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Comparative outcomes of immunochemotherapy regimens in Waldenström macroglobulinaemia

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Summary

Comparative data on immunochemotherapy regimens for Waldenström macroglobulinaemia/lymphoplasmacytic lymphoma (WM/LPL) are lacking. We analysed overall survival (OS), risk of hospitalizations, transfusions and plasmapheresis in a population-based cohort of patients ≥65 years old initiating WM/LPL therapy in 1999–2013. To minimize bias, we applied a propensity score-based causal inference method. We conducted three analyses of: patients treated with or without rituximab, patients treated with rituximab monotherapy or with combination immunochemotherapy, and regimens based on classic purine analogues or alkylators. Among 1310 patients, 78·5% received rituximab. Patients who received rituximab had significantly better OS [hazard ratio (HR) 0·62, 95% confidence interval (CI) 0·55–0·71] and lower risk of transfusions (risk difference −3·3%, 95% CI −6·3 to −0·3) than those who did not, without a significant difference in hospitalizations or plasmapheresis. We observed no significant difference in OS (HR 0·91, 95% CI 0·79–1·04) between rituximab monotherapy and combination immunochemotherapy, but toxicity outcomes were lower with rituximab alone. Neither survival (HR 1·10, 95%CI 0·92–1·32) nor toxicity outcomes differed significantly between regimens based on purine analogues or alkylators. The survival advantage strongly supports rituximab as part of upfront therapy for WM/LPL, whereas regimens with either purine analogues or alkylating agents result in similar outcomes.

Keywords: lymphoplasmacytic lymphoma, outcomes research, rituximab, Surveillance, Epidemiology, and End Results-Medicare, Waldenström macroglobulinaemia.

Waldenström macroglobulinaemia (WM) is a rare lymphoproliferative disorder with an incidence of 0·3 per 100 000 person-years, and median age at diagnosis of 70 years (Castillo *et al*, 2015; Gertz, 2017). Its underlying pathology involves a lymphoplasmacytic lymphoma (LPL) infiltrating the bone marrow, spleen and lymph nodes. WM is unique because many of its clinical features are related to the circulating IgM paraprotein, which may cause hyperviscosity, neuropathy, amyloidosis, cryoglobulinaemia or autoimmune haemolytic anaemia (AIHA) (Treon, 2015). Despite these exceptional features, systemic therapy in WM/LPL is extrapolated from other B-cell lymphomas, with few dedicated randomized trials published to date (Leblond *et al*, 2001, 2013; Buske *et al*, 2009). Recent guidelines recommend upfront rituximab in combination with alkylators, purine analogues, proteasome inhibitors, or as monotherapy, largely on the basis of phase 2 experience (Buske *et al*, 2013; Owen *et al*, 2014; Leblond *et al*, 2016). Survival benefits of adding rituximab to chemotherapy, while proven in other lymphomas, have not been quantified in WM, as studies were either single-arm (Dimopoulos *et al*, 2002; Gertz *et al*, 2004; Treon *et al*, 2005) or underpowered (Buske *et al*, 2009). The risk of potentially dangerous IgM flare after rituximab complicates its role as monotherapy or combination immunochemotherapy (Ghobrial *et al*, 2004; Treon *et al*, 2004). No clinical trials addressed the relevant questions, as interest has shifted to the study of novel approaches involving proteasome inhibitors and B-cell receptor inhibitors (Treon *et al*, 2009, 2015; Gavriatopoulou *et al*, 2017; Hunter *et al*, 2017).

Large-scale observational studies that rely on causal inference methods seek to simulate randomized experiments, and thus fill in gaps in knowledge gathered from clinical research

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(Booth & Tannock, 2014; Visvanathan *et al*, 2017). Although they lack the benefit of actual randomization and require scrutiny because of potential bias, they enable assessment of populations under-represented in clinical trials. This is particularly important for older patients, whose therapeutic risk/benefit ratios differ from younger and healthier trial participants. The pre-requisites for a reliable causal inference study include identification of a population eligible to receive either of the compared treatments, and comprehensive data on relevant confounders to help minimize indication bias.

Our objective was to compare overall survival (OS) and rates of specific toxicities (hospitalizations, transfusions and need for plasmapheresis) among older patients with WM/LPL treated with upfront immunochemotherapy. We previously reported that since 1999, treatment in the United States (US) has shifted from cytotoxic chemotherapy to rituximab monotherapy (for about 50% of older patients) or combination immunochemotherapy (for an additional 30%) (Olszewski *et al*, 2016). Here we perform three analyses to compare the effects of upfront systemic regimens in WM/LPL. First, we compared regimens with or without rituximab. Second, we compared rituximab monotherapy with combination immunochemotherapy. Third, we compared regimens based on purine analogues with those based on alkylating agents (adjusting for rituximab use).

