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Hematologic Malignancies

Evolution of Management and Outcomes in Waldenström Macroglobulinemia: A Population-Based Analysis

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Key Words. Waldenström macroglobulinemia • Rituximab • Bortezomib • Bendamustine • Cost of therapy • Health services research

Abstract

Introduction. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (WM) is a rare lymphoma affecting older patients. Its management largely relies on small phase II trials and it is unclear how their results translate into clinical practice in the community.

Method. We evaluated changes in the presentation, management, and survival among 2,666 Medicare beneficiaries diagnosed with WM between 1994 and 2011, using Medicare claims linked to Surveillance, Epidemiology and End Results data.

Results. Prevalence of transfusions, anemia, thrombocytopenia, and neuropathy at diagnosis significantly increased over time, whereas the use of plasmapheresis was low (2.5%) and stable. The proportion of patients starting chemotherapy within 1 year of WM diagnosis increased from 39% in 1994 to 62% in 2011 ($p < .0001$). Treatments based on classic alkylators and purine analogs predominated in the 1990s, but were quickly replaced by rituximab-containing regimens after 2000. Rituximab monotherapy has been prescribed for >50% of patients since 2004, and combination chemoimmunotherapy for a further 30%. Most patients initiating multiagent regimens in 2012–2013 received rituximab with bortezomib or bendamustine. These changes were accompanied by significant improvements in overall and WM-related survival, but also by a significant increase in cost of chemotherapy. Mean Medicare payments for chemotherapy drugs accrued in the first year of treatment rose from $9,464 in 1994–2000 to $29,490 after 2008.

Conclusion. Hematologists have rapidly adopted innovative, expensive therapies for WM before completion of randomized trials. This underscores the need to assess the comparative value of such therapies in rare malignancies through a combination of clinical and observational data. ***The Oncologist*** 2016;21:1377–1386

Implications for Practice: Most older patients with Waldenström macroglobulinemia currently treated in the U.S. receive rituximab as monotherapy or in combination with bortezomib or bendamustine. Newly designed trials should consider control arms aligned with this prevalent real-life standard. Compared with the 1990s, patients diagnosed according to current criteria are more likely to have anemia or neuropathy, or to receive early chemotherapy, but only 2.5% require plasmapheresis at diagnosis. The incremental clinical value of newly introduced agents needs to be assessed through a combination of clinical and health services research, taking into consideration their associated survival benefits, toxicities, and associated costs of care.

Introduction

Waldenström macroglobulinemia (WM) was first described in 1944 by the Swedish hematologist Jan Waldenström, who characterized it as a myeloma-like disease with increased serum γ-globulin, anemia, coagulopathy, and a lymphoplasmacytic infiltrate in the bone marrow [1]. This rare disorder, accounting for less than 2% of lymphoid malignancies, was recognized as a systemic B-cell lymphoma, in which malignant cells produce monoclonal IgM paraprotein, leading to unique clinical complications. Plasmapheresis became the first successful therapy for WM-related hyperviscosity syndrome manifesting with hemostatic, pulmonary, neurologic, and ocular dysfunction, and the procedure remains an important treatment modality for severe cases [2, 3]. Systemic therapy for WM was then developed through case series, single-arm clinical trials, and randomized studies often pooling various indolent B-cell histologies [3, 4].

Research on the epidemiology of WM has been hampered by evolving diagnostic definitions. Most lymphoplasmacytic

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lymphomas (LPL) produce monoclonal IgM (rarely, IgG, IgA, or none), which is also encountered in other types of lymphoma or myeloma, and in the benign monoclonal gammopathy of unknown significance (MGUS) [5]. In population-based registries like the Surveillance, Epidemiology and End Results (SEER) program, WM is inconsistently classified as a "miscellaneous malignancy," whereas LPL is classified as a non-Hodgkin lymphoma [6, 7]. Epidemiologic studies noted that most WM cases occurred in male patients older than 70 years, and that in the U.S., the disease was exceptionally rare among black people [8, 9]. Subsequent research confirmed a familial predisposition, as well as elevated risk for secondary malignancies in this disease [10, 11]. Recent studies suggested better survival [12–14] but could not discern whether this was due to earlier diagnosis (lead-time bias) or therapeutic advances. To our knowledge, no reports described use of health services or prevalence of WM-related complications using population-based data. Important novel treatments for WM introduced over the past 15 years included rituximab [15, 16], bortezomib [17, 18], and chemoimmunotherapy combinations [19–21], culminating with the approval of ibrutinib as the first agent specifically indicated for WM by the U.S. Food and Drug Administration in 2015 [22]. Those advances were chiefly developed through small, single-arm trials while data about WM management in the community have been lacking.

Our objective was to describe trends in baseline presentation, use of systemic therapies, and survival outcomes among patients diagnosed with WM/LPL in the U.S. over the past 20 years. We hypothesized that novel treatments were adopted as a standard of care ahead of publication of phase III data, leading to observable changes in both survival and costs of therapy.

Patients and Methods

Data Source and Cohort Selection

This study used de-identified data from the SEER-Medicare program and was approved by the local institutional review board. The SEER-Medicare dataset links population-based cancer registry (i.e., SEER) records from 18 geographic areas currently covering approximately 28% of Americans, with administrative claims on all covered health services rendered to Medicare beneficiaries [23]. This linkage is successful for 93% of patients aged 65 years or older. The SEER-Medicare data have been widely used for research in hematologic malignancies, although not so far in WM [24, 25].

We selected patients diagnosed with WM (International Classification of Diseases in Oncology, Third Edition [ICD-O-3] code 9761/3 [26]) or LPL (ICD-O-3 code 9671/3) at age 65 years or older, between 1994 and 2011 (Fig. 1). The year 1994 marked a consistent definition of WM/LPL in the Revised European-American Classification of Lymphoid Neoplasms [27]. Because WM and LPL are considered manifestations of the same pathology (distinguished mainly by the presence of circulating IgM), with uncertain consistency of coding and with generally similar clinical characteristics (supplemental online Table 1), we use here the term WM to refer to both. We excluded cases of stage I/II extranodal LPL, which were possibly misclassified extranodal plasmacytomas, as well as fewer than 11 cases with concurrent diffuse large B-cell or Burkitt lymphoma. Finally, as a standard approach in SEER-Medicare studies, patients had to have complete Medicare claims from at least 1 year before diagnosis, until death or censoring, thus excluding enrollees in managed care plans whose records were not available. The last available year of SEER data (for WM diagnosis) was 2011, but Medicare claims were available until December 2013.

