

# Increased Risk of Infectious Complications in Older Patients With Indolent Non-Hodgkin Lymphoma Exposed to Bendamustine

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**Background.** Bendamustine is a potent chemotherapy agent increasingly used to treat indolent non-Hodgkin lymphoma (iNHL). While effective, it causes significant T-cell lymphopenia, which may increase risk of infection. We examined infectious complications associated with bendamustine-containing regimens among older patients with iNHL.

**Methods.** For this Surveillance, Epidemiology, and End Results (SEER)–Medicare cohort study, we identified 9395 patients with iNHL (follicular, marginal zone, Waldenström macroglobulinemia) treated with chemotherapy from 2006 to 2013. Thirteen percent received bendamustine-containing regimens. We compared baseline characteristics and infection incidence rates between patients treated with and without bendamustine. We conducted multivariate Cox proportional hazards regression (adjusting for demographics, comorbidities, disease and treatment characteristics, risk factors for infection, and antimicrobial prophylaxis) to determine infectious risks associated with bendamustine.

**Results.** Bendamustine was associated with an increased risk of both common infections such as bacterial pneumonia (hazard ratio [HR], 1.50 [95% confidence interval {CI}, 1.21–4.85]) and opportunistic infections such as cytomegalovirus (HR, 3.98 [95% CI, 1.40–11.26]), varicella zoster virus (HR, 1.49 [95% CI, 1.18–1.89]), histoplasmosis (HR, 3.55 [95% CI, 1.10–11.42]), and *Pneumocystis jirovecii* pneumonia (when administered as third-line therapy: HR, 3.32 [95% CI, 1.00–11.11]). Risk of infections was more prominent in patients receiving bendamustine as part of later (third-line and above) regimens, and independently associated with well-established factors such as neutropenia and corticosteroid exposure.

**Conclusions.** Bendamustine is associated with an increased risk of common and opportunistic infections in patients with iNHL. Further prospective investigation into the potential role of antimicrobial prophylaxis is needed in these patients.

**Keywords.** infectious complications; non-Hodgkin lymphoma; bendamustine; *Pneumocystis jirovecii* pneumonia; cytomegalovirus.

Indolent non-Hodgkin lymphomas (iNHL) such as follicular lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, and chronic lymphocytic leukemia/small lymphocytic lymphoma are slow-growing but incurable B-cell malignancies [1, 2]. They comprise approximately one-third of all non-Hodgkin lymphoma cases, with an anticipated 25 000 new diagnoses and 7000 attributable deaths in the United States in 2018 [3]. Traditionally, these patients are not considered at high risk for infectious complications.

Bendamustine is a nitrogen mustard–based chemotherapy drug with alkylating and antimetabolite activity [4, 5]. In 2008,

bendamustine was approved as front-line treatment for chronic lymphocytic leukemia and as treatment for rituximab-refractory follicular lymphoma [6]. Bendamustine is frequently used outside of its labeled indication as front-line therapy in follicular lymphoma and other low-grade lymphomas because of presumed safety, tolerability, and efficacy [7–10].

Myelosuppression, particularly CD4<sup>+</sup> lymphopenia, is common after bendamustine administration [11–17]. In clinical trials of bendamustine for iNHL, grade 3–4 lymphopenia occurred in up to 74% of patients and appeared to be prolonged [14–18]. In 56 patients with iNHL, for example, the median CD4<sup>+</sup> lymphocyte count decreased from 282 to 93 cells/μL after bendamustine, recovering to baseline 7–9 months after last bendamustine administration [18].

The risk of infection associated with bendamustine has yet to be fully characterized. Small series and case reports have reported the occurrence of *Pneumocystis jirovecii* pneumonia (PCP) and cytomegalovirus (CMV) after bendamustine exposure [19–22]. Some clinical trials suggested that bendamustine plus rituximab (BR) was associated with fewer infections

Received 4 February 2018; editorial decision 15 May 2018; accepted 24 May 2018; published online May 25, 2018.

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Clinical Infectious Diseases® 2019;68(2):247–55

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than cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) [12, 13], but the same risk of infection as fludarabine and rituximab [14]. Another study found that opportunistic infections (OIs) were slightly more common in patients receiving BR (10%) than R-CHOP (7%) or cyclophosphamide, vincristine, and prednisone plus rituximab (R-CVP; 9%) [15]. The recent GALLIUM trial comparing rituximab vs obinutuzumab for follicular lymphoma showed that treatment with bendamustine was associated with higher infection rates, with grade 3–5 infection in 12.8% of patients receiving BR vs 1.6% and 2.3% of those receiving R-CHOP and R-CVP, respectively [23].

Outside of clinical trials, the risk of infection associated with bendamustine-based regimens is not well understood. Here, we examine infectious complications associated with bendamustine exposure among patients with iNHL on a national, population-based level.

