primary exposure variable of physician volume, several patient-level characteristics were associated with early discontinuation, including advanced age, CLL histology, limited-stage disease, higher comorbidity score, Medicaid dual coverage, and disability. Physician-level variables derived from the AMA Masterfile were not strongly associated with rituximab

Table 2. Physician Characteristics (N=2,684)

Characteristic	n (%)
Degree	
MD	2,586 (96.3)
DO	98 (3.7)
Sex	
Male	2,072 (77.2)
Female	612 (22.8)
US medical school	
Yes	1,778 (66.2)
No	906 (33.8)
Medical school graduation year	
<1980	881 (32.8)
1980s	767 (28.6)
1990s	730 (27.2)
2000s	306 (11.4)
Specialty	
Hematology and/or oncology	2,379 (88.6)
Other	305 (11.4)

discontinuation in the multilevel regression model (supplemental eTable 1, available with this article at JNCCN.org).

Survival Analysis

Median follow-up time from rituximab initiation was 42 months, and 41.8% of patients died by the end of this study (December 31, 2013). After comprehensive adjustment of patient-level covariates, early rituximab discontinuation remained associated with a higher risk of death (adjusted hazard ratio [aHR], 1.39; 95% CI, 1.28–1.52; $P<.001$). Similarly, early rituximab discontinuation was associated with inferior lymphoma-specific survival (aHR, 1.40; 95% CI, 1.21–1.61; $P<.001$) (Figure 2).

Rituximab discontinuation remained associated with survival during sensitivity analyses, including 9- and 12-month landmark analyses (Table 3). Furthermore, survival findings remained consistent in a subgroup analysis limited to beneficiaries receiving combined rituximab and chemotherapy. Dropping rituximab alone after 1 to 2 cycles remained strongly associated with higher risk of death (aHR, 1.47; 95% CI, 1.27–1.70; $P<.001$) (Table 4). Furthermore, an association or trend between rituximab discontinuation and survival persisted when performing the survival analyses separately for NHL subtypes (supplemental eTable 2). Although early rituximab discontinuation was associated with inferior survival, the physician volume measure (0, 1–2, ≥ 3 initiations/year) was not found to be strongly associated with survival when added to the Cox regression models (data not shown).

Discussion

Despite being the most common hematologic malignancy, NHL represents just 5% of all incident cancers.³⁵ We found that 38% of the physicians in our study initiated rituximab on ≤ 1 Medicare beneficiary with NHL each year, and that Medicare beneficiaries initiating rituximab with lower-volume physicians were more likely to experience early discontinuation. Furthermore, early rituximab discontinuation was associated with inferior lymphoma-specific and overall survival, with findings consistent across multiple sensitivity analyses.

Volume–outcome analyses evaluating nonsurgical cancer outcomes are scarce and have primarily focused on hospital-level case volume and overall survival for select malignancies,^{36–39} including NHL.³⁷ More recently, our group found that Medicare beneficiaries with newly diagnosed DLBCL were more likely to receive standard immunochemotherapy and have better survival when managed by oncologists with greater experience treating older adults with lymphoma.⁴⁰ By focusing on outcomes

Table 3. Adjusted RR for Early Discontinuation of Rituximab by Physician Volume

Physician Volume (Initiations/y)	Model 1 ^a (Patient Level)		Model 2 ^{a,b} (Clustered by Physician)		Model 3 ^{a,c} (Clustered + Physician-Level Variables)	
	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
≥ 3	Ref		Ref		Ref	
1–2	1.18 (1.02–1.36)	.023	1.19 (1.03–1.37)	.018	1.19 (1.03–1.37)	.020
0	1.56 (1.34–1.80)	<.001	1.56 (1.35–1.82)	<.001	1.57 (1.35–1.82)	<.001

Abbreviation: RR, relative risk.

^aModels 1 and 2 were adjusted for patient-level variables: age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

^bGeneralized estimating equation with exchangeable correlation was used to account for clustering of patients within physicians.