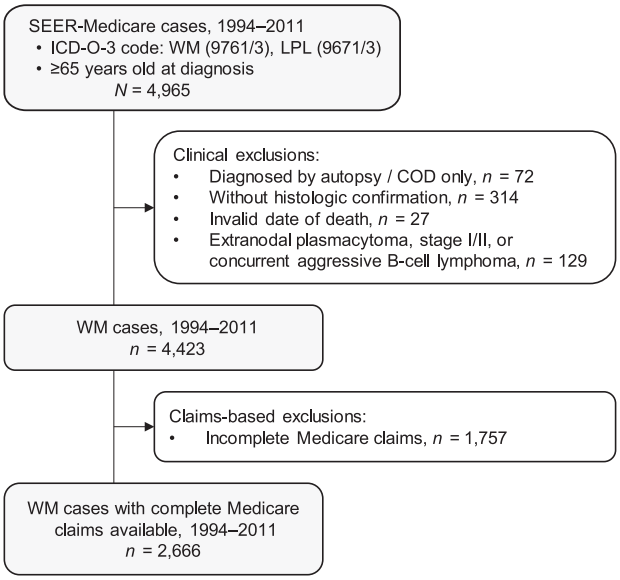

Figure 1. Selection of the analytic cohort from the SEER-Medicare data.

Abbreviations: COD, certificate of death; LPL, lymphoplasmacytic lymphoma; SEER, Surveillance, Epidemiology, and End Results; WM, Waldenström macroglobulinemia.

Variables and Endpoints

The SEER registries provided clinical information on patients' demographics, histology, primary site, and Ann Arbor stage. We used dual coverage by Medicare and Medicaid as an indicator of poverty because Medicaid ("state buy-in") coinsurance is available specifically to low-income Medicare beneficiaries in the U.S. [28, 29]. We classified race/ethnicity as white non-Hispanic, white Hispanic, black, or Asian/other. Other covariates were established by analysis of inpatient and outpatient claims, using algorithms discussed later in this report. The National Cancer Institute modification of the Charlson-Deyo comorbidity index counts comorbid conditions known to affect mortality, which are present within 12 months before diagnosis (or treatment) [30]. Davidoff's disability indicator, constructed from medical services recorded within the same time frame, is a validated measure of patient self-reported poor performance status [31].

We constructed indicators of WM severity using relevant Healthcare Common Procedure Coding System (HCPCS) and International Classification of Diseases Ninth Edition (ICD-9) codes. These were used as a substitute for the International Prognostic Scoring System in WM (IPSSWM) [32] because its direct laboratory components (hemoglobin level, $\leq$11.5 g/dL; platelet count, $\leq 100 \times 10^9$/L; β2-microglobulin level, $>$3 mg/L; and IgM level, $>$7 g/dL) were not available in the dataset. Instead, we identified the use of transfusions, plasmapheresis, and intravenous immunoglobulin (IVIG), as well as diagnoses of anemia, autoimmune hemolytic anemia (AIHA), thrombocytopenia, neuropathy, or amyloidosis—the common clinical complications of WM. To increase specificity, diagnostic codes had to

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appear at least twice, more than 30 days apart, on nonlaboratory claims, as previously described in the context of Medicare claims-based health services research [24, 30]. We confirmed that those indicators replicated survival stratification similar to IPSSWM (supplemental online Fig. 1). We studied prevalence of the indicators in periods defined as "at diagnosis" (from 1 year before to 30 days after WM diagnosis), or "before chemotherapy" (from 1 year before diagnosis to the start of chemotherapy).

First-line chemotherapy regimens were determined from claims for specific drugs administered within the first 60 days of therapy [33, 34]. We classified regimens as follows: (a) alkylator based (containing cyclophosphamide or chlorambucil, with or without other agents); (b) purine analog based (containing fludarabine, cladribine, or pentostatin, with or without other agents), with or without rituximab; (c) rituximab monotherapy; (d) regimens containing any bortezomib or bendamustine; and (e) others. Regimens containing both purine analog and alkylator (mainly fludarabine-cyclophosphamide) were included in the purine analog-based group. Regimens could not be classified if treatment was identified only by generic HCPCS/ICD-9 codes for chemotherapy administration; for example, if it was entirely inpatient. Oral chlorambucil was only captured through such generic codes, except for 248 patients continuously enrolled in Medicare Part D plans since diagnosis, for whom records of filled prescriptions were available.

Overall survival (OS) was calculated from diagnosis until death or administrative censoring on December 31, 2013. Because WM is an indolent disorder affecting older patients who experience a substantial risk for death from other causes, we analyzed the outcomes accounting for those competing risks [35, 36]. Cause of death (derived from death certificates) was available for events until December 31, 2012, so further events were censored. We also calculated mean Medicare payments for the care of WM patients from diagnosis until death, within 1 year from diagnosis, or from treatment initiation. Although Medicare payments do not capture entire costs of care (they exclude copayments, coinsurance, out-of-pocket expenses, as well as prescription costs), they represent an essential burden on the national health care system, and can illustrate trends or differences in total costs [37].

Statistical Analysis

We evaluated proportions using the chi-square test, and trends by log-binomial regression (log-γ for costs). OS was calculated using the Kaplan-Meier method, and cumulative incidence function for specific events was calculated using the competing-risk approach [38]. We also fitted proportional hazard survival models, using Geskus' method for competing-risk models [39]. The proportional hazard assumption was evaluated using Schoenfeld residuals, introducing time-varying terms when necessary. We additionally analyzed the trend in OS by a more sensitive "period survival" method, in which a 3-year OS estimate was calculated for specific 2-year calendar intervals, using only time-at-risk from patients entering each period [40]. Costs were adjusted for inflation to 2013 dollars using the U.S. Consumer Price Index, and calculated from complete claim histories of patients observed until death, subject to weighting by inverse probability of censoring [41]. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, http://www.sas.com) and Stata/MP version 14.1 (StataCorp LP, College Station, TX, http://www.stata.com), reporting 95% confidence intervals (CIs), and with significance level of $p < .05$.

Table 1. Characteristics of patients with Waldenström macroglobulinemia in the SEER-Medicare database, 1994–2011

Variable	*N* (%)
Patients	2,666 (100)
Age at diagnosis, median (IQR) (years)	78 (73–83)
Sex	
Women	1,141 (42.8)
Men	1,525 (57.2)
Race/ethnicity	
White non-Hispanic	2,414 (90.5)
White Hispanic	85 (3.2)
Black	76 (2.9)
Asian/Other	91 (3.4)
Histology code in the registry	
Lymphoplasmacytic lymphoma	1,154 (43.3)
Waldenström macroglobulinemia	1,512 (56.7)
Comorbidity index	
0	2,028 (76.1)
1	364 (13.7)
≥2	274 (10.2)
Poor functional status indicator	141 (5.3)
Medicaid (poverty) indicator	229 (8.6)
Complications at diagnosis[a]	
Blood transfusion	173 (6.5)
Plasmapheresis	66 (2.5)
Anemia	1,263 (47.4)
AIHA	69 (2.6)
Thrombocytopenia	201 (7.5)
Neuropathy	143 (5.4)
Chemotherapy ever administered	1,744 (65.4)
Chemotherapy within 1 year from diagnosis	1,336 (50.1)
Complications before chemotherapy ($n = 1,746$)[b]	
Blood transfusion	279 (16.0)
Plasmapheresis	85 (4.9)
Anemia	1,190 (68.2)
AIHA	71 (4.1)
Thrombocytopenia	208 (11.9)
Neuropathy	161 (9.2)

[a]Prevalence based on Medicare claims from 1 year before to 30 days after diagnosis.
[b]Prevalence based on Medicare claims from 1 year before diagnosis until the start of chemotherapy.
Abbreviations: AIHA, autoimmune hemolytic anemia; IQR, interquartile range.

