HEMATOLOGIC MALIGNANCIES

Treatment and Survival Outcomes of Waldenstrom Macroglobulinemia in Latin American Patients: A Multinational Retrospective Cohort Study

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abstract

PURPOSE
Waldenstrom Macroglobulinemia (WM) is a rare lymphoma with distinct clinical features, and data from Latin American patients are lacking. Therefore, we aim to investigate the clinical, therapy, and outcome patterns of WM in Latin America.

METHODS
We retrospectively analyzed patients with WM diagnosed between 1991 and 2019 from 24 centers in seven Latin American countries. The study outcomes were overall survival (OS) and progression-free survival (PFS).

RESULTS
We identified 159 cases (median age 67 years, male 62%). Most patients (95%) were symptomatic at diagnosis. The International Prognostic Scoring System for WM (IPSSWM) at diagnosis was available in 141 (89%) patients (high-risk 40%, intermediate-risk 37%, and low-risk 23%). Twenty-seven (17%) patients were tested for MYD88L265P, with 89% (n = 24 of 27) carrying the mutation. First-line and second-line therapies were administered to 142 (89%) and 53 (33%) patients, respectively. Chemoimmunotherapy was the most commonly used first-line (66%) and second-line (45%) approach; only 18 (11%) patients received ibrutinib. With a median follow-up of 69 months, the 5-year OS rate was 81%. In treated patients, the 5-year OS and PFS rates were 78% and 59%, respectively. High-risk IPSSWM at treatment initiation was an independent risk factor for OS (adjusted hazard ratio: 4.73, 95% CI, 1.67 to 13.41, P = .003) and PFS (adjusted hazard ratio: 2.43, 95% CI, 1.31 to 4.50, P = .005).

CONCLUSION
In Latin America, the management of WM is heterogeneous, with limited access to molecular testing and novel agents. However, outcomes were similar to those reported internationally. We validated the IPSSWM score as a prognostic factor for OS and PFS. There is an unmet need to improve access to recommended diagnostic approaches and therapies in Latin America.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoma characterized by a monoclonal immunoglobulin M (IgM) paraprotein in the serum and bone marrow infiltration by malignant lymphoplasmacytic cells.1 WM is a rare disease with an estimated incidence of 0.34-0.73 among males and 0.17-0.42 among females per 100,000 persons per year in the United States.2 The incidence of WM in Latin America is unknown. Clinically, WM may present with constitutional symptoms (ie, fever, night sweats, and unintentional weight loss), cytopenias, lymphadenopathy, organomegaly, neuropathy, hemolytic anemia, and hyperviscosity. Consensus guidelines recommend treatment initiation only in symptomatic patients.3,4

The most frequent cytogenetic alteration in WM is the partial loss of the long arm of chromosome 6 (30%-54%), which is associated with a worse prognosis.5 The introduction of whole-genome and next-generation sequencing allowed the detection of somatic activating mutations in the MYD88 and CXCR4 genes, which can be detected in approximately 90% and 40% of WM cases, respectively.6 Several studies have reported the impact of these mutations in the prognosis and therapy responses in WM.7-9
Despite the advent of novel therapeutic strategies, WM remains incurable. A consensus panel has recently updated recommendations for the management of symptomatic WM after the 10th International Workshop for WM. However, the treatment approaches used to manage WM outside of clinical trials are heterogeneous. Because data on WM in Latin America are lacking, two Latin American research groups (Grupo de Estudio Latinoamericano de Linfoproliferativos- GELL and Grupo de Estudio Latinoamericano de Mieloma M´ultiple- GELAMM) conducted a retrospective review of patients with WM from the region to better understand the clinical, therapy, and outcome patterns of Latin American patients with WM.

METHODS

Patients

We conducted an international, multicenter, retrospective cohort study of patients diagnosed with WM in 24 centers from seven Latin American countries between January 1991 and December 2019 (Data Supplement). We reviewed the medical records of individuals age ≥18 years diagnosed using the criteria of the eighth IWWM. The Institutional Review Board of each participating center approved this study.