^cModel 3 was adjusted for all variables in Models 1 and 2 plus physician-level variables: degree, sex, US medical school, medical school graduation year, and primary specialty.

Figure 2. (A) Overall survival and (B) lymphoma-specific survival of Medicare beneficiaries after rituximab initiation.

Survival models were adjusted for age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

Abbreviation: aHR, adjusted hazard ratio.

after rituximab initiation, our current analysis suggests that provider experience may be associated with treatment-specific management in addition to the therapy selection observed in our earlier work.⁴⁰

Along with establishing an association between physician volume and rituximab discontinuation, we found that early discontinuation was associated with worse survival. This is not surprising, given that multiple placebo-controlled clinical trials have established that rituximab-containing regimens improve survival in older adults with NHL.^{10–12} This association between discontinuation and survival persisted on multiple sensitivity analyses, including a survival analysis limited to patients who remained on chemotherapy after discontinuing rituximab alone. Furthermore, early rituximab discontinuation occurred in 7.6% of our study cohort, a rate 2- to 3-fold higher than that typically reported in clinical trials.^{10,13,41}

Our study has important strengths, including the use of a dynamic approach to measure individual physician volume at the time they initiate therapy with the next patient. Most volume–outcome studies categorize volume using one time period.²⁶ Although this static measure offers average case volume, a 12-month look-back approach is more precise and accounts for practice changes at the physician level over time. Second, we had access to rich clinical data through SEER and comprehensive treatment data through Medicare claims. This contrasts with previous analyses evaluating facility-level volume–outcome relationships in cancer, wherein treatment details were limited.^{36–39,42} Finally, we included physician-level variables from the AMA Physician Masterfile to minimize unmeasured variables that could have influenced the study findings.

Although this study has important findings, limitations exist. First, our volume measure was restricted to

Table 4. Role of Early Rituximab Discontinuation in Survival^a

Early Rituximab Discontinuation	Sensitivity Cohort				Beneficiaries Initiating Rituximab + Chemotherapy	
	Alive at Least 9 Months After Rituximab Initiation (n=14,791)		Alive at Least 12 Months After Rituximab Initiation (n=13,758)		Continuing Rituximab Beyond 2 Cycles or Continuing Chemotherapy After Rituximab Discontinuation (n=10,208)	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
No	Ref		Ref		Ref	
Yes	1.35 (1.23–1.49)	<.001	1.34 (1.21–1.48)	<.001	1.47 (1.27–1.70)	<.001

Abbreviation: HR, hazard ratio.

^aCox proportional hazards models adjusted for age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

the Medicare fee-for-service population and should be viewed as a relative measure of rituximab volume. Although Medicare is the largest purchaser of cancer care in the United States and more than half of patients with NHL are aged >65 years,¹⁹ physicians in this study likely initiated rituximab in individuals not captured in these data. Therefore, absolute rituximab initiation numbers at the physician level are underreported in this study. It also is possible that the observed association between rituximab volume and discontinuation is mediated by variability in physician experience/volume of older adults rather than rituximab initiation more broadly. Furthermore, encrypted Medicare claims allowed us to identify treating providers and calculate prior rituximab volume, but did not allow us to accommodate for variation in facility-level case volume. Future studies using electronic health records that capture entire practices and provider-level patient panels may be helpful in measuring volume–outcome relationships in medical oncology.

Although IRRs are suspected to be the driver behind rituximab discontinuation in our claims-based study, the exact reason for early discontinuation is not available in our data. The finding that early discontinuation most likely occurred in patients with known risk factors for infusion reactions, such as circulating disease with CLL/small lymphocytic lymphoma,¹⁶ lends support to the rituximab discontinuation outcome. However, other non-rituximab-related complications, disease progression, nonlymphoma health events, or out-of-pocket costs also could have influenced discontinuation. We attempted to limit the impact of early disease progression as the reason for rituximab discontinuation by requiring patients be alive for at least 6 months after initiation, but there could have been residual confounding. This analysis cannot establish causality, and unmeasured confounders, such as bulky disease or age-specific comorbidities not completely captured by our claims-based comorbidity measures, may contribute to these findings. Additionally, the cause of death within SEER is derived from death certificates, and some lymphoma-related deaths could be misclassified.

