Poster
PCN168

GLOBAL BURDEN OF WALDENSTRÖM MACROGLOBULINEMIA: A SYSTEMATIC LITERATURE REVIEW AND EVIDENCE GAP ANALYSIS

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Background

- Waldenström macroglobulinemia (WM) is a chronic lymphoproliferative disorder characterized by a monoclonal expansion of predominantly small B lymphocytes in the bone marrow.[1,2]
- WM is rare, constituting only 1-2% of all hematologic malignancies, with little consensus for standard of care.[1-3]
- Although WM is an indolent malignancy, it can cause considerable morbidity and detrimental effects on quality of life, especially in the elderly population most commonly affected, and few patients achieve complete remission.[3,4]
- Current treatment options for WM are improving patient outcomes; however, WM remains an incurable disease. Notably, a number of promising treatment options are currently being evaluated, and while understanding of the disease is rapidly evolving, many questions about the disease remain.[1,3-5]

Objective

- The objective of this SLR was to review the global epidemiology and clinical (eg, survival, prognosis, complications), economic (eg, cost-effectiveness, cost of illness), and humanistic (eg, quality of life) burden of WM and evaluate current evidence data gaps.

Methods

- A systematic literature review (SLR) was performed with a predefined methodology and inclusion criteria (Table 1).
- Results were evaluated by geography: United States (US), European countries (EU), China, and rest of the world (ROW).

Table 1. Methodology

Literature source and search strategy	• Online version of Index Medicus produced by the US National Library of Medicine (ie, PubMed) • Pertinent search terms (and all relevant variations) using a combination of MeSH terms and terms in the title and abstract • Bibliographies and review articles were reviewed to identify additional publications
Search time frame	• Jan 2013 to Sept 2018
Inclusion criteria	• Study designs: peer-reviewed clinical trials, prospective/retrospective observational studies, meta-analyses/systematic reviews/survival analyses, database analyses, economic studies • Study outcomes: WM-related epidemiology and/or burden of illness (clinical, economic, and/or humanistic) • Language: English (English abstract acceptable)
Exclusion criteria	• Not relevant to SLR topic of interest • Preclinical/animal studies • Clinical trials with N<40 • Case reports/case series • Editorials • Book chapters • Non-systematic review articles

Results

- Of the 1146 evaluable publications, 51 were included based on search criteria (Figure 1).

Figure 1. Flow Diagram of Study Identification and Inclusion

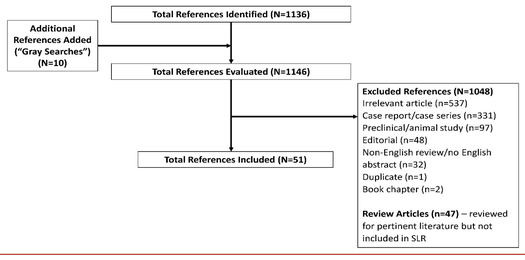
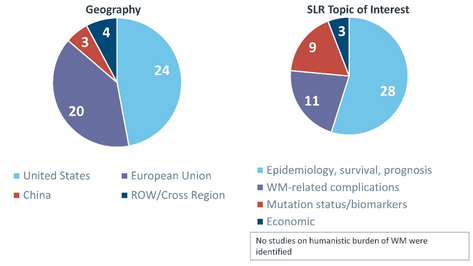


Figure 2. Number of Studies by Geography and SLR Topic



No studies on humanistic burden of WM were identified

SLR Findings: Epidemiology, Survival, and Prognosis of WM

- WM epidemiology and survival trends varied among studies, in part due to methodological limitations of available studies (eg, small population-based registries, lack of diagnosis verification, misclassification rates, missing patient data).
- Most available data suggest an overall stable incidence of WM with considerably increased survival in recent years, though survival rates vary widely among studies (Tables 2 and 3).
- Racial disparities may exist in WM; some studies report significantly reduced overall survival (OS) for Hispanics vs Whites overall and significantly reduced OS for African Americans and Hispanics vs Whites in male patients (Figure 3).