Methods

Data source and study population

This project was approved by the Institutional Review Board at Rhode Island Hospital, and used data from the linked Surveillance, Epidemiology, and End Results-Medicare (SEER-Medicare) database curated by the National Cancer Institute (https://healthcaredelivery.cancer.gov/seermedicare/). The dataset includes records from 18 cancer registries covering approximately 28% of the US population, linked to billing claims for patients enrolled in the Medicare program (Warren *et al*, 2002). Medicare is the provider of health insurance to nearly all US citizens and residents aged 65 years or older. To be included in the study, patients had to have complete Medicare claims available from 12 months before WM/LPL diagnosis onward, and not participate in a managed-care plan (otherwise their records would be incomplete). We selected histologically confirmed WM/LPL using the 2008 World Health Organization histology codes (9671/3 and 9761/3), and year of diagnosis 1994–2011 (Fig 1). We excluded subjects with no record of first-line chemotherapy in 1999–2013, those who had a concurrent aggressive lymphoma, or who received non-qualifying regimens (including any bendamustine or bortezomib).

Variables and endpoints

We identified chemotherapy administration in Medicare claims, using billing codes for specific drugs of interest: rituximab, alkylating agents (cyclophosphamide, chlorambucil), purine analogues (fludarabine, pentostatin, cladribine) and other agents commonly used for WM (vincristine, etoposide, doxorubicin, mitoxantrone), as previously described (Olszewski *et al*, 2015, 2016). Regimens were classified according to drugs administered within the first 60 days of therapy. Alkylator-based regimens included cyclophosphamide in combination with vincristine and/or doxorubicin. The combination of fludarabine and cyclophosphamide was included in the purine analogue-based group (Table SI). Doses and detailed schedules of regimens were not available.

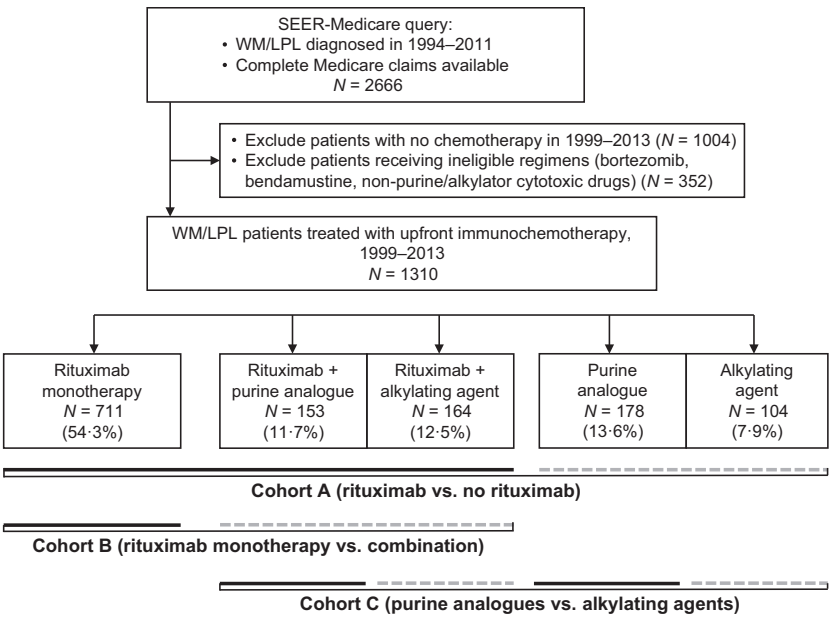

Fig 1. Cohort selection from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database; subgroups used for three comparative analyses are indicated (comparative arms are marked with a solid black and dashed grey lines). WM/LPL: Waldenström macroglobulinaemia/lymphoplasmacytic lymphoma.