## METHODS

### Data Source

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER)–Medicare database links data from SEER cancer registries to Medicare enrollment and claims files. SEER registries collect data including site and extent of disease, first-line therapy, sociodemographic characteristics, and dates of diagnosis and death, and currently covers approximately 28% of the US population [24].

For adults at least 65 years of age enrolled in SEER, record linkage to Medicare claims allows for identification of concomitant health conditions and treatments. Medicare is a federally funded health insurance for US citizens  $\geq 65$  years of age. Part A coverage includes inpatient care, Part B includes physician and outpatient services, and Part D includes prescription drug costs.

This study was approved by the Partners HealthCare Human Research Committee and reviewed by SEER-Medicare staff for compliance with SEER-Medicare data policies.

### Study Cohort

In this cohort study, we included patients at least 65 years of age continuously enrolled in Medicare parts A and B from 2006 to 2013 with iNHL treated with chemotherapy. We used the *International Classification of Diseases–Oncology, Third Edition* and the *International Classification of Diseases, Ninth Revision (ICD-9)* codes to identify patients with follicular lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia (Supplementary Appendix A).

### Exposure

The primary exposure in this study was treatment with bendamustine. Bendamustine is recommended as first-line and salvage therapy for symptomatic, advanced stage, and/or bulky

stage follicular lymphoma and Waldenström macroglobulinemia and conventional chemotherapy for mantle cell lymphoma. When used in combination with rituximab for the treatment of iNHL, bendamustine is considered noninferior to R-CHOP, with a more favorable side effect profile, and is administered as a 90 mg/m<sup>2</sup> dose on days 1–2 of a 28-day treatment cycle for 6–8 cycles [5].

We identified bendamustine exposure and other predefined iNHL chemotherapy regimens (R-CHOP; R-CVP; fludarabine and cyclophosphamide plus rituximab (FCR); fludarabine plus rituximab (FR); rituximab monotherapy) by extracting chemotherapy drugs of interest and their administration frequency using Healthcare Common Procedure Coding System (HCPCS) procedure “J” codes and the National Drug Codes (NDC) (Supplementary Appendix B). We then used an established algorithm to identify number of regimens/lines and cycles [25], whereby a new line of therapy was defined by a switch from one predetermined regimen to another regimen via the addition or discontinuation of  $\geq 1$  drug.

### Outcomes

The primary outcomes were individual and composite bacterial (staphylococcal infection, streptococcal infection, pseudomonal infection, actinomycosis, nocardiosis, tuberculosis, nontuberculous mycobacteria, bacterial pneumonia, bacterial infection not otherwise specified [NOS], sepsis), fungal (PCP, aspergillosis, candidiasis, coccidioidomycosis, histoplasmosis, blastomycosis, cryptococcosis, other mycoses), viral (CMV, varicella zoster virus [VZV], herpes simplex virus [HSV], adenovirus, hepatitis B and C, other viral hepatitis), and parasitic (toxoplasmosis) infections occurring after bendamustine or other chemotherapy regimens. We identified infectious outcomes by ICD-9 codes (Supplementary Appendix C).

### Covariates and Potential Confounders

Covariates for analysis included demographics (age, sex, race), comorbidities (Charlson comorbidity index), disease characteristics (lymphoma subtype, stage), treatment characteristics (lines of chemotherapy, cumulative rituximab exposure), other risk factors for infection (human immunodeficiency virus [HIV], allogeneic or autologous stem cell transplantation, solid organ transplantation, corticosteroid exposure, neutropenia, granulocyte stimulating factor use), and antimicrobial prophylaxis, all of which are factors that might confound the relationship between bendamustine exposure and infectious complications.

Demographics, comorbidity, and disease characteristics were derived directly from SEER-Medicare data (Supplementary Appendix D). The Charlson comorbidity index, a score based on the summation of integer weights assigned to age and a number of conditions, was used to assess comorbidity. This score has been validated in elderly and cancer patients and

adapted for use with SEER-Medicare administrative data (there are validated algorithms to derive this score directly from SEER-Medicare data) [26, 27]. HIV, stem cell transplantation, and solid organ transplantation were identified via Diagnosis Related Group and ICD-9 diagnosis codes (Supplementary Appendix D). Rituximab administration was extracted from HCPCS and NDC codes, and cumulative rituximab exposure was defined as the total number of rituximab doses received by the start of follow-up time.

Potential time-varying factors (corticosteroid exposure, neutropenia, granulocyte stimulating factor use, and antimicrobial prophylaxis) were assessed using either ICD-9 codes (neutropenia) or HCPCS and NDC codes (corticosteroid exposure, antimicrobial prophylaxis; Supplementary Appendix B). Corticosteroid exposure was defined as receipt of prednisone outside of a predefined chemotherapy regimen. Granulocyte stimulating factor exposure was defined by receipt of filgrastim, peg-filgrastim, or sargramostim. Antimicrobial prophylaxis agents were predefined as trimethoprim-sulfamethoxazole, atovaquone, dapsone, or pentamidine for PCP and acyclovir, valacyclovir, valganciclovir, or famciclovir for herpesviruses. Patients were considered to have these time-varying exposures if they were present within 60 days prior to developing incident infectious complications; patients who did not develop infectious complications were considered exposed if they had any of these exposures during the follow-up period.