Clinical Data and Risk Stratification

The demographic and clinical data collected at diagnosis included age, sex, presence of lymphadenopathy, splenomegaly, hepatomegaly, bone marrow infiltration, peripheral neuropathy, and hyperviscosity symptoms (not explained otherwise, epistaxis and headaches). Laboratory data included complete blood cell count, serum creatinine, serum β2 microglobulin, serum albumin, serum lactate dehydrogenase, serum ferritin, IgM, IgG, IgA, and the presence of a monoclonal protein in serum protein electrophoresis and immunofixation (SPEP/IFX). When available, results from cytogenetic and mutational analyses for MYD88 and CXCR4 mutations were collected. The International Prognostic Scoring System for WM (IPSSWM) was used for risk stratification. We also categorized patients according to the type of treating institution (ie, public v private hospitals).

Therapy Approaches and Response Criteria

The therapy approaches used during the first or subsequent lines were divided as follows: monotherapy (ie, rituximab, chlorambucil, fludarabine, cyclophosphamide, ibrutinib, and thalidomide), chemoimmunotherapy (rituximab plus chemotherapy), and others. The overall response rate (ORR) was defined as the sum of minor response (≥25% but <50% reduction in serum IgM levels), partial response (PR, ≥50% but <90% reduction), very good partial response (VGPR, ≥90% reduction or normalization of serum IgM with a persistent monoclonal spike in SPEP/IFX), and complete response (normalization of serum IgM and SPEP/IFX and absence of bone marrow and extramedullary disease). The major response rate (MRR) was defined as the sum of PR, VGPR, and complete response.

Outcomes and Statistical Analysis

We used descriptive statistics to summarize all variables. The primary study outcome was overall survival (OS), defined as the time between diagnosis and death from any cause, loss to follow-up, or end of the study (November 2020). The secondary outcome was progression-free survival (PFS) after frontline therapy, defined as the time from the date of treatment initiation until first relapse, loss to follow-up, death from any cause, or end of the study, whichever occurs first. Differences between groups were identified using the chi-square or Fisher’s exact test, as appropriate.

Survival probabilities were estimated using the Kaplan-Meier method, and the difference between groups was computed using the log-rank test. We estimated proportional hazard ratios (HRs) for OS and PFS with a 95% CI using univariate and multivariate Cox proportional hazard regression models. Two models were constructed to assess the confounding effect of different predictors in the primary and secondary outcomes. The first model included the IPSSWM score at treatment initiation and rituximab use.
The second model included the previous variables plus sex and the type of treating institution. In the regression analysis, patients with low-risk and intermediate-risk IPSSWM scores were grouped into a low-intermediate risk category given the low count in the low-risk group. The variables in our models were selected on the basis of priori assumptions of their public health and clinical relevance regarding survival outcomes rather than their significance in the univariate analysis.\textsuperscript{12} The hazard assumption was tested by plotting Schoenfeld residuals. All feasible two-way interactions between the included variables in both OS and PFS models were assessed in Cox regression analyses. We did not find any significant interaction. Sensitivity analyses were performed in patients with a follow-up of at least 5 years (n = 105). The 95% CI of the response rates was estimated using the Clopper-Pearson method. Outcomes with a P value < .05 were considered statistically significant. We used the R software for analysis.

RESULTS

Demographic and Clinical Features
A total of 159 patients with WM were identified. Table 1 summarizes the demographic and clinical features of the patients. At diagnosis, the median age was 67 (range, 24-89) years with a male predominance (62%). Fifty-two percent of the patients were treated in private centers, and 48% in public centers. Most patients (n = 151, 95%) were symptomatic at diagnosis with symptomatic adenopathy (28%), symptomatic splenomegaly (25%), and hyperviscosity symptoms (20%) as the most common symptoms. The IPSSWM score was available in 141 patients, of whom 40%, 37%, and 23% were classified as high-risk, intermediate-risk, and low-risk disease, respectively. Most patients had anemia (hemoglobin \(\leq 11.5 \) g/dL; 71%) at the time of diagnosis. Serum IgM levels \(\leq 7 \) g/dL and bone marrow involvement of \(\geq 50\% \) were seen in 22% of patients each.