Table 2. WM Epidemiology Data in Current Literature

World Region	Epidemiology Data in Literature
US	Incidence: 0.3 to 0.57/100,000 persons/year; either stable (3 studies) or decreased incidence (1 study) over time
China	Overall incidence not available; one study found 5.4% of all B-CLPDs were classified as LPL/WM (a higher proportion vs Western countries)
EU	
Sweden	Incidence: 1.05 per 100,000 persons/year, relatively stable incidence between 2000 and 2012 (range: 0.88-1.21)
Germany	Prevalence of 0.0060% in 2012
ROW	
Morocco	Overall incidence not available; one study found WM represented 0.1% of all cancers identified and 0.8% of all lymphoid neoplasms identified
Japan/Taiwan	Age-standardized incidence rate: 0.043 per 100,000 person-years in Japan and 0.031 per 100,000 person-years in Taiwan

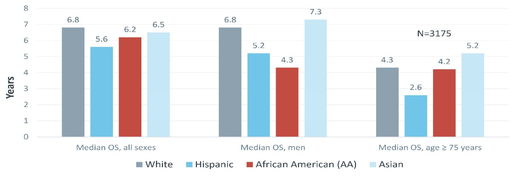
B-CLPD=B-cell chronic lymphoproliferative disorder; LPL=lymphoplasmacytic lymphoma; ROW=rest of world; WM=Waldenström macroglobulinemia

Results, Cont

Table 3. WM Survival – Trends and Prognostic Factors

Survival trends in WM	Considerably increased survival rates in recent years, especially after 2000 • Ex. Patients diagnosed between 2001 and 2010 had higher 5-year (78% vs 67%) and 10-year (66% vs 49%) relative survival rates compared with patients diagnosed between 1980 and 2000 • Ex. Median overall survival (OS) increased from 6 years for patients diagnosed with WM between 1991 and 2000 to 8.2 years for patients diagnosed between 2001 and 2010 cohort (HR 0.73, 95% CI: 0.67 to 0.79; p<0.001)
	Reported 5-year survival rates in US vary widely (52% to 78%)
	Available data demonstrate similar survival rates and trends to US in the EU and Japan (5-year survival ~70%) but lower survival in China (61.8%); data lacking in other regions
Prognostic factors for survival	Male sex and older age at diagnosis (ie, >65-70 years): decreased survival
	Female sex, younger age at diagnosis, and recent year of diagnosis: increased survival
	Other factors associated with decreased survival: elevated lactate dehydrogenase, low hemoglobin, poor performance status, history of lymphoproliferative disorders
	High von Willebrand factor (VWF) antigen levels associated with worse outcomes • Ex. 5-year OS rates for VWF antigen <110, between 110 and 250, and >250 U/dL were 96%, 71%, and 44%, respectively (p<0.0001)

Figure 3. Median Overall Survival by Race: US Population-Based Study[6]



Hazard Ratios, Relative to White 1 (reference):
Race: Hispanic 1.330 (1.031-1.717); AA 1.110 (0.836-1.475); Asian 1.015 (0.761-1.353); overall p=0.16
Males: Hispanic 1.432 (1.048-1.957); AA 1.504 (1.075-2.105); Asian 0.9333 (0.658-1.323); overall p=0.013
Age ≥75 years at diagnosis: Hispanic 1.613 (1.112-2.340); AA 1.063 (0.690-1.640); Asian 0.728 (0.461-1.150); overall p=0.038

SLR Findings: Other Clinical Burden in WM

- Data show WM is associated with a number of complications, including secondary malignancies, thrombosis, renal diseases, symptomatic hyperviscosity, and autoimmune manifestations (Table 4).