#### Follow-up Time

Follow-up time was calculated from the first administration of bendamustine for the bendamustine group and first administration of any chemotherapy regimen for the nonbendamustine group. Follow-up was censored at 365 days or earlier, at the first occurrence of an infectious outcome. There was no crossover between patients in each group and no analysis of repeated outcomes.

#### Statistical Analysis

We conducted Pearson  $\chi^2$  and *t* tests to compare baseline characteristics between groups. We calculated the incidence (per 100 person-years) of and median time to infectious outcome for patients treated with and without bendamustine.

We estimated the cumulative incidence of composite infectious outcomes using the Kaplan-Meier method. We calculated Mantel-Haenszel rate ratios (RRs) with 95% confidence intervals (CIs) and *P* values.

Adjusting for differences in baseline characteristics and potential confounders of the relationship between bendamustine exposure and infection, we conducted multivariate Cox proportional hazards regression to examine the relationship between bendamustine exposure and infectious complications. We stratified by line of bendamustine chemotherapy (first-line, second-line, third-line or higher) to assess whether the

association between bendamustine and infectious complications was dependent on previously administered chemotherapy regimens. Because bendamustine was considered less toxic and administered to more vulnerable patients earlier in its use for iNHL, we stratified our analysis by patients who received bendamustine before and after 2009. We tested the proportional hazards assumption by graphing survival function by time. Models for PCP and herpesviruses incorporating antimicrobial prophylaxis were restricted to the subset of patients enrolled in Medicare Part D (data available from 2007 to 2013) with outpatient prescription data.

For important infections, we calculated the number needed to harm for patients treated with and without bendamustine. For preventable infections (bacterial infection, PCP, CMV, VZV, histoplasmosis), we calculated the number needed to treat with antimicrobial prophylaxis to prevent a case of infection. We assumed antibacterial prophylaxis with levofloxacin with a 44% risk reduction [28], PCP prophylaxis with trimethoprim-sulfamethoxazole with an 85% risk reduction [29], CMV prophylaxis with valganciclovir with a 58% risk reduction [30], VZV/HSV prophylaxis with acyclovir with an 84% risk reduction [31], and histoplasmosis prophylaxis with itraconazole with a 61% risk reduction [32].

All statistical analyses were performed using Stata software version 13 for Windows (StataCorp, College Station, Texas).

## RESULTS

We identified 9395 patients with iNHL treated with chemotherapy from 2006 to 2013, of whom 13.2% received bendamustine (Table 1). Patients who received bendamustine had more advanced clinical disease (47.6% vs 39.8% stage IV disease; *P* < .001), were exposed to more chemotherapy regimens (3.1 vs 2.1 lines of chemotherapy; *P* < .001), and developed neutropenia more frequently (20.3% vs 18.2%; *P* = .04).

Patients exposed to bendamustine experienced 2.71 mean infections per person compared with 2.51 in those not exposed (*P* = .008). The most common infectious complications were bacterial infection NOS, sepsis, VZV, candidiasis, and bacterial pneumonia. Patients treated with bendamustine had higher incidences of bacterial pneumonia (10.5 vs 6.2 per 100 person-years [PY]), CMV (1.0 vs 0.3 per 100 PY), VZV (13.8 vs 8.3 per 100 PY), and histoplasmosis (0.4 vs 0.1 per 100 PY) (Table 2). Median time from chemotherapy to bacterial (82 vs 67 days), viral (134 vs 98 days), and opportunistic (106 vs 75 days) infections was longer for patients receiving bendamustine vs other regimens.

Patients treated with bendamustine had higher cumulative incidences of fungal (RR, 1.23; *P* = .017), viral (RR, 1.82; *P* < .0001), and opportunistic (RR, 1.47; *P* < .0001) infections (Figure 1).

**Table 1. Baseline Characteristics of Patients With Indolent Non-Hodgkin Lymphoma Treated With and Without Bendamustine**