Medicare files do not contain direct clinical records, radiology reports or laboratory values of serum IgM, blood counts and β2-microglobulin. Therefore, for adjustment, we identified claims-based proxies for relevant covariates. As proxies of WM severity, we used indicators of anaemia, AIHA, transfusion, neuropathy and plasmapheresis within 6 months before chemotherapy initiation (Table SII). We previously found these variables to provide OS stratification similar to the clinical International Prognostic Scoring System in WM (Morel *et al*, 2009; Olszewski *et al*, 2016). Sociodemographic indicators included sex, non-white race, primary reason for Medicare entitlement (age or disability), Medicaid co-insurance (an indicator of poverty), marital status and metropolitan residence. Baseline medical status was approximated by the Klabunde-Charlson Comorbidity Index, which consists of 18 weighted comorbid conditions that increase mortality (Klabunde *et al*, 2000), Davidoff's disability indicator, which is a claims-based validated correlate of patients' self-reported performance status (Davidoff *et al*, 2013), and a history of hospitalization. Furthermore, we included variables empirically associated with selection of immunochemotherapy regimens: a visit with a neurologist, dermatologist, performance of bronchoscopy or echocardiogram. We additionally included year of chemotherapy initiation among variables to balance, as it was associated with treatment selection, and probably with improved supportive care and second-line therapy options, thus influencing survival and toxicity.

The main efficacy endpoint was OS, calculated from the first date of chemotherapy until death or administrative censoring on 31 December 2013. Additional toxicity endpoints included occurrence of a hospitalization, transfusion, or plasmapheresis within 3 months after starting chemotherapy. These were ascertained from specific admission and procedure codes in inpatient and outpatient Medicare files.

Statistical analysis

Distribution of baseline variables was compared using the chi-squared or Kruskal–Wallis tests. For analyses, we defined three overlapping subcohorts, as indicated in Fig 1: (A) patients treated with *versus* without rituximab, (B) patients treated with rituximab monotherapy *versus* combination immunochemotherapy and (C) patients treated with purine analogue-based *versus* alkylator-based regimens. To estimate the causal effects of various treatment regimens, we applied the multiple-imputation using two subclassification splines (MITSS) method, as previously described (Dore *et al*, 2013; Gutman & Rubin, 2013). MITSS is a propensity score-based method which explicitly computes potential outcomes for every patient with either treatment under study using multiple imputation. First, a propensity score for receiving either treatment was estimated in a logistic model that included all available confounders. The assumption of positivity (i.e. non-zero probability of receiving either treatment) was enforced by removing observations with non-overlapping propensity score values. Adequate reduction of indication bias was confirmed using the method by Imbens and Rubin (2015). Briefly, the cohort was divided into six blocks. For each variable, a *t*-statistic was calculated for the null hypothesis that the block-adjusted average standardized difference in covariate means was zero. An adequate balance was declared if the *t*-statistics for all variables were <1.

Once the comparative arms were adequately balanced with regard to all patient- and disease-related covariates, outcome models were deployed in the adjusted population. We analysed OS using a Bayesian Weibull mixture cure model, which provided good fit to the data by adequately capturing long-term survivors (non-mixture log-normal and Weibull models were found to provide worse fit; Ibrahim *et al*, 2001). Model convergence was evaluated using the Gelman-Rubin statistic (Gelman & Rubin, 1996). We then sampled from the posterior predictive distribution of survival times, and used these samples to impute censored observations and potential outcomes for each individual, repeating the imputation process 50 times. Predicted survival results were expressed as adjusted survival curves (truncated to 10 years of follow-up), and as paired hazard ratios (HR), with 95% confidence intervals (CI). Binary toxicity outcomes were analysed using Bayesian logistic models. We used the sampled posterior predictive distribution for each individual to impute potential outcomes in 50 imputed datasets, and expressed results as absolute risk difference with 95% CI. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), STATA 14/MP (StataCorp LP, College Station, TX, USA), and R version 3.2.5 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org) with RUNJAGS package (Denwood, 2016).

Results

Among 1310 patients who initiated first-line chemotherapy for WM/LPL between 1999 and 2013, 78·5% received rituximab alone or in combination with chemotherapy (Table I). Median age in the entire cohort was 78 years (range, 65–98), and 57·1% of patients were male. Patients receiving rituximab monotherapy were, on average, older, not married and more often had neuropathy or AIHA. The differences in comorbidities, performance status, pre-treatment rates of plasmapheresis, transfusions or anaemia were not statistically significant. Median time from diagnosis to treatment was 2 months (range, 0–166), and 75·3% of patients started therapy within 1 year from diagnosis. Patients treated with rituximab/chemotherapy combinations had a shorter time to treatment (median 1 month, range 0–126), but there was no significant difference between groups receiving rituximab monotherapy or chemotherapy without rituximab ($P = 0·08$). Most patients who did not receive upfront rituximab were treated before 2004, but even in 2008–13 up to 8·8% did not receive the monoclonal antibody (Figure S1).

Table I. Characteristics of patients, stratified by chemotherapy regimen.