Overall, molecular testing was performed in 21% (n = 23 of 159) of the patients (27% in private and 16% in public centers, \( P = .146 \)). \textit{MYD88}\textsuperscript{265P} testing was performed in 17% (n = 27 of 159), del17p in 6% (n = 9 of 159), and \textit{CXCR4} in 1% (n = 1 of 159). For those in whom genetic testing was performed, 89% (n = 24 of 27) had \textit{MYD88}\textsuperscript{265P} mutation, none had del17p mutation, and the only patient tested for \textit{CXCR4} mutation had \textit{MYD88}\textsuperscript{265P} and \textit{CXCR4} mutations (Data Supplement).

Therapy Approaches and Responses

Figure 1 shows the therapy patterns during the three lines of therapy.

First-line therapy was administered to 142 (89%) patients. Chemoimmunotherapy (n = 94 of 142, 66%) was the most frequently used first-line therapy, followed by monotherapy (n = 35 of 142, 25%). Combination of dexamethasone, rituximab, and cyclophosphamide (DRC) was the most

### Table 1. Demographic and Clinical Features and Outcomes of Latin American Patients With Waldenstrom Macroglobulinemia

| Characteristic | Overall, No. (%) | Missing (%) |
|---------------|-----------------|------------|
| No. of patients | 159 | — |
| Country |
| Argentina | 55 (35) |
| Peru | 32 (20) |
| Mexico | 28 (18) |
| Chile | 15 (9) |
| Uruguay | 13 (8) |
| Colombia | 10 (6) |
| Brazil | 6 (4) |
| Type of insurance |
| Private | 83 (52) |
| Public | 76 (48) |
| Sex, male | 99 (62) | 0 |
| Period of diagnosis |
| 1991-2000 | 11 (7) |
| 2001-2010 | 39 (24) |
| 2011-2020 | 109 (69) |
| Age at diagnosis, years, median (range) | 67 (24-89) | 0 |
| Age at diagnosis > 65 years | 87 (55) | 0 |
| Symptoms at diagnosis |
| Symptomatic adenopathy | 44 (28) |
| Symptomatic splenomegaly | 40 (25) |
| Hyperviscosity symptoms | 32 (20) |
| B symptoms | 28 (18) |
| Symptomatic hepatomegaly | 20 (13) |
| Peripheral neuropathy | 18 (11) |
| Bleeding | 4 (3) |
| IPSSWM score at diagnosis (n = 141) |
| Low | 32 (23) |
| Intermediate | 52 (37) |
| High | 57 (40) |
| Hemoglobin \(\leq 11.5 \) g/dL (n = 149) | 105 (71) | 6 |
| Platelet count \(\leq 100 \times 10^9/L \) (n = 154) | 27 (18) |
| B2 microglobulin \(> 3 \) mg/L (n = 116) | 74 (64) |
| IgM \(> 7 \) g/dL (n = 147) | 33 (22) |
| Albumin \(< 3.5 \) g/dL (n = 138) | 64 (46) |
| LDH—high (n = 138) | 29 (21) |
| Bone marrow involvement \(\geq 50\% \) (n = 107) | 24 (22) |
| Cancer-directed therapy | 142 (89) | 0 |

Abbreviations: B2, Beta-2; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for WM; LDH, lactate dehydrogenase.
FIG 1. Therapy approaches used during (A) first-line (n = 142), (B) second-line (n = 53), and (C) third-line (n = 6) settings. BCD, bortezomib-cyclophosphamide-dexamethasone; BDR, bortezomib-dexamethasone-rituximab; BR, bendamustine-rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; DRC, dexamethasone, rituximab, and cyclophosphamide; FCR, fludarabine-cyclophosphamide-rituximab; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; VAD, vincristine-doxorubicin-dexamethasone.
frequently used regimen (34%, n = 48 of 142). First-line therapy was heterogeneous among countries. Chemoimmunotherapy was more commonly used in Chile (80%), Uruguay (80%), and Argentina (74%) than Peru (58%) or Mexico (46%). Monotherapy use ranged from 7% in Chile to 40% in Mexico (Data Supplement). Neither patient’s age (P = .63) nor IPSSWM risk score (P = .94) influenced the clinician’s decision on the first-line therapy approach used. However, chemoimmunotherapy was more frequently administered at private institutions (74% vs 58%, P = .03), with an upward trend from 16% in the 1991-2010 period to 83% in the 2011-2020 period (P < .001; Data Supplement). The median time to first-line therapy initiation was 35 days (range 0-15 years). Second-line therapy was administered to 53 patients; chemoimmunotherapy (45%) was the most commonly used approach. Bendamustine plus rituximab (17%) and monotherapy with ibrutinib (15%) were the most frequently used regimens. Six patients received third-line therapy, and one patient received fourth-line therapy. Maintenance rituximab was given to 13 (n = 13 of 137, 10%) patients and only after first-line therapy. Ibrutinib was used in 18 (11%) patients anytime during the disease process (14% in private and 12% in public centers, P = .946). Intrathecal chemotherapy was given to five (n = 5 of 142, 4%) patients. Four patients underwent autologous stem-cell transplantation (ASCT) after failing first-line therapy. All but one received a melphalan-based conditioning regimen and remained disease-free (PFS 24, 48, and 60 months, respectively). The fourth patient did not have enough data to be analyzed.