Conclusions

Modern-day cancer care has become increasingly complex, with new advances that have dramatically changed the way cancer is treated. Although novel treatments offer the potential to improve cancer outcomes, research outside the field of oncology suggests clinical volume may be an important factor behind optimal delivery of highly specialized care. Results of our study showed that physician-level volume was strongly associated with risk of early rituximab discontinuation, although rituximab was first approved by the FDA in 1997. These findings are not generalizable to patients with NHL diagnosed at younger ages nor other immunotherapy settings, such as checkpoint inhibitor therapy. However, given the increasing number of newer anticancer therapies with unique and potentially life-threatening adverse effects, future studies should explore the impact of physician-level volume on therapeutic and clinical outcomes.

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Physician Experience and Risk of Rituximab Discontinuation in Older Adults With Non-Hodgkin's Lymphoma

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eTable 1: Adjusted RR for Early Discontinuation of Rituximab by Model

eTable 2: Association of Early Rituximab Discontinuation With Survival, Stratified By Histology

eTable 1. Adjusted RR for Early Discontinuation of Rituximab by Model

Characteristic	Model 1 ^a Patient Level		Model 2 ^{a,b} Clustered by Physician		Model 3 ^{a,c} Clustered + Physician-Level Variables	
	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Physician volume						
≥3	Ref		Ref		Ref	
1–2	1.18 (1.02–1.36)	.023	1.19 (1.03–1.37)	.018	1.19 (1.03–1.37)	.020
0	1.56 (1.34–1.80)	<.001	1.56 (1.35–1.82)	<.001	1.57 (1.35–1.82)	<.001
Sociodemographic						
Age group, y						
66–69	Ref		Ref		Ref	
70–74	1.06 (0.89–1.25)	.53	1.06 (0.89–1.25)	.53	1.05 (0.89–1.25)	.54
75–79	1.03 (0.86–1.22)	.77	1.03 (0.87–1.23)	.73	1.03 (0.87–1.23)	.71
80–84	1.22 (1.02–1.46)	.032	1.23 (1.02–1.48)	.032	1.23 (1.02–1.48)	.032
≥85	1.64 (1.34–2.01)	<.001	1.65 (1.34–2.04)	<.001	1.65 (1.34–2.04)	<.001
Sex						
Female	Ref		Ref		Ref	
Male	0.93 (0.83–1.05)	.24	0.93 (0.83–1.05)	.24	0.93 (0.83–1.05)	.24
Race						
White	Ref		Ref		Ref	
Black	0.93 (0.70–1.23)	.59	0.93 (0.70–1.24)	.63	0.93 (0.70–1.24)	.63
Other	0.97 (0.74–1.29)	.86	0.96 (0.73–1.28)	.80	0.98 (0.74–1.29)	.87
Marital status						
Married	Ref		Ref		Ref	
Unmarried	1.02 (0.90–1.16)	.73	1.02 (0.90–1.16)	.73	1.02 (0.90–1.16)	.73
Other	0.95 (0.76–1.18)	.65	0.96 (0.78–1.19)	.73	0.96 (0.77–1.19)	.70
Year of diagnosis						
2004	Ref		Ref		Ref	
2005	0.93 (0.73–1.18)	.53	0.93 (0.74–1.18)	.57	0.93 (0.74–1.19)	.58
2006	1.03 (0.81–1.31)	.79	1.04 (0.82–1.32)	.76	1.04 (0.82–1.32)	.74
2007	0.88 (0.69–1.12)	.31	0.88 (0.70–1.12)	.30	0.89 (0.70–1.12)	.32
2008	0.80 (0.63–1.02)	.073	0.81 (0.63–1.03)	.079	0.80 (0.63–1.03)	.079
2009	0.93 (0.73–1.17)	.53	0.93 (0.73–1.18)	.53	0.93 (0.73–1.19)	.57
2010	0.90 (0.71–1.15)	.41	0.90 (0.70–1.15)	.41	0.91 (0.71–1.17)	.45
2011	0.99 (0.77–1.25)	.90	0.99 (0.77–1.26)	.91	0.99 (0.77–1.27)	.95
Geographic region						
Northeast	Ref		Ref		Ref	
Midwest	1.01 (0.84–1.21)	.94	1.04 (0.85–1.27)	.73	1.02 (0.83–1.24)	.88
South	0.76 (0.63–0.91)	.002	0.79 (0.65–0.95)	.011	0.79 (0.66–0.95)	.014
West	0.86 (0.74–0.99)	.037	0.90 (0.76–1.05)	.18	0.91 (0.77–1.07)	.24