Characteristic	Bendamustine (n = 1239)	No Bendamustine (n = 8156)	P Value
Age, y, mean (SD)	74.9 (6.1)	75.0 (6.6)	<.001 <sup>a</sup>
Sex, %			<.001
Male	53.2	46.6	
Female	46.8	53.4	
Race/ethnicity, %			.08
White	87.7	86.1	
African American	2.7	3.0	
Hispanic	5.4	5.6	
Asian	2.8	3.9	
Other	1.5	1.4	
Subtype, %			.24
Follicular lymphoma	74.4	76.6	
Waldenström macroglobulinemia	22.5	20.5	
Marginal zone lymphoma	3.1	2.9	
American Joint Committee on Cancer Stage, %			<.001
I	15.7	25.7	
II	13.1	16.5	
III	23.6	18.1	
IV	47.6	39.8	
Lines of chemotherapy, mean (SD)	3.1 (2.0)	2.1 (1.6)	<.001 <sup>a</sup>
First-line chemotherapy, %			<.001
R-CHOP	23.1	42.6	
Rituximab monotherapy	24.1	31.5	
R-CVP	16.4	18.1	
Rituximab plus bendamustine	31.3	0.0	
FR or FCR	2.5	3.2	
Other	2.7	4.6	
Cumulative rituximab dose, mean (SD)	13.8 (10.6)	9.2 (8.2)	<.001
Infectious risk factor, %			
Stem cell transplantation (allogeneic or autologous)	1.0	0.9	.76
Human immunodeficiency virus	0.5	0.8	.12
Solid organ transplantation	0.3	0.4	.41
Corticosteroid exposure	36.5	40.0	.02
Neutropenia	20.3	18.2	.04
Granulocyte stimulating factor use	24.4	22.2	.05
Charlson comorbidity index score, %			.24
0	59.5	59.0	
1	24.3	24.5	
2	8.7	7.6	
≥3	7.5	8.9	

Unless otherwise specified, P values are determined by Pearson  $\chi^2$  test.

Abbreviations: FCR, fludarabine and cyclophosphamide plus rituximab; FR, fludarabine plus rituximab; R-CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab; R-CVP, cyclophosphamide, vincristine, and prednisone plus rituximab; SD, standard deviation.

<sup>a</sup>P value determined by t test.

Adjusting for age, sex, lymphoma subtype and stage, cumulative rituximab exposure, number of chemotherapy lines, corticosteroid exposure, neutropenia, granulocyte stimulating factor use, and antimicrobial prophylaxis, bendamustine exposure was associated with increased hazards of viral infections (hazard ratio [HR], 1.39 [95% CI, 1.17–1.64]) and opportunistic infections (HR, 1.16 [95% CI, 1.02–1.33]), specifically CMV (HR, 3.98 [95% CI, 1.40–11.26]), VZV (HR, 1.49 [95% CI, 1.18–1.89]), and histoplasmosis (HR, 3.55 [95% CI, 1.10–11.42])

(Figure 2 and Table 3). Among common infections, bendamustine was associated with an increased hazard of bacterial pneumonia (HR, 1.50 [95% CI, 1.21–4.85]) and bacterial infection NOS (HR, 1.17 [95% CI, 1.02–1.35]).

In multivariate models stratified by line of bendamustine, there was an increased hazard of PCP in patients receiving bendamustine as third-line therapy (HR, 3.32 [95% CI, 1.00–1.11]). Point estimates for bacterial infections overall (third-line HR, 1.32 [95% CI, 1.10–1.61]), bacterial pneumonia (third-line HR,

**Table 2. Incidence Rates of Infectious Complications Among Indolent Non-Hodgkin Lymphoma Patients Treated With and Without Bendamustine With Incidence Rate Ratio Comparing the 2 Groups**

Infection	Incidence Rate (per 100 PY)		IRR
	Bendamustine	No Bendamustine	
<b>Bacterial infection</b>	53.7	42.4	1.27
<b>Fungal infection</b>	22.8	17.8	1.28
<b>Viral infection</b>	28.4	15.4	1.84
<b>Opportunistic infection<sup>a</sup></b>	43.0	28.5	1.51
Staphylococcal infection	3.6	3.9	0.92
Streptococcal infection	3.6	3.9	0.92
Pseudomonal infection	2.4	2.0	1.19
Actinomycosis	0.1	0.1	0.66
Tuberculosis	0.3	0.7	0.37
Nontuberculous mycobacteria	0.9	0.5	1.68
Bacterial pneumonia	10.5	6.2	1.70
Sepsis	18.4	17.6	1.05
Bacterial infection NOS	27.1	20.2	1.34
Hepatitis B reactivation	1.1	0.9	1.14
Hepatitis C	1.0	0.7	1.31
Other viral hepatitis	0.4	0.3	1.05
Cytomegalovirus	1.0	0.3	3.62
Varicella zoster virus	13.8	8.3	1.67
Herpes simplex virus	0.0	<0.1	...
Adenovirus	0.4	0.1	2.63
Nocardiosis	0.1	0.1	1.64
<i>Pneumocystis</i> pneumonia	0.7	0.4	1.95
Aspergillosis	0.3	0.3	1.31
Candidiasis	12.5	11.5	1.09
Blastomycosis	0.1	0.0	...
Coccidioidomycosis	0.1	0.1	0.94
Histoplasmosis	0.4	0.1	3.28
Cryptococcosis	0.2	0.1	2.19
Other mycoses NOS	1.8	1.1	1.64
Toxoplasmosis	0.2	<0.1	6.56

Boldface terms indicate composite outcomes.

