Healthcare Resource Utilization and Total Direct Costs of Care Among Patients With Waldenström Macroglobulinemia (WM) Initiating Ibrutinib in First-Line vs Later Lines

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BACKGROUND

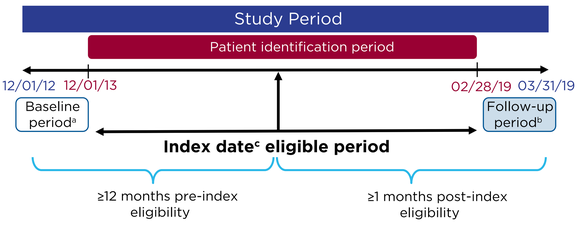
- Waldenström macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma, is a rare type of non-Hodgkin lymphoma characterized by an overproduction of monoclonal immunoglobulin M (IgM) protein.[1] It is a slow-progressing and currently incurable lymphoma with an estimated age-adjusted incidence of 0.38 to 0.55 per 100,000 people and up to 2.85 per 100,000 in people ≥80 years of age.[2-4]
- Ibrutinib is the only once-daily inhibitor of Bruton's tyrosine kinase (BTK) approved in the US as single-agent therapy and in combination with rituximab for patients with WM.[5]
- Ibrutinib provided a superior progression-free survival (PFS) in combination with rituximab in a phase 3 randomized trial vs rituximab alone, an established therapy in WM.[6]
  - Real-world data on ibrutinib in WM are generally consistent with clinical trial results.[7]
  - Sustained single-agent efficacy and safety of ibrutinib in WM were shown in a long-term study follow-up of nearly 4 years.[8]
- Real-world evidence is lacking that quantifies the benefits in terms of healthcare resource utilization (HRU) and total direct costs of care (TDCs; pharmacy+medical) of initiating ibrutinib first-line vs later in patients' treatment journey.

OBJECTIVE

- The objective of this study was to compare HRU and TDCs in adults initiating ibrutinib as first-line (1L) vs later line (2L+) treatment for WM.

METHODS

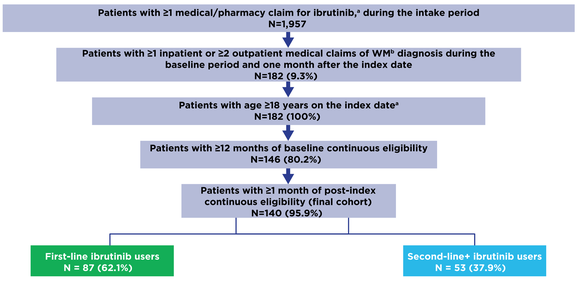
Figure 1. Study Design



[a]*12 months prior to the index date.*
[b]*Period between the index date and the earliest of treatment change, end of continuous enrollment, or study end date. Outcomes are evaluated in the follow-up period.*
[c]*The first claim for ibrutinib between 12/1/2013 and 2/28/2019.*

- Study Design and Data Source
  - This study used a retrospective, observational, medical and pharmacy claims-based, cohort study design using the HealthCore Integrated Research Database (HIRD®) during the period 12/1/2012 to 3/31/2019 (study period) (**Figure 1**).
  - The HIRD contains integrated, longitudinal claims data on more than 65 million people across 14 geographically diverse health plans across the US.
- Study Population
  - This study identified patients with ≥1 claim(s) for ibrutinib in the HIRD during the study period; additional inclusion criteria and patient attrition data are shown in **Figure 2**.

Figure 2. Patient Attrition



[a]*The earliest claim for ibrutinib as identified from GPI code (21534033000x) during the intake period is defined as the index date.*
[b]*WM was identified using ICD-9 code 273.3x and ICD-10 code C88.0x.*
GPI, generic product identifier.