(continued on next page)

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; RR, relative risk. ^aModels 1 and 2 were adjusted for patient-level variables: age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

^bGeneralized estimating equation with exchangeable correlation was used to account for clustering of patients within physicians.

^cModel 3 was adjusted for all variables in Models 1 and 2 plus physician-level variables: degree, sex, US medical school, medical school graduation year, and primary specialty.

eTable 1. Adjusted RR for Early Discontinuation of Rituximab by Model (cont.)

Characteristic	Model 1 ^a Patient Level		Model 2 ^{a,b} Clustered by Physician		Model 3 ^{a,c} Clustered + Physician-Level Variables	
	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Sociodemographic (cont.)						
Median household income						
≥\$63,000	Ref		Ref		Ref	
\$50,000–\$62,999	1.16 (0.99–1.37)	.073	1.16 (0.98–1.38)	.075	1.16 (0.99–1.38)	.074
\$40,000–\$49,999	1.06 (0.90–1.25)	.51	1.06 (0.89–1.26)	.49	1.06 (0.89–1.26)	.50
\$33,000–\$39,999	1.02 (0.84–1.24)	.83	1.03 (0.84–1.26)	.81	1.02 (0.83–1.26)	.84
<\$33,000	1.11 (0.91–1.34)	.31	1.09 (0.89–1.32)	.40	1.08 (0.89–1.31)	.44
Metropolitan status of residence						
Metropolitan	Ref		Ref		Ref	
Non-metropolitan	1.05 (0.89–1.24)	.56	1.06 (0.90–1.26)	.49	1.07 (0.91–1.27)	.41
Medicaid dual coverage						
No	Ref		Ref		Ref	
Yes	1.28 (1.07–1.54)	.007	1.27 (1.06–1.52)	.011	1.27 (1.06–1.53)	.011
Clinical						
Histology						
CLL/SLL	Ref		Ref		Ref	
Mantle cell lymphoma	0.54 (0.42–0.70)	<.001	0.54 (0.42–0.70)	<.001	0.54 (0.42–0.70)	<.001
Lymphoplasmacytic/MZL	0.50 (0.41–0.61)	<.001	0.50 (0.40–0.61)	<.001	0.49 (0.40–0.60)	<.001
DLBCL	0.36 (0.31–0.41)	<.001	0.35 (0.30–0.41)	<.001	0.35 (0.30–0.41)	<.001
Follicular lymphoma	0.37 (0.31–0.44)	<.001	0.37 (0.31–0.44)	<.001	0.37 (0.31–0.44)	<.001
Disease stage						
Early/Limited	Ref		Ref		Ref	
Advanced	0.83 (0.74–0.93)	.001	0.83 (0.73–0.93)	.002	0.83 (0.74–0.93)	.002
Unknown	0.84 (0.64–1.10)	.20	0.81 (0.61–1.09)	.16	0.81 (0.61–1.08)	.16
Elixhauser comorbidity score						
0	Ref		Ref		Ref	
1–2	1.03 (0.92–1.17)	.59	1.03 (0.92–1.17)	.59	1.03 (0.92–1.17)	.60
>3	1.43 (1.23–1.68)	<.001	1.43 (1.22–1.68)	<.001	1.43 (1.22–1.68)	<.001
Disability						
Not disabled	Ref		Ref		Ref	
Disabled ²⁹	1.39 (1.13–1.72)	.002	1.40 (1.14–1.73)	.002	1.41 (1.14–1.74)	.002
Treatment						
Type of therapy						
Rituximab monotherapy	Ref		Ref		Ref	
Rituximab + chemotherapy	1.55 (1.34–1.80)	<.001	1.54 (1.31–1.81)	<.001	1.54 (1.31–1.81)	<.001
Receipt of radiation						
No	Ref		Ref		Ref	
Yes	1.53 (1.31–1.78)	<.001	1.51 (1.29–1.76)	<.001	1.52 (1.30–1.77)	<.001