Results

A majority of 2,666 WM patients were male and white non-Hispanic (Table 1). Nine percent had records of monoclonal paraproteinemia within the year before (but excluding 60 days immediately preceding) the WM diagnosis. Anemia was the most prevalent complication at diagnosis and before

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Table 2. Trends in the prevalence of indicators of Waldenström macroglobulinemia severity

Indicator	% by range of years[a]				*p* value[b]
	1994–2000	2001–2004	2005–2008	2009–2013	
At diagnosis (years) ($N = 2,666$)					
Transfusion	3.6	5.8	8.5	8.0	<.0001
Plasmapheresis	2.7	2.1	2.1	3.1	.88
Anemia	44.0	45.6	50.9	49.1	.0067
AIHA	3.2	2.3	2.4	2.6	.44
Thrombocytopenia	5.9	7.2	7.7	9.7	.0034
Neuropathy	4.0	4.4	6.6	6.7	.024
Amyloidosis[c]	<1.0	<1.0	<1.0	<1.0	.91
IVIG use[c]	<1.0	<1.0	<1.0	<2.0	.42
Before chemotherapy ($n = 1,746$)					
Transfusion	14.9	14.8	16.6	17.2	.30
Plasmapheresis	3.5	5.9	4.6	5.0	.94
Anemia	65.1	69.0	68.9	68.4	.39
AIHA	4.8	4.1	3.7	4.0	.32
Thrombocytopenia	11.1	11.3	9.8	15.3	.037
Neuropathy	4.2	8.2	10.0	12.3	.0008
Amyloidosis[c]	<2.0	<2.0	<2.0	<2.0	.84
IVIG use[c]	<2.0	<2.0	<1.0	<2.0	.51

[a]Year of diagnosis (1994–2011) for prevalence at diagnosis, or year of first treatment (1994–2013) for prevalence before chemotherapy.
[b]*p* for a linearized yearly trend in a log-binomial model.
[c]Exact values suppressed for patient confidentiality, according to the National Cancer Institute policy.
Abbreviations: AIHA, autoimmune hemolytic anemia; IVIG, intravenous immunoglobulin.

chemotherapy. Other complications were present in <8% of patients at diagnosis, and the percentages of all roughly doubled by the time of starting chemotherapy. The prevalence of IVIG use or amyloidosis was <1% at diagnosis and 1.1% at the time of treatment initiation. During the entire period of observation (until death or censoring), 35% of patients ever underwent a transfusion, 8% had undergone plasmapheresis, 4% received IVIG, and the following was recorded: 86%, anemia; 6%, AIHA; 31%, thrombocytopenia; 22%, neuropathy; and 3%, amyloidosis. Eighty-two percent of cases designated as LPL had stage IV disease, and essentially all cases coded as WM were diagnosed from blood or bone marrow. Otherwise, the LPL/WM groups differed in the proportions of men, race/ethnicities, plasmapheresis at diagnosis, and type of initial chemotherapy, but not in other characteristics or outcomes (supplemental online Table 1).

Trends in Baseline Characteristics

Median age ($p = .14$), proportions of men ($p = .68$), and of races/ethnicities ($p = .51$) did not significantly change between 1994 and 2011. In contrast, the proportion of patients receiving transfusions ($p < .0001$), with recorded anemia ($p = .007$), thrombocytopenia ($p = .003$), or neuropathy ($p = .024$) at diagnosis significantly increased, while the rates of plasmapheresis, IVIG use, AIHA, or amyloidosis did not (Table 2). There was no significant change in the proportion of patients requiring transfusion, plasmapheresis, or IVIG by the time of starting chemotherapy, and only prevalences of thrombocytopenia and neuropathy increased.

Treatment Administration

Within 1 year of diagnosis, 50% (95% CI, 48–52) of WM patients started chemotherapy, while 10% (95% CI, 9–11) died without treatment (Fig. 2A). These estimates were 63% (95% CI, 61–65) and 21% (95% CI, 20–23), respectively, at 5 years, with 16% of patients surviving without any treatment. The 5-year risk for death without treatment significantly decreased from 30% before 2001% to 17% after 2005 ($p < .001$), whereas the proportion receiving active chemotherapy increased from 55% to 67%, respectively ($p < .001$; supplemental online Fig. 2). Median time to from diagnosis to chemotherapy was 9 months (95% CI, 8–11), decreasing from 25 months in 1994–2000 to 4 months in 2009–2013 ($p < .0001$). The proportion of patients starting chemotherapy within 1 year of diagnosis accordingly increased from 39% in 1994 to 62% in 2011 ($p < .001$; Fig. 2B).

Over the entire period of the study, the most common chemotherapy regimen was single-agent rituximab (45%), followed by purine analogs without rituximab (15%), alkylators with rituximab (11%), purine analogs with rituximab (10%), alkylating agents without rituximab (9%), bortezomib (4%, of which 78% was with rituximab), and bendamustine (2%, of which 88% was with rituximab). Additional breakdown of regimens is provided in supplemental online Table 2.