- **Cohort Definitions**
  - **1L therapy:** Patients without WM-related medication use (bendamustine, bortezomib, carfilzomib, cladribine, cyclophosphamide, doxorubicin, everolimus, fludarabine, ibrutinib, ofatumumab, rituximab, vincristine, allogeneic or autologous stem cell transplant) during the baseline period, excluding 30 days before the index date, were identified as 1L patients.
  - **2L+ therapy:** Patients with ≥1 medical/ pharmacy claim for ≥1 WM-related regimen during the baseline period, excluding 30 days before the index date, were identified as 2L+ patients.
- **Study Outcomes Definition**
  - All-cause and WM-related HRU that includes inpatient hospitalizations, inpatient length of stay (LOS), emergency department (ED) visits, physician office visits, and prescription fills were evaluated during the follow-up period. The results were presented on a per-patient-per-month (PPPM) basis.
  - WM-related HRU: any medical claims associated with WM diagnosis regardless of diagnosis position; and any pharmacy claims for WM medications including ibrutinib and other WM-recommended medications.
  - All-cause and WM-related TDCs were assessed during the follow-up period and presented on a PPPM basis. WM-related healthcare resource costs were defined as costs associated with any medical claims with WM diagnosis regardless of diagnosis position; and any pharmacy claims for WM medications.
- **Analyses**
  - Descriptive statistics including mean, standard deviation (SD), and median for continuous variables, and relative frequencies and percentages for categorical variables were computed.
  - Inverse-probability-of-treatment-weighing (IPTW) was used to account for differences in baseline characteristics including age, gender, region, educational status, insurance type, index year, fatigue, neuropathy, bulky lymphadenopathy, QCI groups, residence area, health plan type, cytopenia, organomegaly, and other WM conditions.
  - IPTW-adjusted all-cause and WM-related HRU and TDCs (pharmacy+medical) were compared between 1L and 2L+ groups using a generalized linear model with poisson and gamma distribution, respectively, and log link, offset by the log of follow-up time.
  - Mean differences between both cohorts were reported on a PPPM basis.
  - Mean monthly cost difference (MMCD) was calculated as mean ibrutinib costs in 2L+ minus mean ibrutinib costs in 1L.

RESULTS

Table 1. Patient Demographics and Comorbidities Before and After IPTW

Demographic characteristics	Total	Before IPTW 1L	Before IPTW 2L+	Before IPTW Std. diff	After IPTW 1L	After IPTW 2L+	After IPTW Std. diff
Number of patients, n	140	87	53	-	138	141	-
Age (years)							
Mean (SD)	71.2 (11.2)	71.1 (11.3)	71.4 (11.2)	-0.027	70.9 (14.5)	70.1 (17.8)	0.048
Sex, n (%)							
Female	47 (33.6)	28 (32.2)	19 (35.8)	0.077	42 (30.4)	42 (29.8)	-0.011
Male	93 (66.4)	59 (67.8)	34 (64.2)		96 (69.6)	99 (70.2)	
Income[a]							
Mean (SD)	$101,912 ($54,834)	$100,539 ($53,442)	$104,131 ($57,472)	-0.065	$102,839 ($69,766)	$105,597 ($94,922)	-0.033
Education level[a], n (%)							
More than high school	125 (89.3)	76 (87.4)	49 (92.5)	**-0.169**	124 (90.0)	127 (90.0)	0.001
Less than high school	15 (10.7)	11 (12.6)	* (*)		14 (10.0)	14 (10.0)	
Residence region, n (%)							
Midwest	34 (24.3)	23 (26.4)	11 (20.8)	**0.439**	31 (22.3)	25 (17.8)	**0.105**
Northeast	25 (17.9)	* (*)	15 (28.3)		22 (16.1)	25 (17.8)	
South	30 (21.4)	20 (23)	* (*)		30 (22.0)	33 (23.5)	
West	51 (36.4)	34 (39.1)	17 (32.1)		55 (39.6)	58 (40.8)	
Insurance type, n (%)							
Commercial	65 (46.4)	44 (50.6)	21 (39.6)	**0.222**	69 (49.8)	75 (53.1)	0.060
Medicare Advantage	32 (22.9)	18 (20.7)	14 (26.4)		27 (20.0)	27 (19.4)	
Medicare Supplemental/Part D	43 (30.7)	25 (28.7)	18 (34)		42 (30.2)	39 (27.5)	
Plan type, n (%)							
CDHP	* (*)	* (*)	* (*)	**0.257**	* (*)	* (*)	0.053
HMO	35 (25)	20 (23)	15 (28.3)		32 (22.9)	34 (23.8)	
PPO	98 (70)	61 (70.1)	37 (69.8)		99 (71.7)	99 (70.4)	
Year of index date, n (%)							
2016 or before	57 (40.7)	37 (42.5)	20 (37.7)	-0.098	61 (44.5)	57 (40.6)	-0.079
2017 and after	83 (59.3)	50 (57.5)	33 (62.3)		77 (55.5)	84 (59.4)	
Quan-Charlson Comorbidity Index, n (%)							
0-1	* (*)	* (*)	* (*)	**0.247**	* (*)	* (*)	0.021
2	52 (37.1)	36 (41.4)	16 (30.2)		51 (36.8)	53 (38.0)	
≥3	82 (58.6)	47 (54.0)	35 (66.0)		82 (59.0)	82 (58.3)	
WM-related symptoms and conditions, n (%)							
Cytopenias associated with WM	81 (57.9)	48 (55.2)	33 (62.3)	**-0.144**	80 (57.9)	78 (55.4)	0.051
Fatigue	58 (41.4)	29 (33.3)	29 (54.7)	**-0.441**	55 (39.6)	56 (39.9)	-0.004
Neuropathy	32 (22.9)	14 (16.1)	18 (34.0)	**-0.422**	35 (25.0)	36 (25.6)	-0.013
Bulky lymphadenopathy	29 (20.7)	13 (14.9)	16 (30.2)	**-0.371**	28 (20.6)	27 (19.1)	0.039
Organomegaly	27 (19.3)	13 (14.9)	14 (26.4)	**-0.286**	27 (19.5)	24 (16.9)	0.067
Other WM symptoms[b]	40 (28.6)	18 (20.7)	22 (41.5)	**-0.286**	40 (29.2)	45 (31.7)	-0.054