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Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; RR, relative risk.
^aModels 1 and 2 were adjusted for patient-level variables: age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

^bGeneralized estimating equation with exchangeable correlation was used to account for clustering of patients within physicians.

^cModel 3 was adjusted for all variables in Models 1 and 2 plus physician-level variables: degree, sex, US medical school, medical school graduation year, and primary specialty.

eTable 1. Adjusted RR for Early Discontinuation of Rituximab by Model (cont.)

Characteristic	Model 1 ^a Patient Level		Model 2 ^{a,b} Clustered by Physician		Model 3 ^{a,c} Clustered + Physician-Level Variables	
	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Treatment (cont.)						
Location of treatment						
NCI-designated outpatient hospital	Ref		Ref		Ref	
Non-NCI-designated outpatient hospital	0.98 (0.78–1.24)	.87	0.98 (0.77–1.24)	.85	0.96 (0.76–1.22)	.73
Community-based	0.64 (0.51–0.80)	<.001	0.64 (0.51–0.80)	<.001	0.62 (0.50–0.79)	<.001
Physician characteristics						
Degree						
MD					Ref	
DO					1.34 (0.99–1.81)	.054
US medical school						
Yes					Ref	
No					1.02 (0.89–1.17)	.74
Sex						
Female					Ref	
Male					0.98 (0.84–1.14)	.77
Medical school graduation year						
<1980					Ref	
1980s					0.85 (0.73–0.98)	.028
1990s					0.90 (0.77–1.06)	.20
2000s					0.91 (0.71–1.15)	.43
Specialty						
Hematology and/or oncology					Ref	
Other					0.90 (0.66–1.23)	.51

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; RR, relative risk. ^aModels 1 and 2 were adjusted for patient-level variables: age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, histology, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.

^bGeneralized estimating equation with exchangeable correlation was used to account for clustering of patients within physicians.

^cModel 3 was adjusted for all variables in Models 1 and 2 plus physician-level variables: degree, sex, US medical school, medical school graduation year, and primary specialty.

eTable 2. Association of Early Rituximab Discontinuation With Survival, Stratified By Histology^a

Histology	% Discontinued	Overall Survival		Lymphoma-Specific Survival	
		HR (95% CI)	P Value	HR (95% CI)	P Value
CLL/SLL	13.6	1.43 (1.23–1.67)	<.001	1.43 (1.11–1.84)	.006
Mantle cell lymphoma	7.9	1.42 (1.01–2.01)	.046	1.53 (0.92–2.54)	.101
Lymphoplasmacytic/MZL	6.6	1.35 (0.99–1.83)	.056	1.85 (1.15–2.96)	.011
DLBCL	6.3	1.35 (1.17–1.56)	<.001	1.22 (0.97–1.53)	.094
Follicular lymphoma	5.2	1.46 (1.13–1.89)	.004	1.43 (0.95–2.15)	.088

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; MZL, marginal zone lymphoma.

^aHistology-specific models estimated the hazard associated with early discontinuation of rituximab vs non-early discontinuation (ref). Cox proportional hazards models adjusted for age group, sex, race, marital status, year of diagnosis, geographic region, median household income, metropolitan status of residence, Medicaid dual coverage, disease stage, Elixhauser comorbidity score, disability status, type of therapy, receipt of radiation, and location of treatment.