Table 4. Complications Reported in Patients with WM

Complication	N of Studies	Key Findings
Secondary Malignancies (SM)	5	• Risk of SM appears considerably high (~49% higher risk vs general population; ~1.7-fold increased risk vs general population) • Most common are hematologic SMs, but solid malignancies also occur • Associated with decreased survival in WM patients vs non-WM patients • Risk may be linked to WM treatments, disease-related immune dysregulation, disease transformation, or genetic predisposition; age-appropriate cancer screening is recommended
Hyperviscosity (HV)	2	• Although rare in WM (~13-14%), symptomatic HV may be associated with serious/life-threatening complications (eg, stroke, hearing loss, retinal bleeding), but doesn't appear to affect overall survival and symptoms respond to treatment
Renal Disease	2	• Renal disease in WM patients was found to be relatively common (~3-5%) • Survival was shorter in WM-related nephropathy and longer in patients with stable or improved renal function after treatment; therefore, monitoring for renal disease is recommended
Histological Transformation (HT)	2	• Although rare in WM (1-3.8%), HT to an aggressive malignancy can occur at any time during disease course and is associated with worse outcomes (ie, shorter survival) • Median time from WM diagnosis to HT was 4.6 years (95% CI: 1.4 to 8.9)
Other Reported Complications	2	• Venous thrombosis (~2- to 4-fold increased risk); highest in 1st year of diagnosis • Autoimmune manifestations (eg, immune cytopenias, autoimmune neurologic disorders, immune nephropathies, rheumatic diseases)

SLR Findings: Economic Burden in WM

- Current studies evaluating the economic burden of WM are lacking.
- A US study found that although treatment innovations (such as rituximab, bortezomib, and bendamustine) contribute to improved survival, they may also significantly increase costs; ie, mean Medicare costs in first treatment year: $9,464 before 2000 to $29,490 after 2008 (2013 US dollars, most recent data available).[7]
- A 2017 Italian economic model found the novel agent ibrutinib had an incremental cost effectiveness ratio (ICER) of €52,698/life-year gained (LYG), which the authors considered below a willingness-to-pay (WTP) threshold of €60,000/LYG.[8]
- A 2018 UK economic model concluded the most plausible ICER for ibrutinib was at least £54,100/quality-adjusted LYG, which the authors stated exceeded a WTP threshold of £30,000/quality-adjusted LYG.[9]

Current Evidence Gaps in WM Based on SLR Findings
Large, real world epidemiologic studies using diagnosis verification
Data on WM burden largely restricted to US and EU populations; data in Asia-Pacific, Latin America, and other regions of the world are limited
Data evaluating ethnic, racial, and geographic disparities in WM incidence, clinical presentation, and outcomes
Studies on WM-related economic burden (eg, cost of illness, healthcare utilization) and humanistic burden (eg, effects on quality of life, activities of daily living, caregiver health)
Effects of mutation status and biomarkers on WM outcomes and evaluations of effective therapies targeting these alterations
The economic and clinical burden of secondary malignancies in WM, and effective therapies with a lower risk of secondary malignancies

Conclusions

- This study reviewed the burden of WM across regions (US, EU, China).
- Although rare, WM results in significant clinical (eg, complications, survival) burden; economic burden data are limited but suggest treatment innovations may be associated with both clinical benefits and increased costs.
- Unmet needs and data gaps on WM-burden exist; future studies are needed to understand the true burden of WM in the current treatment landscape.

References

1. Dimopoulos MA, et al. Ann Oncol 2016;27(2):233-40.
2. Atienza J, et al. Leuk Lymphoma 2015;56(4):1179-80.
3. Castillo JJ, et al. Ther Adv Hematol 2016;7(4):179-86.
4. Buske C, Leblond V. Leukemia 2014;27(4):762-72.
5. Abeykoon JP, et al. Cancer Manag Res 2017;9:73-83.
6. Ailawadhi, et al. Oncology 2014;86(5-6):253-62.
7. Olszewski AJ, et al. Oncologist 2016;21(11):1377-86.
8. Aiello A, et al. J Mark Access Health Policy 2017;5(1):1393308.
9. Tappenden P, et al. Pharmacoeconomics 2019;37(1):7-18.

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