Table 2 summarizes the clinical features and responses of patients who received therapy. Most patients had an intermediate-risk (41%) or high-risk (43%) IPSSWM score at therapy initiation. The ORR to first-line therapy was 86% (95% CI, 79 to 92), and the MRR was 85% (95% CI, 77 to 91). No differences were seen in ORR (83%, 95% CI, 70 to 93 vs 88%, 95% CI, 79 to 94; P = .62) and MRR (81%, 95% CI, 67 to 91 vs 87%, 95% CI, 77 to 94; P = .56) between patients managed at private versus public centers, respectively. The ORR and MRR in patients who received the first-line chemoimmunotherapy regimen was 86% (n = 107 of 124; 95% CI, 79 to 92) and 84% (n = 105 of 124; 95% CI, 60 to 78), respectively (Data Supplement).

In the subset of patients with MYD88-L265P mutation who received therapy (chemoimmunotherapy n = 15 and ibrutinib n = 5), the ORR, MRR, and VGPR rates were 100%, 95%, and 15%, respectively (Data Supplement). The ORR in the five patients treated with ibrutinib was
of whom four (80%) achieved PR and one (20%) attained a VGPR. The one patient with CXCR4 mutation received ibrutinib and attained a PR.

**Disease Outcomes**

With a median follow-up of 69 months (95% CI, 59 to 90), the overall 5-year OS was 81% (95% CI, 76 to 89) and the median OS was not reached. In patients who received therapy, the 5-year OS and PFS rates were 78% (95% CI, 70 to 86) and 59% (95% CI, 50 to 69), respectively, with median survival times not reached for both outcomes.

Worse 5-year OS ($P = .003$) and PFS ($P = .004$) rates were seen in patients with a high-risk IPSSWM score (OS: 64%; PFS: 35%) compared with patients with intermediate-risk (OS: 88%; PFS: 59%) and low-risk (OS: 100%; PFS: 82%) diseases (Figs 2 and 3). Males had worse 5-year OS (75% vs 94%, $P = .006$) and PFS (50% vs 72%, $P = .004$) rates than females (Figs 2 and 3). The use of rituximab did not influence the survival estimates in the study periods of 2001-2010 (OS, $P = .16$; PFS, $P = .86$), 2011-2020 (OS, $P = .73$; PFS, $P = .73$), and 2001-2020 (OS, $P = .32$; PFS, $P = .69$; Data Supplement).

### TABLE 2. Demographic and Clinical Features and Outcomes of Latin American Patients With Waldenstrom Macroglobulinemia According to the Treating Institution