	Rituximab monotherapy		Rituximab with chemotherapy		Chemotherapy without rituximab		
	N	%	*N*	%	*N*	%	*P*
Number of patients	711		317		282		
Age, median (IQR)	79 years (75–84)		77 years (72–81·5)		77 years (73–81·5)		<0·001
Sex							
Women	325	45·7	121	38·2	116	41·1	0·06
Men	386	54·3	196	61·8	166	58·9	
Race							
White	654	92·0	287	90·5	263	93·3	0·47
Non-white	57	8·0	30	9·5	19	6·7	
Medicaid co-insurance							
No	659	92·7	296	93·4	263	93·3	0·77
Yes	52	7·3	21	6·6	19	6·7	
Marital status							
Married	381	53·6	195	61·5	179	63·5	0·005
Other	330	46·4	122	38·5	103	36·5	
Area of residence							
Metropolitan	630	88·6	273	86·1	232	82·3	0·029
Urban or rural	81	11·4	44	13·9	50	17·7	
Prior malignancy							
No	494	69·5	243	76·7	207	73·4	0·052
Yes	217	30·5	74	23·3	75	26·6	
Number of comorbidities*							
0	373	52·5	173	54·6	163	57·8	0·41
1	156	21·9	73	23·0	62	22·0	
≥2	182	25·6	71	22·4	57	20·2	
Poor performance status*	58	8·2	16	5·0	13	4·6	0·06
Indicators of WM severity†							
Neuropathy	58	8·2	18	5·7	<11	<3·0‡	0·007
Plasmapheresis	25	3·5	17	5·4	18	6·4	0·11
Transfusion	139	19·5	61	19·2	43	15·2	0·27
Anaemia	441	62·0	198	62·5	166	58·9	0·60
AIHA	27	3·8	<11	<2·0‡	<11	<2·0‡	0·040
Hospitalization	239	33·6	138	43·5	105	37·2	0·010
Time from diagnosis to treatment							
≥12 months	198	27·8	52	16·4	74	26·2	<0·001
<12 months	513	72·2	265	83·6	208	73·8	
Histology code							
WM	403	56·7	170	53·6	175	62·1	0·11
LPL	308	43·3	147	46·4	107	37·9	
Year of treatment							
1999/03	120	16·9	69	21·8	168	59·6	<0·001
2004/07	271	38·1	121	38·2	71	25·2	
2008/13	320	45·0	127	40·1	43	15·2	

AIHA, autoimmune haemolytic anaemia; IQR, interquartile range; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinaemia.
*Based on Medicare claims within 12 months prior to start of chemotherapy.
†Based on Medicare claims within 6 months prior to start of chemotherapy.
‡Exact cell value suppressed according to the SEER-Medicare policy.

With a median follow-up of 5 years for censored patients, unadjusted 5-year OS was 49·1% (95% CI, 46·2–52·0) and median OS was 4·9 years (95% CI, 4·4–5·3). Five-year OS was 42·0% for patients treated without rituximab, 50·6% for rituximab monotherapy and 51·9% for combination immunochemotherapy (Figure S2).

Regimens with or without rituximab

The comparative analysis of regimens with *versus* without rituximab (Cohort A) included 1301 patients with overlapping propensity score values. All available patient- and disease-related covariates listed in Table I were adequately

balanced in the first stage of the analysis, assuring equal distribution of factors like comorbidities and performance status between the treatment arms (Fig 2A). In adjusted outcome models, OS was significantly improved for patients who received rituximab (Fig 2B), with a paired HR of 0·62 (95% CI, 0·55–0·71). Patients treated with rituximab had also a significantly lower rate of transfusions (risk difference, −3·3%, 95% CI, −6·3 to −0·3), but no significant difference in hospitalizations or need for plasmapheresis within 3 months of starting therapy (Table II).

Rituximab monotherapy versus *combination immunochemotherapy*

In the second analysis, we compared 1028 patients who received upfront rituximab alone or a multi-agent immunochemotherapy (Cohort B). Treatment arms were adequately balanced after the propensity score adjustment (Fig 3A). The adjusted difference in survival between groups was not statistically significant, with a HR of 0·91 (95% CI, 0·79–1·04, Fig 3B). Proportions of patients with any of the toxicity endpoints were significantly lower in the group treated with single-agent rituximab (Table II).