Abbreviations: IRR, incidence rate ratio; NOS, not otherwise specified; PY, person-years; ..., unable to perform statistical comparison due to zero values.

<sup>a</sup>Opportunistic infection defined as composite outcome of pneumocystis pneumonia, varicella zoster virus, cytomegalovirus, herpes simplex virus, adenovirus, toxoplasmosis, nocardiosis, candidiasis, coccidioidomycosis, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, other mycoses, and opportunistic mycoses.

1.56 [95% CI, 1.09–2.23]), and VZV (second-line HR, 1.84 [95% CI, 1.29–2.64]; third-line HR, 1.52 [95% CI, 1.10–2.10]) (Table 3) were higher in patients who received bendamustine with later lines of chemotherapy.

Among patients receiving bendamustine as second-line or later therapy, adjusting for type of first-line chemotherapy did not change the overall strength, direction, or significance of the association between bendamustine exposure and infectious risks. Patients with iNHL who received bendamustine before 2009 (when bendamustine was perceived to be more tolerable in terms of side effects than R-CHOP) had statistically similar hazards of CMV (pre-2009: HR, 1.35 [95% CI, 1.06–1.73]; post-2009: HR, 1.25 [95% CI, 1.01–1.57]), VZV (pre-2009: HR, 1.32 [95% CI, 1.04–1.70]; post-2009: HR, 1.21 [95% CI, .96–1.53]),

and bacterial pneumonia (pre-2009: HR, 1.68 [95% CI, 1.24–2.28]; post-2009: HR, 1.38 [95% CI, 1.05–1.82]), compared with patients who received bendamustine-containing regimens after 2009. The increased risk of histoplasmosis was only observed in patients who received bendamustine prior to 2009 (HR, 7.32 [95% CI, 1.94–27.58] vs post-2009: HR, 1.10 [95% CI, .13–9.08]).

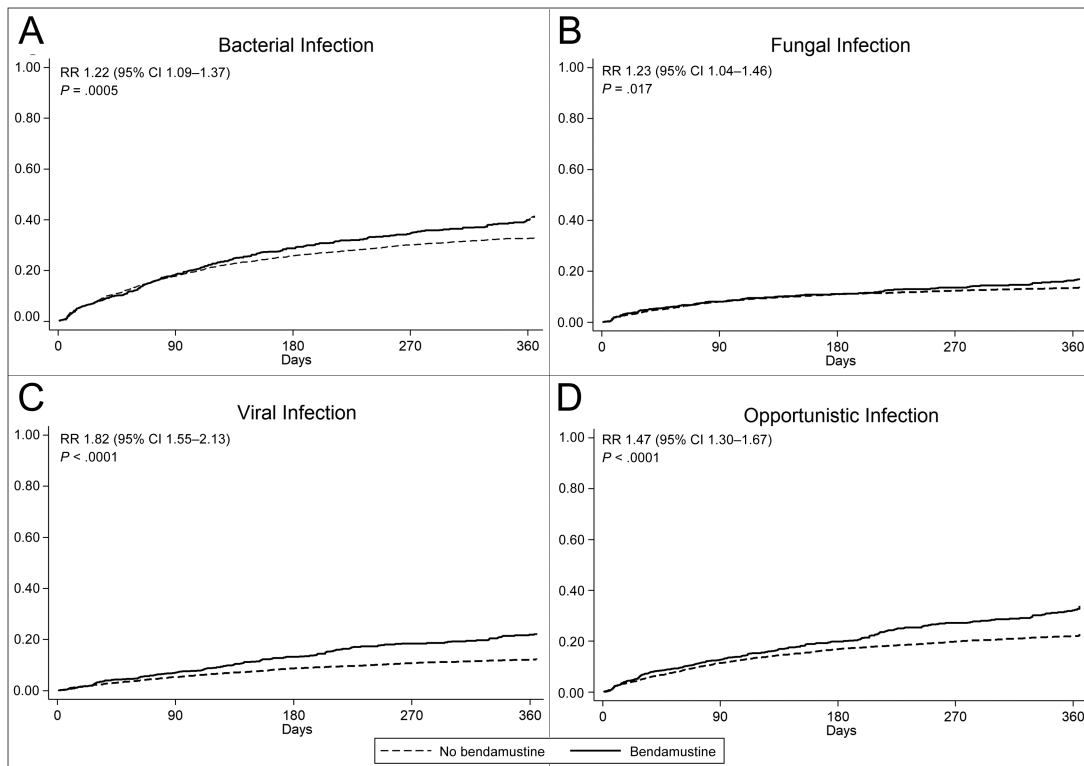
In multivariate Cox models, increasing lines of chemotherapy were independently associated with increased hazards of all OIs (HR, 1.09 [95% CI, 1.07–1.11]) and bacterial infections (HR, 1.09 [95% CI, 1.08–1.11]). Notably, cumulative rituximab exposure was only associated with an increased hazard of VZV (HR, 1.07 [95% CI, 1.01–1.04]). Corticosteroid exposure was associated with increased risk of tuberculosis (HR, 1.84 [95% CI, 1.18–2.89]) and histoplasmosis (HR, 2.91 [95% CI, 1.02–8.26]). Neutropenia was associated with a range of infectious complications including staphylococcal infection (HR, 1.80 [95% CI, 1.31–2.46]), pseudomonal infection (HR, 2.68 [95% CI, 1.74–4.13]), candidiasis (HR, 1.50 [95% CI, 1.25–1.79]), nocardiosis (HR, 10.75 [95% CI, 1.16–99.51]), and nontuberculous mycobacterial infection (HR, 1.94 [95% CI, 1.68–2.25]).