The use of rituximab rapidly increased after 1999 (Fig. 3A). By 2003, more than half of patients were receiving the monoclonal antibody as a single agent, and nearly a third received it in combination with chemotherapy. The use of purine analogs and alkylators alone, predominating in the 1990s, declined to <10% after 2008. Although the absolute numbers of patients treated with bortezomib ($n = 51$) or bendamustine ($n = 24$) were low, these 2 agents surpassed all other classic cytotoxic drugs in 2012/2013 data. Among patients with complete records of oral prescriptions, only 7%

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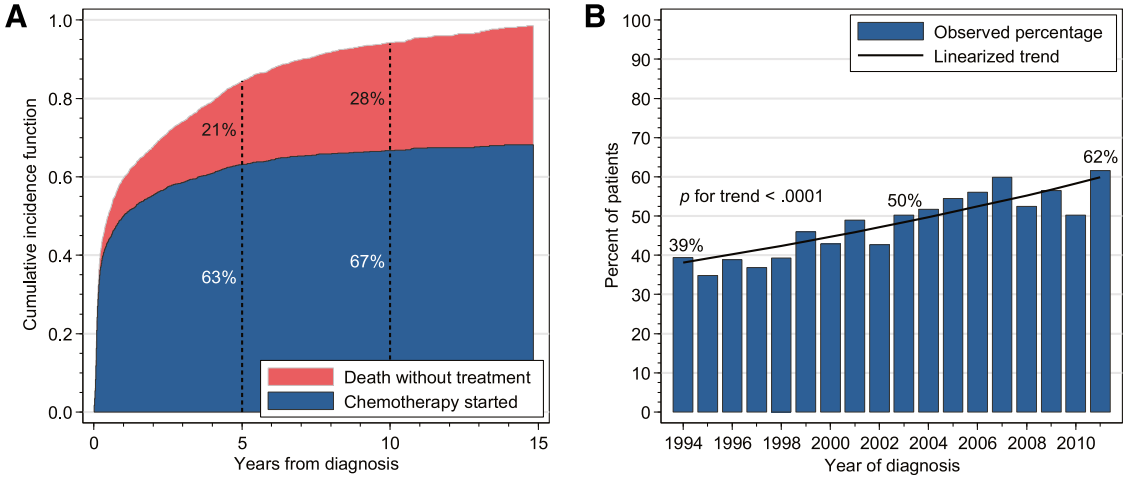

Figure 2. Administration of first-line chemotherapy in Waldenström macroglobulinemia. **(A):** Cumulative incidence of starting chemotherapy or death without treatment. **(B):** Trend in the proportion of patients starting chemotherapy within 1 year of diagnosis.

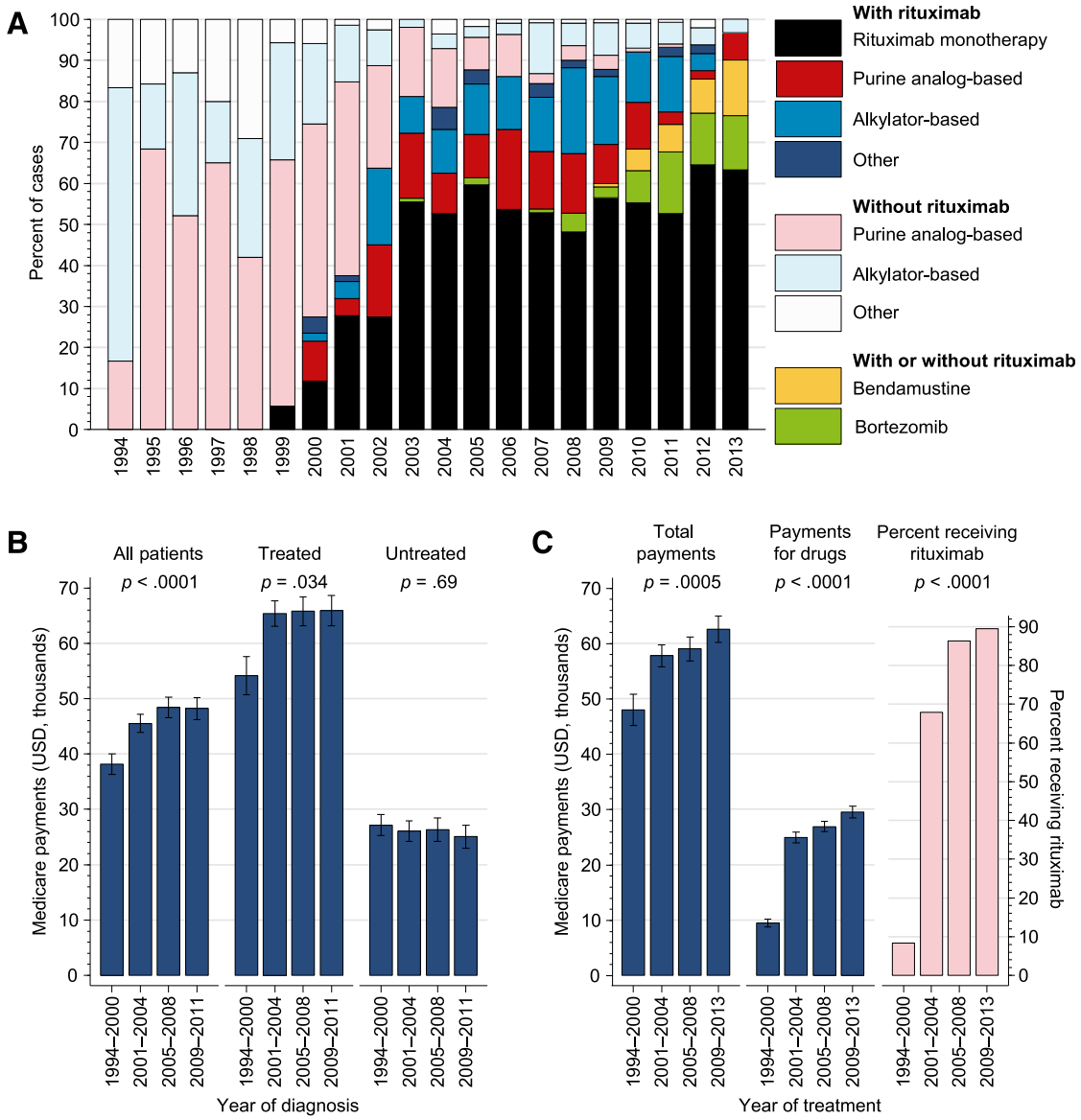

Figure 3. Upfront chemotherapy regimens administered to patients with Waldenström macroglobulinemia. Data in bar graphs are stratified by year of treatment **(A)**, mean cumulative Medicare payments for care accrued within 1 year of diagnosis **(B)**, or within 1 year of starting chemotherapy **(C)**, in the context of increasing rituximab use. Range bars indicate SE; *p* values are for linearized yearly trends in log-γ models for costs.