| Characteristic                     | Overall, No. (%) | Treating institutions, No. (%) |   |   |
|------------------------------------|------------------|-------------------------------|---|---|
| No. of patients                    | 142              | 66                            | 76 |   |
| Period of treatment initiation (n = 137) |                  |                               |   |   |
| 1991-2000                          | 9 (7)            | 9 (15)                        | 0 (0) |   |
| 2001-2010                          | 30 (22)          | 15 (24)                       | 15 (20) |   |
| 2011-2020                          | 98 (71)          | 38 (61)                       | 60 (80) |   |
| IPSSWM score at treatment (n = 111) |                   |                               |   |   |
| Low                                | 18 (16)          | 8 (19)                        | 10 (14) |   |
| Intermediate                       | 45 (41)          | 18 (42)                       | 27 (40) |   |
| High                               | 48 (43)          | 17 (39)                       | 31 (46) |   |
| Age > 65 years at treatment (n = 137) | 77 (56)          | 35 (57)                       | 42 (56) |   |
| Hemoglobin ≤ 11.5 g/dL (n = 130)    | 108 (83)         | 49 (88)                       | 59 (80) |   |
| Platelet count ≤ 100 × 10^9/L (n = 130) | 123 (95)         | 56 (100)                      | 67 (91) |   |
| B2 microglobulin > 3 mg/L (n = 90)  | 63 (70)          | 28 (76)                       | 35 (66) |   |
| IgM > 7 g/dL (n = 107)              | 19 (18)          | 4 (10)                        | 15 (22) |   |
| Intrathecal chemotherapy (n = 140)  | 5 (4)            | 4 (6)                         | 1 (1) |   |
| Maintenance rituximab (n = 137)    | 13 (10)          | 6 (10)                        | 7 (9) |   |
| First-line regimen                 |                  |                               |   |   |
| Chemoimmunotherapy                 | 94 (66)          | 38 (58)                       | 56 (74) |   |
| Monotherapy                        | 35 (25)          | 23 (35)                       | 12 (16) |   |
| Others                             | 13 (9)           | 5 (7)                         | 8 (10) |   |
| Treatment response—ORR (n = 124)   | 107 (86)         | 40 (83)                       | 67 (88) |   |
| Treatment response—MRR (n = 124)   | 105 (84)         | 39 (81)                       | 66 (87) |   |
| Treatment response (n = 124)       |                  |                               |   |   |
| CR                                 | 20 (16)          | 7 (15)                        | 13 (17) |   |
| PR                                 | 66 (53)          | 27 (56)                       | 39 (51) |   |
| VGPR                               | 19 (15)          | 5 (10)                        | 14 (19) |   |
| MR                                 | 2 (2)            | 1 (2)                         | 1 (1) |   |
| SD                                 | 7 (6)            | 2 (4)                         | 5 (7) |   |
| PD                                 | 10 (8)           | 6 (13)                        | 4 (5) |   |
| First relapse at 5 years           | 38 (27)          | 11 (17)                       | 27 (36) |   |
| Mortality at 5 years               | 29 (20)          | 12 (18)                       | 17 (22) |   |

Abbreviations: B2, Beta-2; CR, complete response; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for WM; MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

100%, of whom four (80%) achieved PR and one (20%) attained a VGPR. The one patient with CXCR4 mutation received ibrutinib and attained a PR.
In the univariate analysis, a high-risk IPSSWM at treatment initiation was a predictor of mortality (HR, 4.76, 95% CI, 1.71 to 13.28) and PFS (HR, 2.56, 95% CI, 1.39 to 4.70). After adjusting for sex, type of treating institution, and rituximab use, a high-risk IPSSWM score remained an independent risk factor for OS (adjusted hazard ratio [aHR], 4.73, 95% CI, 1.67 to 13.41, \( P = .003 \)) and PFS (aHR, 2.43, 95% CI, 1.31 to 4.50, \( P = .005 \); Table 3). In addition, male sex was associated with mortality (aHR, 3.75, 95% CI, 1.08 to 13.04, \( P = .038 \)) and PFS (aHR, 2.64, 95% CI, 1.29 to 5.40, \( P = .008 \); Table 3). This outcome was not modified by the IPSSWM score (\( P \) for interaction = .998), treatment period (\( P \) for interaction = .743), or treating institution (\( P \) for interaction = .904). In the sensitivity analysis, a high-risk IPSSWM was a predictor for mortality (aHR, 6.24, 95% CI, 2.19 to 17.82, \( P = .001 \)) and PFS (aHR, 3.77, 95% CI, 1.87 to 7.62, \( P < .001 \); Data Supplement).

**FIG 2.** OS of patients with Waldenstrom Macroglobulinemia according to (A) treatment IPSSWM score, (B) sex, (C) rituximab use, and (D) type of treating institution. IPSSWM, International Prognostic Scoring System for WM; OS, overall survival.
After 5 years from diagnosis, 38 (26%) patients had relapsed and 29 (20%) had died. Cause of death was reported in 19 cases; the most common were infection (n = 7) and disease progression/transformation to aggressive non-Hodgkin lymphoma (n = 5).