Among patients with iNHL treated with bendamustine vs other chemotherapy regimens, the number needed to harm was 17 for all OIs, 318 for PCP, 156 for CMV, 19 for VZV, and 355 for histoplasmosis (Table 3). The number needed to treat with antimicrobial prophylaxis to prevent a case of infection in patients receiving bendamustine was 70 for all bacterial infections, 374 for PCP, 269 for CMV, and 23 for VZV (Table 3).

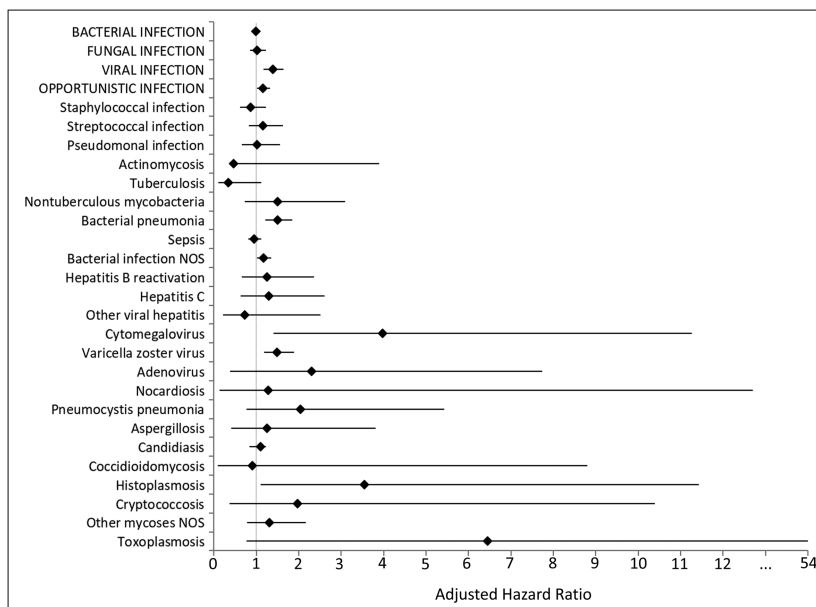
## DISCUSSION

In this study, we demonstrate that older patients with iNHL treated with bendamustine experience higher rates of both common and opportunistic infections compared to patients receiving other chemotherapies. Among OIs, there is particularly increased risk of infections controlled by cell-mediated immunity such as PCP, herpesvirus reactivation, and histoplasmosis, which is likely secondary to CD4<sup>+</sup> lymphopenia induced by this agent [16–22, 33, 34].

To our knowledge, this is the first systematic investigation of bendamustine-associated infectious risks on a population level. The GALLIUM trial reported higher rates of grade 3–5 infection among patients receiving bendamustine compared with CHOP and CVP combined with rituximab and obinutuzumab, but did not delineate specific infectious complications [23]. A meta-analysis assessing grade 3–4 infections in iNHL patients enrolled in clinical trials did not find a significant increase in infections with bendamustine-containing regimens [35]. Clinical trials are designed to assess for oncologic outcomes rather than infectious risks, with inclusion and exclusion criteria that likely select for healthier study participants than those receiving bendamustine in a real-life clinical setting.



**Figure 1.** Cumulative incidence of composite bacterial infections (A), fungal infections (B), viral infections (C), and opportunistic infections (D) among patients with indolent non-Hodgkin lymphoma treated with vs without bendamustine. Mantel-Haenszel rate ratio (RR) with 95% confidence interval (95% CI) and *P* values are presented. “Opportunistic infection” is composite outcome of pneumocystis pneumonia, varicella zoster virus, cytomegalovirus, herpes simplex virus, adenovirus, toxoplasmosis, nocardiosis, candidiasis, coccidioidomycosis, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, other mycoses, and opportunistic mycoses.