Purine analogue- versus *alkylator-based regimens*

The third analysis included 599 patients treated with either purine analogue- or alkylator-based chemotherapy regimens (Cohort C). Purine-based regimens were more common when histology was designated as WM, while alkylators were frequently used for nodal LPL. The use of purine analogues relative to alkylators decreased over time, with 71% of patients receiving purine analogues in 1999/2003 and 35% in 2008/13. Rituximab use was balanced between the arms as an additional covariate in the propensity score (Fig 4A). There was no evidence of a significant difference in OS between the arms, with a HR of 1·10 (95% CI, 0·92–1·32, Fig 4B). Moreover, we found no statistically significant difference in transfusions, hospitalisations, or plasmapheresis between the study arms.

Discussion

In this observational study using a population-based cohort of older patients with WM/LPL, we have demonstrated improved OS after rituximab-containing therapy, with no increase in hospitalizations, transfusions or need for plasmapheresis during the first 3 months of treatment. We also found decreased toxicity and similar survival outcomes with rituximab alone compared with multi-agent immunochemotherapy. Finally, there was no significant difference in outcomes between regimens based on classical purine analogues (mainly fludarabine) or alkylating agents (mainly cyclophosphamide).

Our results fill an important gap in the knowledge regarding optimal frontline treatment of WM/LPL. Rituximab-based regimens are now universally endorsed on the basis of high response rates (85–95%) derived from single-arm studies and one randomized trial (Gertz *et al*, 2004; Treon *et al*, 2005; Dimopoulos *et al*, 2007; Buske *et al*, 2009; Herth *et al*, 2015). In that trial, 64 patients received cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy with or without rituximab. The rituximab-containing arm achieved a higher response rate (94% vs. 67%) and time

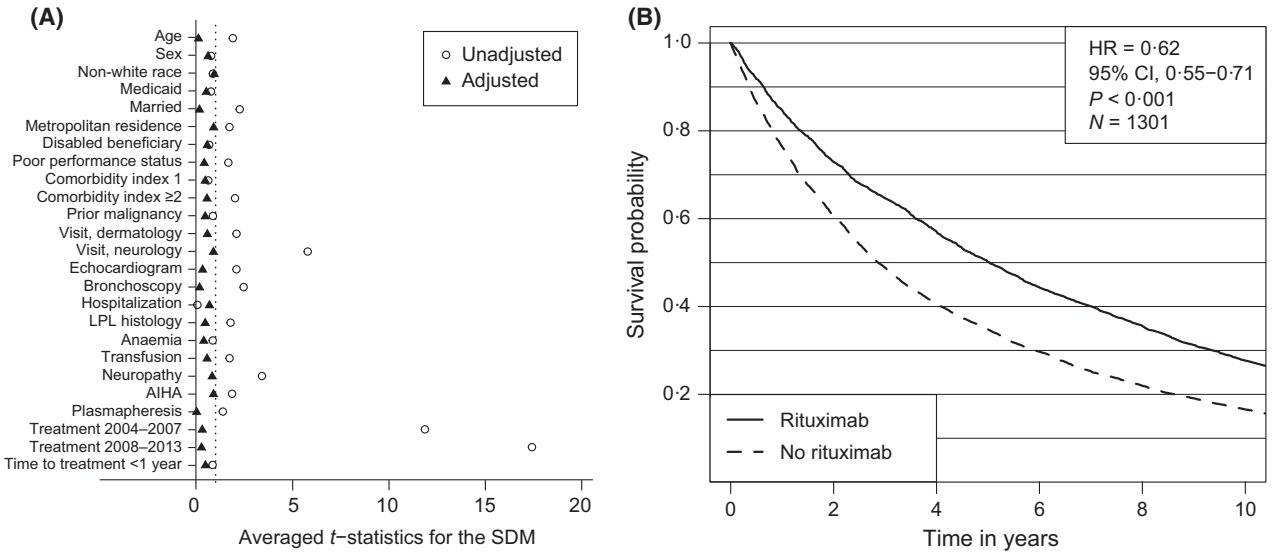

Fig 2. Results of comparative analysis: rituximab ***versus*** no rituximab: (A) balance of confounders, expressed as averaged *t*-statistics for standardized differences in covariate means (SDM); *t*-statistic <1 indicates adequate balance; (B) adjusted Kaplan–Meier plot of overall survival. AIHA, autoimmune haemolytic anaemia; HR, hazard ratio; lymphoplasmacytic lymphoma; 95% CI, 95% confidence interval.

Table II. Toxicity outcomes in the comparative analyses.