**DISCUSSION**

Herein, we describe the clinical features, therapy approaches, and survival outcomes of patients with WM encountered in 24 centers from seven Latin American countries over the past three decades. We found that treatment patterns are heterogeneous with limited access to molecular testing and novel agents. Although chemoimmunotherapy was the most commonly used approach, there was heterogeneity in the choice of treatments across the countries. Nonetheless, the survival outcomes were comparable with those reported in high-income countries. In addition, the use of rituximab did not seem to have an
impact on patient outcomes. To the best of our knowledge, this is the first study that provides real-world data on WM in Latin America.

In our cohort, the median age at diagnosis was 67 years, with a slight male predominance. These features were similar to those reported in previous studies. Less than 5% of our patients were asymptomatic during the initial presentation. This number is lower compared with historical data of 25%. In this study, the most common indications for therapy were organomegaly, anemia, and hyperviscosity symptoms, with a median time to therapy initiation of 35 days. Although the reasons why our patients required early therapy are out of the scope of this work, we believe that delayed access to specialized cancer care by a saturated health care system might have contributed to the observed outcome. Indeed, a late diagnosis has been associated with a more aggressive course of the disease and a worse prognosis.

The \textit{MYD88}^{L265P} mutation has been reported in more than 90% of patients with WM, allowing in some cases the distinction from other IgM-secreting malignancies. The \textit{CXCR4} mutation has been associated with a more aggressive course of the disease and resistance to ibrutinib. In our study, most patients did not undergo molecular testing because of the lack of molecular laboratories in many of the participating institutions and its high cost. In addition, given that ibrutinib is not readily available in most Latin American countries, cytogenetics or mutational analysis does not influence clinicians' choice of therapy.

Despite these caveats, ibrutinib therapy was associated with a high response rate in our patients, similar to reported clinical trials.

| Predictor                      | Univariate Analysis | Multivariate Analysis |
|--------------------------------|---------------------|-----------------------|
|                                | HR (95% CI)         | P                     | aHR (95% CI) | P  | aHR (95% CI) | P  |
| OS                             |                     |                       |             |    |               |    |
| Treatment IPSSWM score         |                     |                       |             |    |               |    |
| Low-intermediate               | Ref                 | —                     | Ref         | —  | Ref           | —  |
| High                           | 4.76 (1.71 to 13.28) | .003                  | 4.86 (1.74 to 13.59) | .003 | 4.73 (1.67 to 13.41) | .003 |
| Rituximab use                  |                     |                       |             |    |               |    |
| No                             | Ref                 | —                     | Ref         | —  | Ref           | —  |
| Yes                            | 1.53 (0.57 to 4.10) | .398                  | 1.80 (0.52 to 6.21) | .351 | 2.46 (0.70 to 8.62) | .161 |
| Sex                            |                     |                       |             |    |               |    |
| Female                         | Ref                 | —                     | —           | Ref | —             | —  |
| Male                           | 4.66 (1.40 to 15.58) | .012                  | —           | —  | 3.75 (1.08 to 13.04) | .038 |
| Type of treating institution   |                     |                       |             |    |               |    |
| Private hospital               | Ref                 | —                     | —           | Ref | —             | —  |
| Public hospital                | 1.09 (0.50 to 2.39) | .828                  | —           | —  | 1.02 (0.38 to 2.72) | .970 |
| PFS                            |                     |                       |             |    |               |    |
| Treatment IPSSWM score         |                     |                       |             |    |               |    |
| Low-intermediate               | Ref                 | —                     | Ref         | —  | Ref           | —  |
| High                           | 2.56 (1.39 to 4.70) | .003                  | 2.55 (1.38 to 4.71) | .003 | 2.43 (1.31 to 4.50) | .005 |
| Rituximab use                  |                     |                       |             |    |               |    |
| No                             | Ref                 | —                     | —           | Ref | —             | —  |
| Yes                            | 1.29 (0.67 to 2.47) | .445                  | 1.02 (0.49 to 2.14) | .954 | 1.24 (0.59 to 2.61) | .569 |
| Sex                            |                     |                       |             |    |               |    |
| Female                         | Ref                 | —                     | —           | —  | Ref           | —  |
| Male                           | 2.58 (1.32 to 5.04) | .006                  | —           | —  | 2.64 (1.29 to 5.40) | .008 |
| Type of treating institution   |                     |                       |             |    |               |    |
| Private hospital               | Ref                 | —                     | —           | Ref | —             | —  |
| Public hospital                | 1.53 (0.85 to 2.76) | .155                  | —           | —  | 1.18 (0.61 to 2.27) | .624 |