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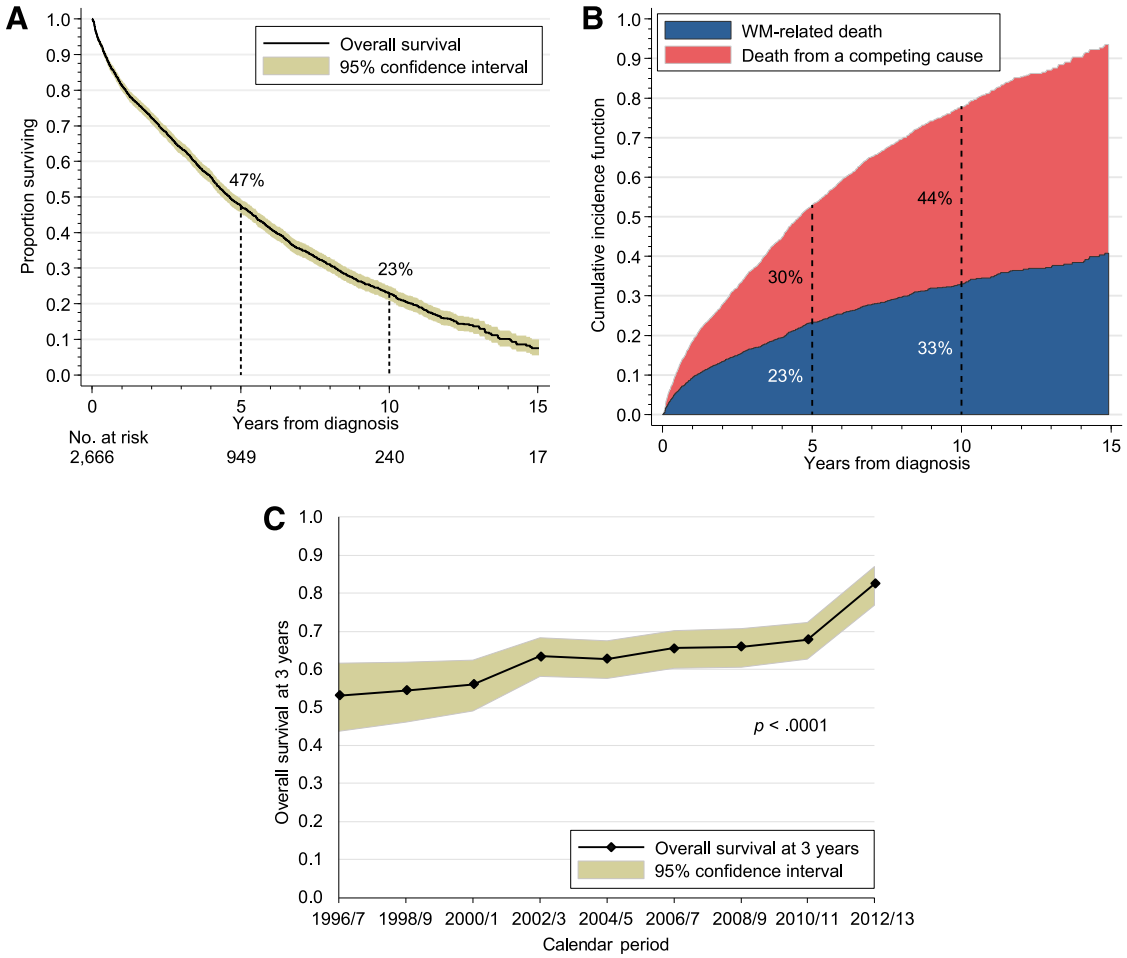

Figure 4. Plots of overall survival, period survival, and cumulative incidence of death. **(A):** Overall survival. **(B):** Stacked cumulative incidence of death from Waldenström macroglobulinemia or from competing causes. **(C):** Period survival, which illustrates the probability of 3-year survival using time-at-risk confined to a specific calendar period.

received single-agent chlorambucil, and 2% received single-agent fludarabine—treatments compared in the most recent published phase III trial in WM [42]. In a multivariable model fitted for patients treated in 2000–2013 ($n = 1,226$; supplemental online Table 3), administration of single-agent rituximab was associated with increasing age, female sex, treatment >1 year from diagnosis, and presence of neuropathy or AIHA. After adjustment for patient- and disease-related factors, a significant physician-level preference was evident, accounting for 29% of residual variation in treatment selection.

Costs of Management

Estimated mean total Medicare payments for the care of a WM patient accrued within 15 years from diagnosis were $163,432. In the subgroup of patients who received chemotherapy at some point during the follow-up period, these costs were nearly twice as high ($193,150) compared with those who never received chemotherapy ($106,705; $p < .0001$). Mean costs accrued within 1 year of diagnosis increased from $38,179 in 1994–2000 to $48,199 in 2009–2011 ($p < .0001$; Fig. 3B). This increase was restricted to patients who started chemotherapy during the first year from diagnosis ($p = .034$), and was absent among those observed without treatment ($p = .69$). Similarly, a surge in cumulative payments within 1 year of starting therapy was evident ($p = .0005$; Fig. 3C), for which the cost of antineoplastic drugs was largely responsible, tripling from $9,463 before 2001 to $29,490 after 2008. Consequently, the proportion of expenditures covering the cost of drugs increased from 20% to 47%, respectively. This shift occurred immediately after 2000 and coincided with widespread rituximab use.

Survival and End-of-Life Care

With median follow-up of 5.4 years, median OS was 4.6 years (95% CI, 4.4–4.9), and 5-year OS estimate was 47% (95% CI, 45–49; Fig. 4A). The risk for dying of a competing event (30% at 5 years; 95% CI, 28–32) was higher than the risk for dying from WM (23%; 95% CI, 22–25; Fig. 4B). In a multivariable model, advanced age, male sex, poverty and poor baseline health, transfusion or plasmapheresis at diagnosis, presence of anemia (but not AIHA), or amyloidosis were associated with worse OS (Table 3). Adjusting for those factors, survival of WM patients significantly improved between 1994 and 2000 and later epochs, which was also evident in the period survival analysis (Fig. 4C). In competing-risk models, improvement over time occurred both for WM-related and for other causes of death (supplemental online Table 4). For patients initiating rituximab-containing therapy in 2004–2013, median survival from the first treatment was 5.8 years (95% CI, 5.0–6.5).