Cohort/Endpoint	Treatment arm	% With outcome	Risk difference		
			%	95% confidence interval	*P*
Rituximab *versus* no rituximab					
Transfusion	Rituximab	19·5	−3·3	−6·3 to −0·3	0·022
	No rituximab	22·8			
Plasmapheresis	Rituximab	4·8	0·8	−0·7 to 2·2	0·27
	No rituximab	4·0			
Hospitalization	Rituximab	29·0	−2·8	−6·3 to 0·8	0·10
	No rituximab	31·8			
Rituximab monotherapy *versus* combination					
Transfusion	Monotherapy	17·3	−9·4	−12·9 to −5·9	<0·001
	Combination	26·7			
Plasmapheresis	Monotherapy	2·8	−3·3	−5·0 to −1·6	<0·001
	Combination	6·1			
Hospitalization	Monotherapy	24·7	−13·5	−17·6 to −9·4	<0·001
	Combination	38·2			
Purine analogue *versus* alkylator-based					
Transfusion	Purine analogue	25·7	3·4	−1·3 to 8·2	0·13
	Alkylator	22·3			
Plasmapheresis	Purine analogue	7·1	0·8	−1·9 to 3·5	0·56
	Alkylator	6·3			
Hospitalization	Purine analogue	38·9	5·1	−0·6 to 10·8	0·06
	Alkylator	33·8			

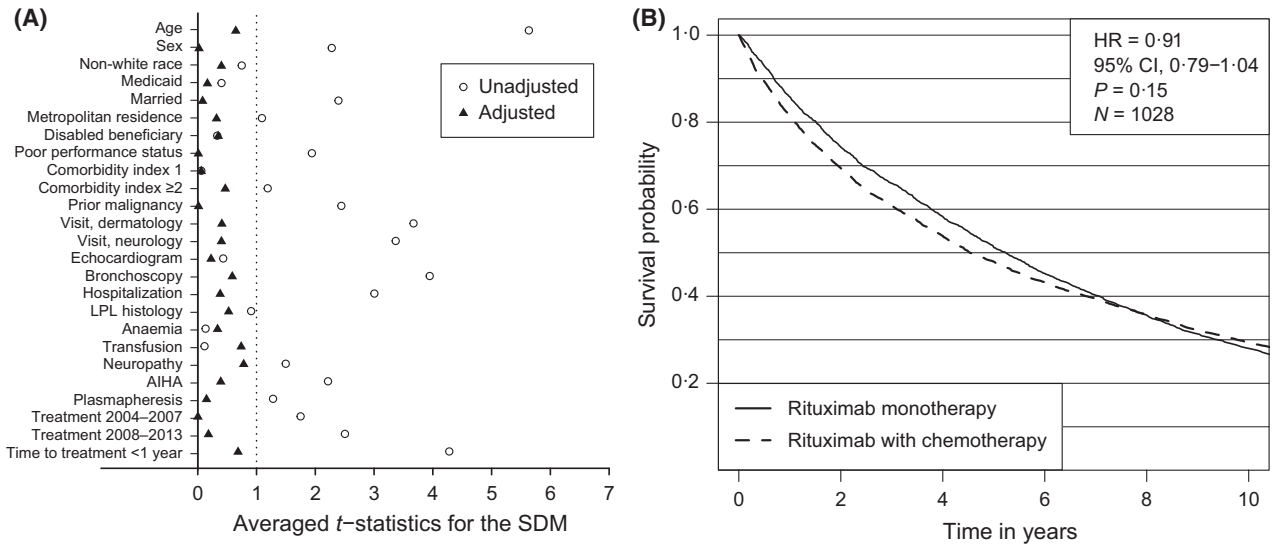

Fig 3. Results of comparative analysis: rituximab monotherapy ***versus*** combination immunochemotherapy: (A) balance of confounders, expressed as averaged *t*-statistics for standardized differences in covariate means (SDM); *t*-statistic <1 indicates adequate balance; (B) adjusted Kaplan–Meier plot of overall survival. AIHA, autoimmune haemolytic anaemia; HR, hazard ratio; lymphoplasmacytic lymphoma; 95% CI, 95% confidence interval.

to treatment failure (63 vs. 22 months), but without a significant difference in OS ($P = 0{\cdot}11$) (Buske *et al*, 2009). Our study indicates that up to 9% of older US patients treated in 2009–13 did not receive the anti-CD20 antibody. Our analytic approach assured balance of factors important for treatment selection, such as comorbidities or performance status indicators. It also accounted for the significant temporal trends in the use of WM/LPL regimens, recognising the increasing use of rituximab monotherapy, and declining use of purine analogues. Although medical frailty or high serum IgM (which poses a risk of hyperviscosity flare) may preclude clinicians from prescribing rituximab at the outset of therapy, the survival advantage strongly supports delivering rituximab whenever feasible. Furthermore, it appears that

