Oligosecretory Waldenstrom macroglobulinemia exhibits excellent treatment response and outcomes

Lymphoplasmacytic lymphoma (LPL) is characterized by a monoclonal expansion of predominantly small B lymphocytes with variable differentiation from plasmacytoid lymphocytes to plasma cells.[1] Waldenstrom macroglobulinemia (WM) is a rare B-cell malignancy characterized as an immunoglobulin M-secreting LPL, while it does not require the quantification of immunoglobulin M (IgM).[2,3] Most WM patients present with elevated IgM and 15% of them may present with hyperviscosity at diagnosis.[4] Moreover, in many clinical trials and studies, some patients have very low IgM levels, or even levels in the normal IgM range.[5-7] According to the latest response criteria consensus from the 11th International Workshop on Waldenstrom's macroglobulinemia and National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2022),[8,9] a reduction in serum IgM ≥90% and ≥50% is defined as very good partial response (VGPR) and partial response (PR), respectively.[10] When the IgM level is within twice the upper limit of normal (ULN), it is impossible to make an accurate efficacy evaluation. Therefore, in our study, patients with an initial IgM quantification lower than or equal to two times the ULN were defined as "oligosecretory WM". Those with twice higher than the ULN value were defined as "measurable WM". The characteristics and prognosis of these patients have not been studied. Here, we aimed to: 1) present the clinical features of oligosecretory WM; 2) evaluate the tumor burden of oligosecretory WM; and 3) explore the treatment response and outcomes of oligosecretory WM.

We, therefore, performed a retrospective study based on the database of the Chinese Registration Network for Waldenstrom Macroglobulinemia (CRNWM) which included 1,420 LPL/WM patients diagnosed between January 2003 and September 2020 in 35 hematologic centers in China.[11] A total of 1,274 patients with newly diagnosed WM were included in the analysis. Patients receiving two or more courses of treatment were defined as systemic treatment. The treatment response in measurable WM patients was assessed according to the NCCN guidelines (Version 2.2022) of Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma and the latest consensus from the 11th International Workshop on Waldenstrom's macroglobulinemia.[8,9] A complete response (CR) requires the absence of serum monoclonal IgM protein by immunofixation, complete resolution of extramedullary disease, and morphologically normal bone marrow (BM) aspirate. This CR criterion was applied to all the WM patients. For oligosecretory WM patients, bone marrow biopsy (BMB), flow cytometry (FCM), extramedullary disease, and clinical manifestations were combined to make a comprehensive judgment of PR. When the tumor cells of BM were reduced by ≥50% (by BMB and/or FCM), accompanied by a reduction in spleen volume and lymph node size, and improvement in clinical symptoms, it was defined as ≥PR. When BM tumor cells were increased by more than 50% (by BMB or FCM) from nadir (requires confirmation) and/or progression in clinical features attributed to the disease, it was defined as progressive disease (PD). Informed consent was obtained from each patient, and the study was approved by the institutional ethics committee of each center (IIT2021030-EC-1).

Patients' characteristics were summed using median and interquartile range (IQR) for continuous variables, and absolute and relative frequencies for categorical variables. The association between two categorical variables was analyzed using χ^2 or Fisher's exact test for the qualitative variables and independent sample *t* test for quantitative variables.

Among the 1,274 enrolled patients, 80 (6.3%) were classified as oligosecretory WM based on our definition; median serum IgM level was 3.52g/L (range: 0.15-5.92 g/L). The clinical characteristics of oligosecretory WM and measurable WM are described in Table 1. Median age of oligosecretory WM patients was 65 years (range: 31-88), with a male-to-female ratio of 2.5:1, and median hemoglobin (Hb) of 8.4 g/dL (interquartile range [IQR]: 6.4-10.5). Age and sex distribution, and Hb levels were similar between the two groups. Using allele-specific polymerase chain reaction, 47 patients in the oligosecretory WM group and 607 patients in the measurable WM group had *MYD88*^{L265P} mutation, with positivity rates of 83.0% and 70.3% (*P*=0.065) respectively, although differences between the two groups were not significant. Importantly, compared with the measurable WM, oligosecretory WM had a higher proportion of thrombocytopenia (41.2% *vs.* 27.4%, *P*=0.008) and a lower proportion of hypoalbuminemia (32.9% *vs.* 64.6%, *P*<0.001) and elevated serum β2-microglobulin (57.1% *vs.* 73.8%, *P*=0.002). Information on the International Prognostic Scoring System for Waldenstrom macroglobulinemia (IPSSWM) was available for 75 patients in the oligosecretory WM group and 1,042 patients in the measurable WM group. In the oligosecretory WM group, the proportion of high-risk patients was lower than that of the measurable WM group (40.0% *vs.* 51.5%, *P*=0.054) (Table 1).