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Table 3. Factors associated with overall survival in a multivariable model ($N = 2,666$)

Variable	Hazard ratio	95% confidence interval	*p* value
Age at diagnosis (years)			
65–69	Reference		<.0001
70–74	1.32	(1.10–1.60)	
75–79	1.73	(1.45–2.07)	
≥80	2.94	(2.48–3.48)	
Sex			
Men	Reference		.0002
Women	0.83	(0.75–0.91)	
Race/ethnicity			
White non-Hispanic	Reference		.51
White Hispanic	1.03	(0.79–1.34)	
Black	1.13	(0.85–1.49)	
Asian/other	0.85	(0.65–1.11)	
Medicaid (poverty) indicator	1.68	(1.41–1.99)	<.0001
Indicators of baseline health[a]			
Comorbidity index:			.32
0	Reference		
1	1.10	(0.95–1.26)	
≥2	1.09	(0.93–1.28)	
Disability indicator[a]	0.89	(0.70–1.14)	.37
Cancer screening[a]	0.81	(0.72–0.90)	.0002
Any vaccination[a]	0.85	(0.76–0.94)	.003
WM complications at diagnosis[b]			
Transfusion	1.43	(1.18–1.74)	.0002
Plasmapheresis	1.37	(1.02–1.85)	.038
Anemia	1.96	(1.69–2.29)	<.0001
Time-varying term[c]	0.93	(0.90–0.96)	
AIHA	1.03	(0.78–1.37)	.83
Thrombocytopenia	1.16	(0.97–1.39)	.09
Neuropathy	1.10	(0.89–1.36)	.38
Amyloidosis	2.00	(1.17–3.43)	.012
Year of diagnosis			
1994–2000	Reference		<.0001
2001–2004	0.77	(0.68–0.86)	
2005–2008	0.68	(0.60–0.77)	
2009–2011	0.51	(0.42–0.60)	

[a]Based on Medicare claims within 1 year before diagnosis.
[b]Based on Medicare claims from 1 year before to 30 days after diagnosis.
[c]Introduced because of nonproportional hazard.
Abbreviation: AIHA, autoimmune hemolytic anemia.

Twenty-seven percent of patients who died had enrolled in hospice before death, without difference between those whose cause of death was ascribed to WM or not ($p = .43$). The use of hospice services markedly increased over time, from <5% among cases who died before 2005 to >50% among those who died after 2009. Among patients who used hospice services, median time from WM diagnosis to hospice enrollment was 4.0 years (95% CI, 3.6–4.5), which was longer for those who received chemotherapy (median, 4.5 years) than those who were never treated (median, 2.8 years). Median survival from the date of hospice enrollment was only 17 days (95% CI, 13–23).

Discussion

To our knowledge, we have conducted the first population-based analysis of health services, costs, and outcomes in WM, providing a contemporary appraisal of its management in the U.S. community. Our study focused on older people in the U.S., and specifically on fee-for-service Medicare beneficiaries, who are representative of the WM population at large, considering the demographic profile in this disease. We found the prevalence of baseline indicators of WM severity, including use of transfusions and rate of early chemotherapy initiation, to have significantly increased over the years. Despite that,

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overall and WM-related mortality improved, which was paralleled by the expanding use of rituximab-based chemoimmunotherapy and by increasing costs of care.

Because our analysis relied on administrative claims, some of the WM complications, like anemia or neuropathy, were only identified if patients received related medical services. The prevalence of those claims-based indicators was lower than in clinicopathologic case series, which were largely based on data from the 1990s and likely oversampled symptomatic WM. In those series, hyperviscosity syndrome was reported in 8%–30% cases, cryoglobulinemia or neuropathy in 6%–20%, anemia in 40%–60%, AIHA in 2%–4%, and amyloidosis in 2% [43–47]. Up to 16% of patients required plasmapheresis, which is much lower in our contemporary SEER-Medicare data ($<$3%, and up to 8% when looking at the patients' entire history). We could not capture other features of WM, such as lymphadenopathy, splenomegaly, visual disturbances, coagulopathy, constitutional symptoms, or laboratory values of IgM, hemoglobin, or β2-microglobulin levels. Somewhat surprisingly, we found a trend for increase in the baseline prevalence of many WM complications and for earlier application of chemotherapy. Although changes in the overall prevalence of, for example, neuropathy or anemia in the general population, as well as changes in billing-related Medicare coding could affect some trends, records of procedures (transfusions, plasmapheresis, chemotherapy) are unlikely to be influenced by such changes. The observed increase does not support the notion that diagnostic patterns in WM shifted toward earlier, asymptomatic phases of the disease, or that lead-time bias created spurious survival gains [12, 13]. Conversely, many patients previously presumed to have WM may now be designated as IgM MGUS in the absence of typical histologic findings and clinical symptoms. In the World Health Organization classification, the diagnosis of WM requires demonstration of lymphoplasmacytic infiltrate in the bone marrow, and this invasive diagnostic procedure might be deferred in clinical practice for asymptomatic older patients until progression. Improvements in systemic therapy or in supportive care may thus be truly responsible for the favorable survival trends when survival is calculated from the WM diagnosis as reported to the cancer registry. This evolution of diagnostic patterns and baseline presentations should be considered when interpreting results of any studies comparing current WM patients with historical control subjects. Our results are corroborated by a recent report from the Greek Myeloma Study Group, which described 408 symptomatic WM patients treated between 1982 and 2013 [36]. There was an increased prevalence of neuropathy (2.5% before 2000 and 7.5% after), cytopenias (39% and 45%, respectively), and a less favorable IPSSWM profile after 2000. Of patients treated after 2000, 79% received rituximab, 20% received alkylators, and 1% received purine analogs. OS was longer (8.8 years), and the cumulative incidence of WM-related death was 21% at 5 years, with 8% risk for a competing event in this cohort encompassing patients of all ages.

We demonstrated that U.S. clinicians rapidly adopted rituximab for WM management on the basis of preliminary data [15, 16, 48–50], even though a randomized trial showing the beneficial use of rituximab in WM/LPL (in combination with rarely used anthracycline-based chemotherapy) was reported only in 2009 [51]. Moreover, such adoption took place despite concerns for the IgM flare reaction associated with the monoclonal antibody [52]. Rituximab monotherapy remains the most frequent treatment prescribed to over 50% of patients, particularly those with neuropathy or AIHA, although response rates (50%–66%) appear somewhat lower than in trials combining rituximab with cyclophosphamide, fludarabine, or bortezomib (83%–96%) [16, 19, 20, 50, 53]. Those frequently used combinations are consistent with successive recommendations of the International Workshops on WM [54]. The fact that more patients are receiving chemotherapy and fewer die without treatment may reflect the favorable toxicity profile of rituximab, facilitating its use in elderly patients. Conversely, single-agent chlorambucil or fludarabine, compared in the most recent phase III trial in WM, are no longer in common use [42]. Bortezomib, despite phase II experience dating back to 2007 [18, 55], has not been widely embraced for upfront therapy, possibly considering its neurotoxicity and cost. Future analyses can reveal to what extent bortezomib and bendamustine, or even newer (and costlier) approaches including carfilzomib or ibrutinib, will replace classic cytotoxic agents [21, 22, 56]. Ibrutinib is the first drug specifically approved in the U.S. for treatment of WM on the basis of experience in 63 previously treated patients and with response rate (of 90% in the published analysis) as primary outcome [22]. Ultimately, several ongoing phase III trials comparing chemoimmunotherapy with or without bortezomib (NCT01788020), rituximab-bendamustine with or without maintenance (NCT00877214), and ibrutinib with rituximab monotherapy (NCT02165397) will provide higher-level evidence of clinical efficacy and toxicity.