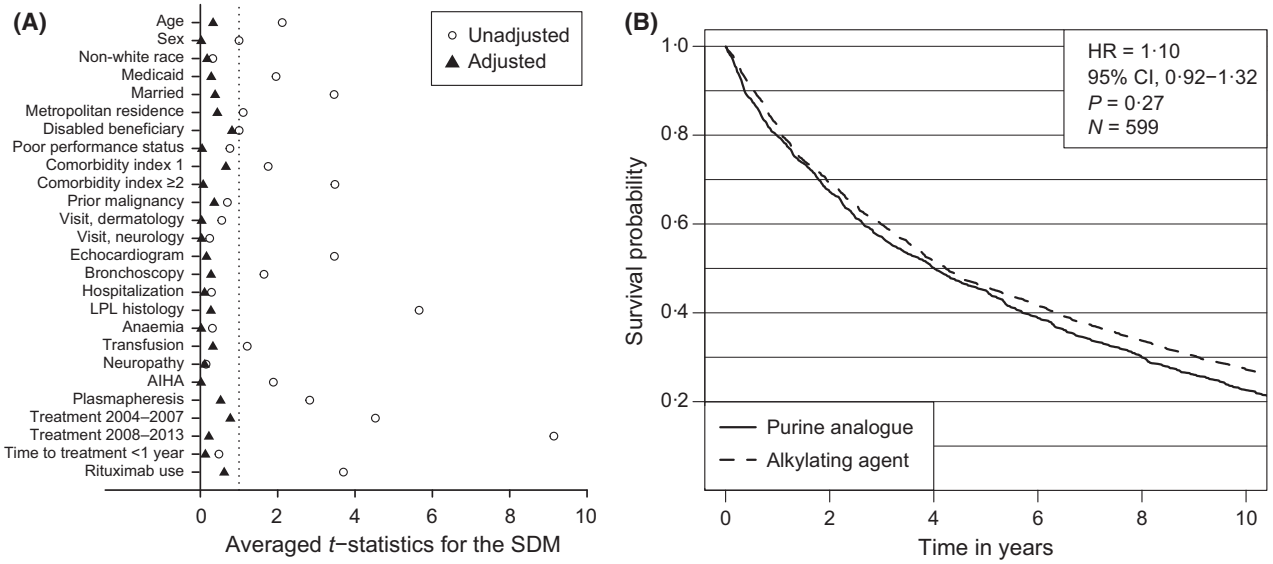

Fig 4. Results of comparative analysis: purine analogue- ***versus*** alkylator-based regimens: (A) balance of confounders, expressed as averaged *t*-statistics for standardized differences in covariate means (SDM); *t*-statistic <1 indicates adequate balance; (B) adjusted Kaplan–Meier plot of overall survival. AIHA, autoimmune haemolytic anaemia; HR, hazard ratio; lymphoplasmacytic lymphoma; 95% CI, 95% confidence interval.

judicious use of rituximab did not lead to more plasmapheresis or hospitalizations in US practice. One caveat is that we cannot rule out additional treatment selection based on pre-treatment IgM levels (not directly recorded in Medicare data), or pre-emptive use of plasmapheresis – even though the overall use of plasmapheresis was low. Therefore, we reiterate here the International Workshop on Waldenström Macroglobulinaemia guideline recommending prophylactic plasmapheresis and/or withholding rituximab whenever baseline IgM level exceeds 40 g/l (Leblond *et al*, 2016).

Our other findings provide further insight into the role of classical cytotoxic agents in WM/LPL. One phase 3 trial conducted in the pre-rituximab era demonstrated a better progression-free survival and OS with fludarabine rather than chlorambucil (Leblond *et al*, 2013). Another randomized phase 2 study reported no OS difference between fludarabine and a cyclophosphamide-based regimen in relapsed/refractory WM (Leblond *et al*, 2001). We observed no significant difference between purine analogue- and alkylator-based regimens in a contemporary setting, with most patients receiving rituximab. Five-year OS in our cohort (49·1%) was lower than in clinical trials (60–70%), reflecting the advanced age of the Medicare population (Leblond *et al*, 2013; Kastritis *et al*, 2015; Gavriatopoulou *et al*, 2017). Currently, an increasing number of patients receive bendamustine – a novel alkylator with efficacy supported by a phase 3 trial in various indolent lymphomas (Rummel *et al*, 2013). The comparative advantage of this therapy, as well as novel approaches using proteasome inhibitors (Treon *et al*, 2014; Gavriatopoulou *et al*, 2017), remains to be evaluated in a population-based setting. Response rates of about 90% achieved with bendamustine or bortezomib suggest a potential advantage over classical chemotherapy. We excluded patients receiving those agents, as they were not used throughout most of the study period. Additionally, the B-cell receptor inhibitor, ibrutinib, received US approval for treatment of WM in 2015 (Treon *et al*, 2015; Hunter *et al*, 2017). With rate of durable responses of 90% in relapsed/refractory WM, its upfront role in comparison with immunochemotherapy remains to be clinically defined (Dimopoulos *et al*, 2017).