**Figure 2.** Adjusted hazard ratio (black diamond) with 95% confidence intervals (black bars) of individual and composite infectious complications among indolent non-Hodgkin lymphoma patients treated with vs without bendamustine. Hazard ratios calculated using multivariable Cox proportional hazard models adjusted for age, sex, lymphoma subtype and stage, lines of chemotherapy, cumulative rituximab exposure, corticosteroid exposure, neutropenia, granulocyte stimulating factor use, and antimicrobial prophylaxis when appropriate. “Opportunistic infection” is composite outcome of pneumocystis pneumonia, varicella zoster virus, cytomegalovirus, adenovirus, toxoplasmosis, nocardiosis, candidiasis, coccidioidomycosis, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, and opportunistic mycoses. Abbreviation: NOS, not otherwise specified.

**Table 3. Adjusted Hazard Ratios of Key Infectious Complications Stratified by Line of Bendamustine, With Number Needed to Harm Attributed to Bendamustine and Number Needed to Treat With Antimicrobial Prophylaxis to Prevent a Case of Infection**

Infectious Complication	Line of Bendamustine									
	Overall, HR (95% CI)	P Value	First-line, HR (95% CI)	P Value	Second-line, HR (95% CI)	P Value	Third-line, HR (95% CI)	P Value	NNH	NNT
Opportunistic infections	1.16 (1.02–1.33)	<b>.03</b>	1.09 (.86–1.38)	.45	1.18 (.94–1.47)	.15	1.20 (.99–1.47)	.06	17	NA
PCP	3.26 (1.20–8.84)	.15	...	...	2.03 (.46–8.95)	.35	3.32 (1.00–11.11)	<b>.05</b>	318	252 <sup>a</sup>
CMV	3.98 (1.40–11.26)	<b>.01</b>	4.89 (.99–24.32)	<b>.05</b>	...	...	6.43 (1.90–21.75)	<b>&lt;.01</b>	156	269 <sup>b</sup>
VZV	1.49 (1.18–1.89)	<b>&lt;.01</b>	1.02 (.61–1.73)	.93	1.84 (1.29–2.64)	<b>&lt;.01</b>	1.52 (1.10–2.10)	<b>.01</b>	19	23 <sup>c</sup>
Bacterial	0.99 (.88–1.11)	.80	0.80 (.63–1.00)	.05	0.96 (.78–1.17)	.67	1.15 (.98–1.37)	.09	31	70 <sup>d</sup>
pneumonia	1.50 (1.21–4.85)	<b>&lt;.01</b>	1.05 (.67–1.65)	.84	1.56 (1.09–2.23)	<b>.01</b>	1.75 (1.30–2.34)	<b>&lt;.01</b>	27	NA
Bacterial infection NOS	1.17 (1.02–1.35)	<b>.02</b>	0.98 (.75–1.28)	.86	1.15 (.91–1.46)	.24	1.32 (1.10–1.61)	<b>&lt;.01</b>	20	NA
NTM	1.50 (.73–3.09)	.27	2.76 (.97–7.89)	.06	2.70 (1.06–6.89)	<b>.03</b>	0.24 (.03–1.95)	.18	304	NA
Fungal	1.03 (.86–1.23)	.79	1.04 (.77–1.42)	.79	0.89 (.65–1.23)	.49	1.12 (.86–1.46)	.41	67	NA
Histoplasmosis	3.55 (1.10–11.42)	<b>.03</b>	2.88 (.35–23.53)	.32	4.31 (.90–20.53)	.07	3.35 (.57–19.59)	.18	355	562 <sup>e</sup>
Viral	1.39 (1.17–1.64)	<b>&lt;.01</b>	1.11 (.81–1.53)	.51	1.52 (1.16–1.99)	<b>&lt;.01</b>	1.50 (1.18–1.90)	<b>&lt;.01</b>	17	NA

Hazard ratios were calculated using multivariable Cox proportional hazard models adjusted for age, sex, lymphoma subtype and stage, lines of chemotherapy, cumulative rituximab exposure, corticosteroid exposure, neutropenia, granulocyte stimulating factor use, and antimicrobial prophylaxis when appropriate. Boldface text indicate statistical significance at a P-value of .05.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; HR, hazard ratio; NA, not applicable; NNH, number needed to harm attributed to bendamustine; NNT, number needed to treat with prophylaxis to prevent a case of infectious complication; NTM, nontuberculous mycobacteria; PCP, *Pneumocystis jirovecii* pneumonia; VZV, varicella zoster virus; ... , no events in subgroup.

<sup>a</sup>PCP prophylaxis with trimethoprim-sulfamethoxazole with an 85% risk reduction [29]; NNT is calculated for patients receiving bendamustine as third-line therapy or above.

<sup>b</sup>CMV prophylaxis with valganciclovir with a 58% risk reduction [30].

<sup>c</sup>VZV/herpes simplex virus prophylaxis with acyclovir with an 84% risk reduction [31].

<sup>d</sup>Antibacterial prophylaxis with levofloxacin with a 44% risk reduction [28].

<sup>e</sup>Histoplasmosis prophylaxis with itraconazole with a 61% risk reduction [32].