Our data suggest that the significant improvements in WM survival over the past 15 years can be plausibly attributed to better care, including more efficacious systemic therapy. However, these advances came with substantially increased costs of care, which appear to be concentrated in chemotherapy-related expenditure, as costs for patients who remained untreated did not change. The rise in chemotherapy-related payments closely followed the proportion of patients treated with rituximab. Imminent further increase can be expected, considering replacement of older cytotoxic agents with bortezomib and bendamustine, each of which costs more than $5,000 per month of therapy. With emphasis on the value of novel treatments, a concept that encompasses not only clinical efficacy, but also toxicity in the real-world population and quality-of-life-adjusted costs of therapy, analysis of observational population-based data can provide insight unavailable from clinical trials or from traditional cost-effectiveness models, particularly when studies are sponsored by drug manufacturers [57]. One systematic review using such models concluded a reasonable value of novel therapies in hematologic malignancies, although not specifically in WM [58]. However, a reanalysis of the same data with different assumptions yielded opposite conclusions in many instances [59]. The approach to comparing effectiveness of cancer therapy from observational data is also still facing methodologic challenges [60, 61], and in this paper we focused on descriptive analyses.

The scope of questions answerable from the SEER-Medicare data is limited by the fact that the registry does not contain any actual laboratory results, response to therapy, duration of remission, progression events, or direct assessments of patients' symptoms and performance status. For our survival analysis, despite inability to reconstruct the IPSSWM scores, we achieved comparable discrimination of risk using

claims-based indicators of WM severity. We cannot rule out influence of changes in coding and billing practices on some of our results, although we carefully considered historical codes for drugs and procedures. The use of alkylating agents is underestimated because oral chlorambucil was not specifically identified in most cases and only captured through generic ICD-9 codes. Nevertheless, data from the Part D subcohort indicate that only a small proportion of beneficiaries have received chlorambucil after 2007 and, before that, it was not reimbursable by Medicare, creating an additional financial barrier. Furthermore, in a small proportion of cases (3%) whose treatment was only captured through inpatient admission codes, we could not identify the chemotherapy regimen. We should also emphasize that the observed associations should not be interpreted causally or applied to management of individual patients, with the possible exception of using our estimates of competing risks for mortality in WM for prognostic counseling. Even so, death certificates are known to misclassify causes of mortality, particularly when infections, organ failure, or secondary malignancies are indirectly attributable to WM [62]. The selection bias introduced by excluding patients enrolled in managed care plans, who are generally younger and healthier, should also be kept in mind.

Conclusion

The OS improvement in WM does not appear to be explained by changes in demographics or earlier diagnoses and may be plausibly ascribed to early adoption of innovative therapies in this rare disease. Escalating costs of care underscore the need to evaluate the value of novel agents and their combinations in comparative trials against standards of care prevalent in real-life clinical practice, which is not possible in small single-arm studies or subsets of trials pooling various histologies. Similar considerations arise for other rare hematologic malignancies like hairy cell leukemia or myelofibrosis, for which targeted therapies have recently emerged. Further research based on observational data might provide valuable evidence in settings where the pace of innovation exceeds the capacity of clinical research infrastructure.

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Disclosures

Jorge J. Castillo: Alexion, Biogen, Celgene, Otsuka, Pharmacyclics (CA), Abbvie, Gilead, Millennium, Pharmacyclics (RF). The other authors indicated no financial relationships.

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References

1. Waldenström J. Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia—a new syndrome? Acta Med Scand 1944;117:216–247.

2. Schwab PJ, Fahey JL. Treatment of Waldenstrom's macroglobulinemia by plasmapheresis. N Engl J Med 1960;263:574–579.

3. Treon SP. How I treat Waldenström macroglobulinemia. Blood 2015;126:721–732.

4. Ghobrial IM. Choice of therapy for patients with Waldenstrom macroglobulinemia. J Clin Oncol 2013;31:291–293.

5. Owen RG, Treon SP, Al-Katib A et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: Consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 2003; 30:110–115.

6. Herrinton LJ, Weiss NS. Incidence of Waldenström's macroglobulinemia. Blood 1993;82:3148–3150.

7. Morton LM, Wang SS, Devesa SS et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265–276.

8. Phekoo KJ, Jack RH, Davies E et al. The incidence and survival of Waldenström's macroglobulinaemia in South East England. Leuk Res 2008;32:55–59.

9. Groves FD, Travis LB, Devesa SS et al. Waldenström's macroglobulinemia: Incidence patterns in the United States, 1988-1994. Cancer 1998;82:1078–1081.

10. Kristinsson SY, Björkholm M, Goldin LR et al. Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia patients: A population-based study in Sweden. Blood 2008; 112:3052–3056.

11. Castillo JJ, Olszewski AJ, Hunter ZR et al. Incidence of secondary malignancies among patients with Waldenström macroglobulinemia: An analysis of the SEER database. Cancer 2015;121:2230–2236.

12. Kristinsson SY, Eloranta S, Dickman PW et al. Patterns of survival in lymphoplasmacytic lymphoma/Waldenström macroglobulinemia: A population-based study of 1,555 patients diagnosed in Sweden from 1980 to 2005. Am J Hematol 2013;88:60–65.

13. Castillo JJ, Olszewski AJ, Cronin AM et al. Survival trends in Waldenström macroglobulinemia: An analysis of the Surveillance, Epidemiology and End Results database. Blood 2014;123:3999–4000.

14. Ailawadhi S, Kardosh A, Yang D et al. Outcome disparities among ethnic subgroups of Waldenström's macroglobulinemia: A population-based study. Oncology 2014;86:253–262.

15. Dimopoulos MA, Zervas C, Zomas A et al. Treatment of Waldenström's macroglobulinemia with rituximab. J Clin Oncol 2002;20:2327–2333.

16. Gertz MA, Rue M, Blood E et al. Multicenter phase 2 trial of rituximab for Waldenström macroglobulinemia (WM): An Eastern Cooperative Oncology Group Study (E3A98). Leuk Lymphoma 2004;45: 2047–2055.

17. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC et al. Treatment of relapsed or refractory Waldenström's macroglobulinemia with bortezomib. Haematologica 2005;90:1655–1658.

18. Treon SP, Hunter ZR, Matous J et al. Multicenter clinical trial of bortezomib in relapsed/refractory Waldenstrom's macroglobulinemia: Results of WMCTG Trial 03-248. Clin Cancer Res 2007;13: 3320–3325.

19. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol 2007;25: 3344–3349.

20. Treon SP, Ioakimidis L, Soumerai JD et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. J Clin Oncol 2009;27:3830–3835.

21. Rummel MJ, Niederle N, Maschmeyer G et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label,

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multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203–1210.