**In instances where the reported data variables represent small groups, eg, less than or equal to 10, the results are reported as "* (*)."*
[a]*Information extracted from American Community Survey database.*
[b]*Other WM symptoms include weight loss, recurrent fever, night sweats, hyperviscosity, amyloidosis, cold agglutinin disease, and cryoglobulinemia.*
Accounted covariates in IPTW - age, gender, region, educational status, insurance type, index year, fatigue, neuropathy, bulky lymphadenopathy, QCI groups, residence area, health plan type, cytopenia, organomegaly, other WM conditions.
1L, first line; 2L+, second line or later; IPTW, inverse-probability-of-treatment-weighing; std. diff., standard difference.
Bolded values *indicate significance (SD >0.10 or <-0.10).*

- Before IPTW, there were significant differences in education level, geographic region, insurance type, plan type, comorbidity burden, and prevalence of WM-related symptoms between 1L and 2L+ patients. After IPTW, the groups were well balanced (**Table 1**).

Table 2. Adjusted All-Cause and WM-Specific HRU

	Adjusted mean difference	Confidence interval	Adjusted *P*-values[a]
All-cause			
Inpatient admission	0.06	(-0.01, 0.21)	0.125
Emergency room visits	0.05	(0, 0.22)	0.078
Physician office visits	0.2	(-0.2, 0.5)	0.328
Other outpatient visits[b]	1.1	(0.6, 1.7)	**<0.001**
Prescription use	0.1	(-0.2, 0.6)	0.500
WM-specific utilization			
Inpatient admission	0.055	(-0.01, 0.21)	0.115
Emergency room visits	0.05	(0, 0.34)	0.056
Physician office visits	-0.08	(-0.27, 0.17)	0.518
Other outpatient visits[b]	0.3	(0, 0.7)	0.074
Prescription use	0	(-0.2, 0.2)	0.909

[a]*P-values were derived from poisson model.*
[b]*Other outpatient visits include outpatient procedures, lab tests, imaging, other tests, PT/OT speech therapy, and other physician services including behavioral therapy.*
HRU, healthcare resource utilization; OT, occupational therapy; PT, physical therapy.
Bolded values *indicate significance (P<0.05).*

- Adjusted all-cause HRU findings indicated that 1L patients used significantly fewer outpatient services compared to 2L+ patients (1.1; *P*<0.001) (**Table 2**).