Our analysis has a number of limitations, and raises additional questions which could not be addressed using the SEER-Medicare data: the role of rituximab maintenance, specific drug combinations or schedules (which were probably quite heterogeneous in our community-based analysis), effects on health-related quality of life, progression-free survival or specific toxicities. The rates of secondary myelodysplasia or histological transformation would be of interest, but these were not recorded consistently enough in the available data. Although the specific histology designation (WM or LPL) was associated with treatment selection, the consistency of this designation in cancer registry data was uncertain, and we did not analyse treatment effects stratified by histology. The study used a population of older patients, and cannot be generalized to younger individuals with WM/LPL. There may be significant differences between various regimens grouped together in the current analysis (for example, single-agent chlorambucil, CHOP, and dexamethasone-cyclophosphamide-rituximab were all classified as 'alkylator-based'), which would violate the assumption of effect homogeneity. Moreover, lack of direct clinical records limits our confidence about potential unobserved confounding, even though our claims-derived indicators of disease severity can effectively stratify survival in WM/LPL (Olszewski *et al*, 2016). The SEER-Medicare data could not distinguish certain

contraindications to specific drugs, like allergies, varying degrees of renal or liver dysfunction, or baseline IgM levels, although we adjusted the analysis for claims-derived indicators of anaemia, neuropathy and severe hyperviscosity. Residual confounding might explain the minor early survival advantage of rituximab monotherapy over chemoimmunotherapy combinations, as multi-agent regimens may have been offered to patients with more advanced or aggressive disease. Similarly, we cannot rule out residual bias related to clinically premature initiation of rituximab monotherapy in asymptomatic patients, although we did not observe a shorter time from diagnosis to therapy or a lower prevalence of disease severity indicators in the monotherapy group. Although a formal sensitivity analysis would be needed to quantify residual confounding, such bias is unlikely to abrogate the evident large OS advantage of rituximab.

In conclusion, rituximab offers a significant survival benefit as a component of first-line therapy for WM/LPL. Rituximab monotherapy, considering its lower toxicity and similar survival compared with combination regimens, remains an attractive option for older patients who do not have a strong indication for cytotoxic chemotherapy, although the risk of IgM flare should be kept in mind. Further research can establish whether novel approaches using bendamustine, bortezomib or ibrutinib compare favourably, in terms of efficacy, toxicity and cost, with currently available options when deployed throughout the community. Our analysis illustrates that cautiously conducted large-scale observational studies may provide disease-specific evidence in rare cancers like WM, when clinical research is too expensive, protracted or logistically challenging.

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Authors contributions

Concept and Design: Olszewski, Gutman, Treon, Castillo. Acquisition and Analysis of Data: Olszewski, Chen, Gutman. Drafting of the manuscript: Olszewski, Gutman, Treon, Castillo. Final approval: Olszewski, Chen, Gutman, Treon, Castillo.

Conflict of interest

AJO reports research funding (for the institution) from Genentech, TG Therapeutics, and Incyte. SPT reports honoraria from Janssen Pharmaceuticals, consulting or advisory roles and research funding from Janssen Pharmaceuticals and Pharmacyclics. JJC reports consulting or advisory roles for Otsuka Pharmaceuticals, Biogen, and Pharmacyclics, honoraria from Celgene and Janssen, and research funding from Millennium, Pharmacyclics, Gilead Sciences, and Abbvie. Other authors have declared no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. Proportion of patients with Waldenström macroglobulinemia/lymphoplasmacytic lymphoma included in this study, receiving various immunochemotherapy regimens, stratified by year of starting chemotherapy.

Fig S2. Unadjusted overall survival of patients with Waldenström macroglobulinemia/lymphoplasmacytic lymphoma included in the study, stratified by type of upfront chemotherapy regimen.

Table SI. Chemotherapy regimens administered to Medicare beneficiaries with Waldenström macroglobulinemia/lymphoplasmacytic lymphoma included in the study.

Table SII. Ascertainment of claims-based covariates.

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