22. Treon SP, Tripsas CK, Meid K et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med 2015;372:1430–1440.

23. Warren JL, Klabunde CN, Schrag D et al. Overview of the SEER-Medicare data: Content, research applications, and generalizability to the United States elderly population. Med Care 2002;40 (8 suppl):IV-3–18.

24. Olszewski AJ, Castillo JJ. Comparative outcomes of oncologic therapy in gastric extranodal marginal zone (MALT) lymphoma: Analysis of the SEER-Medicare database. Ann Oncol 2013;24: 1352–1359.

25. Lam CJ, Curtis RE, Dores GM et al. Risk factors for second acute myeloid leukemia/myelodysplastic syndrome among survivors of non-Hodgkin lymphoma. Leukemia 2016;30:1187–1190.

26. World Health Organization. International Classification of Diseases in Oncology, 3rd edition. Geneva, Switzerland: World Health Organization, 2014.

27. Harris NL, Jaffe ES, Stein H et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.

28. Bach PB, Guadagnoli E, Schrag D et al. Patient demographic and socioeconomic characteristics in the SEER-Medicare database applications and limitations. Med Care 2002;40(8 suppl):IV-19–25.

29. Davidoff AJ, Weiss Smith S, Baer MR et al. Patient and physician characteristics associated with erythropoiesis-stimulating agent use in patients with myelodysplastic syndromes. Haematologica 2012;97:128–132.

30. Klabunde CN, Potosky AL, Legler JM et al. Development of a comorbidity index using physician claims data. J Clin Epidemiol 2000;53:1258–1267.

31. Davidoff AJ, Zuckerman IH, Pandya N et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. J Geriatr Oncol 2013;4:157–165.

32. Morel P, Duhamel A, Gobbi P et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood 2009;113:4163–4170.

33. Danese MD, Griffiths RI, Gleeson M et al. An observational study of outcomes after initial infused therapy in Medicare patients diagnosed with chronic lymphocytic leukemia. Blood 2011;117: 3505–3513.

34. Olszewski AJ, Shafqat H, Ali S. Disparate survival outcomes after front-line chemoimmunotherapy in older patients with follicular, nodal marginal zone and small lymphocytic lymphoma. Leuk Lymphoma 2015; 56:942–950.

35. Castillo JJ, Olszewski AJ, Kanan S et al. Overall survival and competing risks of death in patients with Waldenström macroglobulinaemia: An analysis of the Surveillance, Epidemiology and End Results database. Br J Haematol 2015;169: 81–89.

36. Kastritis E, Kyrtsonis MC, Morel P et al. Competing risk survival analysis in patients with symptomatic Waldenström macroglobulinemia: The impact of disease unrelated mortality and of rituximab-based primary therapy. Haematologica 2015;100:e446–e449.

37. Yabroff KR, Lamont EB, Mariotto A et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 2008;100:630–641.

38. Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. J Clin Oncol 2008;26: 4027–4034.

39. Geskus RB. Cause-specific cumulative incidence estimation and the Fine and Gray model under both left truncation and right censoring. Biometrics 2011;67:39–49.

40. Brenner H, Hakulinen T. Period estimates of cancer patient survival are more up-to-date than complete estimates even at comparable levels of precision. J Clin Epidemiol 2006;59:570–575.

41. Bang H, Tsiatis A. Estimating medical costs with censored data. Biometrika 2000;87:329–343.

42. Leblond V, Johnson S, Chevret S et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. J Clin Oncol 2013; 31:301–307.

43. Dimopoulos MA, Panayiotidis P, Moulopoulos LA et al. Waldenström's macroglobulinemia: Clinical features, complications, and management. J Clin Oncol 2000;18:214–226.

44. García-Sanz R, Montoto S, Torrequebrada A et al. Waldenström macroglobulinaemia: Presenting features and outcome in a series with 217 cases. Br J Haematol 2001;115:575–582.

45. Facon T, Brouillard M, Duhamel A et al. Prognostic factors in Waldenström's macroglobulinemia: A report of 167 cases. J Clin Oncol 1993;11: 1553–1558.

46. Ghobrial IM, Fonseca R, Gertz MA et al. Prognostic model for disease-specific and overall mortality in newly diagnosed symptomatic patients with Waldenstrom macroglobulinaemia. Br J Haematol 2006;133:158–164.

47. Morel P, Monconduit M, Jacomy D et al. Prognostic factors in Waldenström macroglobulinemia: a report on 232 patients with the description of a new scoring system and its validation on 253 other patients. Blood 2000;96:852–858.

48. Byrd JC, White CA, Link B et al. Rituximab therapy in Waldenstrom's macroglobulinemia: Preliminary evidence of clinical activity. Ann Oncol 1999;10:1525–1527.

49. Treon SP, Agus TB, Link B et al. CD20-directed antibody-mediated immunotherapy induces responses and facilitates hematologic recovery in patients with Waldenstrom's macroglobulinemia. J Immunother (1991) 2001;24:272–279.

50. Treon SP, Emmanouilides C, Kimby E et al. Extended rituximab therapy in Waldenström's macroglobulinemia. Ann Oncol 2005;16:132–138.

51. Buske C, Hoster E, Dreyling M et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: Results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23:153–161.

52. Treon SP, Branagan AR, Hunter Z et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. Ann Oncol 2004;15:1481–1483.

53. Treon SP, Branagan AR, Ioakimidis L et al. Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. Blood 2009;113: 3673–3678.

54. Treon SP, Gertz MA, Dimopoulos M et al. Update on treatment recommendations from the Third International Workshop on Waldenstrom's macroglobulinemia. Blood 2006;107:3442–3446.

55. Chen CI, Kouroukis CT, White D et al. Bortezomib is active in patients with untreated or relapsed Waldenstrom's macroglobulinemia: A phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1570–1575.

56. Treon SP, Tripsas CK, Meid K et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. Blood 2014; 124:503–510.

57. Schnipper LE, Davidson NE, Wollins DS et al. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33: 2563–2577.

58. Saret CJ, Winn AN, Shah G et al. Value of innovation in hematologic malignancies: A systematic review of published cost-effectiveness analyses. Blood 2015;125:1866–1869.

59. Chhatwal J, Mathisen M, Kantarjian H. Are high drug prices for hematologic malignancies justified? A critical analysis. Cancer 2015;121:3372–3379.

60. Olszewski AJ, Falah J, Castillo JJ. Survival claims from observational data on cancer therapy. J Clin Oncol 2016;34:1425–1427.

61. Hershman DL, Wright JD. Comparative effectiveness research in oncology methodology: Observational data. J Clin Oncol 2012;30:4215–4222.

62. Hoel DG, Ron E, Carter R et al. Influence of death certificate errors on cancer mortality trends. J Natl Cancer Inst 1993;85:1063–1068.

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