**Abbreviations:** aHR, adjusted hazard ratio; IPSSWM, International Prognostic Scoring System for WM; OS, overall survival; PFS, progression-free survival; ref, reference.
2013, single-agent rituximab (45%) and purine analogs (15%) were the most frequently used frontline approaches. In Europe, monotherapy (eg, chlorambucil, rituximab, and fludarabine) was the most frequent frontline approach (43%), whereas chemoimmunotherapy (predominantly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) was used in 36% of patients. In our study, chemoimmunotherapy was the most common approach in the first-line and second-line setting, often with dexamethasone, rituximab, and cyclophosphamide and bendamustine-rituximab, respectively. Bortezomib or ibritinib was given to <10% of our patients. In Latin America, both drugs require either institutional approval for reimbursement or the cost is borne by the patient, which might explain the low rate of use of these agents. We did not find differences in responses or outcomes between patients managed at private versus public institutions, which is not surprising considering that access to therapies is mostly similar in both settings.

The role of ASCT has been explored in small series in the relapsed or refractory setting. The largest European experience using ASCT in WM reported a 5-year PFS of 49% and an OS of 69%, with a nonrelapse mortality of 4% at 1 year. A more recent review by Gertz et al showed that this strategy is effective but currently underutilized, possibly because of the high rate of toxicity and not being a curative strategy. In our study, four patients underwent ASCT after failing frontline therapy. Thus, although ASCT is available in the region, it is rarely used for WM.

In this study, both the median OS and PFS were not reached. At a 5-year follow-up, 81% of patients were alive and survival rates in those treated were 78% and 59% for OS and PFS, respectively. These results are similar to previous real-world reports. In addition, we were able to validate the IPSSWM score in Latin American patients. We could not validate the revised IPSSWM scoring system because of inconsistency in lactate dehydrogenase reporting. In our cohort, the use of rituximab did not seem to have an impact on survival. Clinical trials have shown improved responses and delayed disease progression with rituximab-based therapies. However, neither randomized controlled studies nor observational studies have demonstrated improvement in OS. A recent study using the US SEER database identified a lower mortality risk in patients receiving rituximab-based regimens, but no difference in OS when comparing rituximab monotherapy versus combination with chemotherapy. Although we cannot entirely explain our finding, residual confounding such as patient comorbidities, delayed diagnosis, and delayed access to therapy might have influenced the observed outcome. Therefore, we recommend that current therapy guidelines on the use of rituximab in WM should be followed.

We found a worse survival in males. Previous studies have described that males with WM have a worse survival and higher risk of mortality. This study did not find an effective modification between males and females by IPSSWM score, treatment period, or type of treating institution. The observed outcome may indicate unmeasured confounders in the WM population not explained by high-risk disease, treatment variation over time, and the demographic variables accounted for in this study. Thus, further research is needed to understand this disparity.

Our study is limited by its retrospective nature. Patients were classified using archived records, laboratory, and pathology reports. The absence of a centralized pathology review in this international study lays a risk for selection bias. Similarly, response assessment was evaluated by each investigator, which is subjected to observer bias. However, our outcomes are consistent with previous studies. Our main strength is this study's multinational scale, which included patients seen at specialized cancer centers in Latin America.

In conclusion, to our knowledge, this is the first study to provide real-world data on WM in Latin America. We found that in Latin America, the management of WM is heterogeneous, with limited access to molecular testing and modern therapies. Despite that, outcomes were similar to those reported internationally. Moreover, we validated the IPSSWM score as a predictor of OS and PFS. We believe that the clinical information gathered in this cohort study should provide invaluable insight and guidance into treating this relatively rare and challenging disease, especially in resource-limited settings. Finally, there is an unmet need to improve access to recommended diagnostic approaches and therapies in our region.

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