Table 3. Adjusted All-Cause and WM-Specific Costs

	Adjusted mean monthly cost difference ($)[a]	Confidence interval	Adjusted *P*-values[b]
All-cause			
Total costs	2307	(78, 4946)	**0.042**
Total medical costs	1928	(463, 4094)	**0.005**
Inpatient	975	(2, 3089)	**0.049**
ER	96	(35, 208)	**<0.001**
Physician office	52	(6, 111)	**0.026**
Other outpatient services[c]	804	(13, 1991)	**0.045**
Prescription costs	379	(-1254, 2337)	0.671
WM-specific			
Total costs	1767	(-351, 4333)	0.108
Total medical costs	1545	(348, 3535)	**0.005**
Inpatient	1047	(93, 3172)	**0.023**
ER	72	(32, 147)	**<0.001**
Physician office	13	(-16, 54)	0.412
Other outpatient services[c]	412	(-41, 1190)	0.083
Prescription costs	222	(-1516, 2371)	0.819

[a]*Difference is from 2L+ patients to 1L patients.*
[b]*P-values were derived from generalized linear model with gamma distribution and log link.*
[c]*Other outpatient services include outpatient procedures, lab tests, imaging, other tests, PT/OT speech therapy, and other physician services including behavioral therapy.*
Bolded values *indicate significance (P<0.05).*

- Patients who were treated with ibrutinib in 1L incurred significantly lower TDCs compared to patients treated with ibrutinib in 2L+, with a monthly mean cost difference (MMCD) of -$2,307; *P*=0.042 after IPTW adjustments (**Table 3**).
- Total medical costs were almost half among 1L compared to 2L+ patients, with a MMCD of -$1,928; *P*=0.005 (**Table 3**).
- 1L ibrutinib patients had significantly lower costs compared to 2L+ patients for inpatient admissions (MMCD=-$975; *P*=0.049), ER visits (MMCD=-$96; *P*<0.001), physician office visits (MMCD=-$52; *P*=0.026), and other outpatient visits (MMCD=-$804; *P*=0.045) (**Table 3**).
- Ibrutinib 1L patients incurred more than two-fold lower WM-related medical costs compared to 2L+ patients with MMCD of -$1,545; *P*=0.005) (**Table 3**).
- 1L patients had significantly lower WM-related costs compared to 2L+ patients for inpatient admissions (MMCD=-$1,047; *P*=0.023) and ER (MMCD=-$72; *P*<0.001) (**Table 3**).

LIMITATIONS

- Limitations include those common to administrative claims database analyses, including potential coding errors and incomplete data, which may result in misclassification of patients.
- Due to the rare nature of WM and ibrutinib as a relatively new treatment option, the study is limited to a small sample size.

CONCLUSIONS

- In WM patients, 1L ibrutinib use significantly reduced HRU due to fewer outpatient visits and was associated with significantly lower TDC compared to patients who used ibrutinib in later lines. These data support the value of reduced health-system burden and economic benefits of using ibrutinib early in a patient's treatment journey.

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DISCLOSURES AND ACKNOWLEDGEMENTS

RI: employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; patents, royalties, or other intellectual property with Express Scripts; **MS:** employment with and stock ownership in Anthem; research funding from Pharmacyclics LLC, an AbbVie Company; **NG & SW:** employment with Anthem; research funding from Pharmacyclics LLC, an AbbVie Company; **CS:** past employment with AbbVie and Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; **TM:** past employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie; current affiliation with Boston University, Boston, MA, USA; **IA:** employment with Pharmacyclics LLC, an AbbVie Company; stock ownership in AbbVie and Bristol-Myers Squibb.

This study was funded by Pharmacyclics LLC, an AbbVie Company. Editorial support was provided by Meghan Sullivan, PhD, and was funded by Pharmacyclics LLC, an AbbVie Company.