Here, we characterize a range of bacterial, viral, fungal, and parasitic infections and assess the risk for developing them among patients with iNHL treated with bendamustine. Patients receiving bendamustine have significant higher risk of both common infections such as bacterial pneumonia and OIs such as PCP, CMV, VZV, and histoplasmosis than patients receiving other chemotherapy regimens.

Within this population, the risk of potentially preventable infections such as bacterial pneumonia, PCP, and CMV appears to be highest among patients receiving bendamustine as part of later (third-line or above) chemotherapy regimens, suggesting that underlying immune dysfunction conferred by more advanced disease and prior immunomodulating chemotherapies may be compounded by the immunosuppressive effects of bendamustine. Additionally, patients who received bendamustine before 2009 for iNHL due to its perceived better tolerability had statistically similar risks of CMV, VZV, and bacterial pneumonia, suggesting that underlying patient vulnerability does not fully explain the infectious risks associated with bendamustine.

These findings are of particular clinical importance as patients with iNHL are traditionally considered to be at low risk of OIs. Our analyses suggest that an OI occurs in 1 of every 17 patients treated with bendamustine, who otherwise would not have developed this OI had they received another chemotherapy regimen. Some patients receiving bendamustine-containing chemotherapy regimens may benefit from antimicrobial prophylaxis against certain preventable OIs associated with substantial morbidity and mortality. We estimate that 1 bacterial infection per 70 patients, 1 PCP case per 374 patients, 1 CMV case per 269 patients, 1 VZV case per 23 patients, and 1 histoplasmosis case per 582 patients with iNHL treated with bendamustine-containing chemotherapy could be prevented with prophylaxis.

This study is limited by the structure of SEER-Medicare administrative and claims data. Although there is potential for undercoding and misclassification of treatment and infectious outcomes, these are unlikely to be differential in nature in the 2 groups, biasing results toward patients treated with bendamustine. Medicare claims have high sensitivity and specificity for identifying chemotherapy administration across all cancer sites [36]. Prior studies have successfully used SEER-Medicare data to characterize common infectious risks among older patients with lymphoid and myeloid malignancies [37, 38]. ICD-9 codes for OIs such as aspergillosis have low positive predictive value but are sufficiently sensitive to identify most cases of invasive aspergillosis [39]. While we recognize limitations of administrative databases for studying the characteristics and severity of infectious complications in detail (eg, whether fungal infections met European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria for proven or probable invasive fungal disease or whether VZV infections had the characteristic

rash), we are confident that our analysis captures treatment and significant infectious complications within the limits of the existing data.

As SEER-Medicare only includes patients who are at least 65 years of age, is it unknown whether these findings are generalizable to younger patients with iNHL, or if bendamustine-induced T-lymphocyte depletion on a background of immunosenescence particularly increases the risk of OIs. However, the median age of patients with iNHL falls within the age range of this Medicare cohort, so our findings are directly applicable to many patients with iNHL. Additionally, the use of population-based data means that these findings are more representative than using hospital databases or specialized registers.

Another possible limitation is the potential for residual confounding. Performance status, bone marrow involvement, and laboratory markers were not available in the SEER-Medicare database and we therefore could not adjust for these factors [40]. We did, however, correct for known prognostic indicators of iNHL including age, stage, comorbidity, and response to therapy. We also conduct stratified analyses by line of bendamustine administration, type of prior chemotherapy regimens, and time period of bendamustine administration, which we believe account for potential confounding to the extent possible using administrative data. Indeed, one of the main strengths of our study is the large, population-based sample of patients with iNHL available from the SEER cancer registries, composing a uniquely large, demographically diverse, multi-center cohort to study.

Further prospective studies of the immune consequences of bendamustine exposure are needed. Meanwhile, clinicians should be aware of the potentially increased risk of both common and opportunistic infections in patients receiving bendamustine-containing chemotherapy regimens, particularly with later lines of chemotherapy, to facilitate timely diagnosis and treatment, and to consider the potential benefit of prophylaxis against OIs.

#### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

#### Notes

**Financial support.** This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grant numbers K23 AI097225, R21 AI119692, R21 AI130669, and R21 AI133330 to S. K.).

**Potential conflicts of interest.** A. F. is on the drug and safety monitoring board for Axio, Bayer, and Immune Design. D. F. has consulted for Viracor and received research funding from Astellas. E. J. has consulted for Merck, Seattle Genetics, Spectrum, Pharmacyclics, Bayer, and AstraZeneca and received research funding from Celgene. P. L. N. has consulted for Genome DX, Ferring, Astellas, Bayer, Dendreon, Augmenix, Blue Earth, and Nanobiotix and received research funding from Astellas and Janssen.



S. K. has consulted for Infinity Pharmaceuticals and GI Windows, received research funding from Wako Diagnostics and Merck, and holds patents on methods for analysis of breath for diagnosis of infectious diseases. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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