Besides IgM level, we also evaluated patient tumor burden according to: malignant cells by FCM in BM, malignant cells by BMB, splenomegaly, and lymphadenopathy. No difference was observed in median malignant BM cells by FCM (9.9% *vs.* 8.9%, *P*=0.114), splenomegaly (38.4% *vs.* 35.2%, *P*=0.583), or lymphadenopathy (44.8% *vs.* 39.1%,

Table 1. Baseline characteristics of newly diagnosed Waldenstrom macroglobulinemia with oligosecretory Waldenstrom macroglobulinemia and measurable disease.

Characteristic	Oligosecretory WM N=80	Measurable WM N=1,194	*P*
Age in years Median (range) ≥65, N (%)	 65 (31-88) 37 (46.3)	 64 (27-90) 538 (45.1)	 0.831 0.836
Gender, male, N (%)	57 (71.3)	874 (73.2)	0.685
B symptoms, N (%)	17 (23.6)	252 (22.9)	0.891
Lymphadenopathy ≥1.5 cm, N (%)	26 (44.8)	296 (39.1)	0.390
Splenomegaly ≥15 cm, N (%)	28 (38.4)	321 (35.2)	0.583
MYD88^{L265P} mutation, N (%)	39/47 (83.0)	427/607 (70.3)	0.065
Hemoglobin, g/L Median (IQR) ≤115, N (%)	 84 (67-105) 69 (86.2)	 84 (69-103) 1,010 (85.0)	 0.998 0.764
Platelets, x10^9/L Median (IQR) ≤100, N (%)	 137 (61-237) 33 (41.2)	 164 (95-250) 316 (27.4)	 0.045 0.008
ALC, x10^9/L, median (IQR)	1.69 (0.94-2.93)	1.63 (1.13-2.54)	0.766
Serum β2-microglobulin, mg/L Median (IQR) >3 mg/L, N (%)	 3.25 (2.43-3.54) 40 (57.1)	 4.1 (2.91-5.80) 736 (73.8)	 0.874 0.002
LDH, U/L Median (IQR) ≥250, N (%)	 175 (142.3-236.5) 13 (17.1)	 146 (112.4-197.5) 138 (12.7)	 0.040 0.275
Serum albumin, g/L Median (IQR) <35 g/L, N (%)	 37.7 (32.1-42.0) 26 (32.9)	 32.0 (27.5-36.7) 749 (64.6)	 0.000 0.000
Malignant cells by FCM of BM, %, median (IQR)	9.9 (3.6-44.5)	8.9 (2.5-26.0)	0.114
Malignant cells by BMB >50%, N (%)	14/26 (53.8)	496/912 (54.4)	0.957
IPSSWM Low-risk, N (%) Intermediate-risk, N (%) High-risk, N (%)	 14 (18.7) 31 (41.3) 30 (40.0)	 139 (13.2) 366 (35.1) 537 (51.5)	 0.195 0.278 0.054

WM: Waldenstrom macroglobulinemia; N: number; IQR: interquartile range; ALC: absolute lymphocyte count; LDH: lactic dehydrogenase; FCM: flow cytometry; BM: bone marrow; BMB: bone marrow biopsy; IPSSWM: International Prognostic Scoring System for Waldenstrom macroglobulinemia.

P=0.390) between the two groups. Malignant cells by BMB were given in four groups: percentage of malignant cells ≤5%, 5-20%, 20-50%, and ≥50%. The percentage of malignant cells by BMB of different ranges were also similar between the two groups (malignant cells ≤5%, 11.5% *vs.* 6.9%, *P*=0.645; 5-20%, 19.2% *vs.* 15.2%, *P*=0.305; 20-50%, 15.4% *vs.* 23.5%, *P*=0.336; ≥50%, 53.8% *vs.* 54.4%, *P*=0.957). Furthermore, there was a significantly higher proportion of patients with >50% abnormal cells in oligosecretory WM patients compared with the measurable WM group (22.7% *vs.* 12.4%, *P*=0.048) by FCM, suggesting that some patients with low IgM levels still had high tumor infiltration of BM (Figure 1). Overall, the BM tumor burden for oligosecretory WM was comparable with the measurable WM.

Treatment information was available for 45 (56.3%) and 682 (57.1%) patients in the oligosecretory WM group and measurable WM group, respectively. We summarized the treatment options for all patients into four regimens: rit-

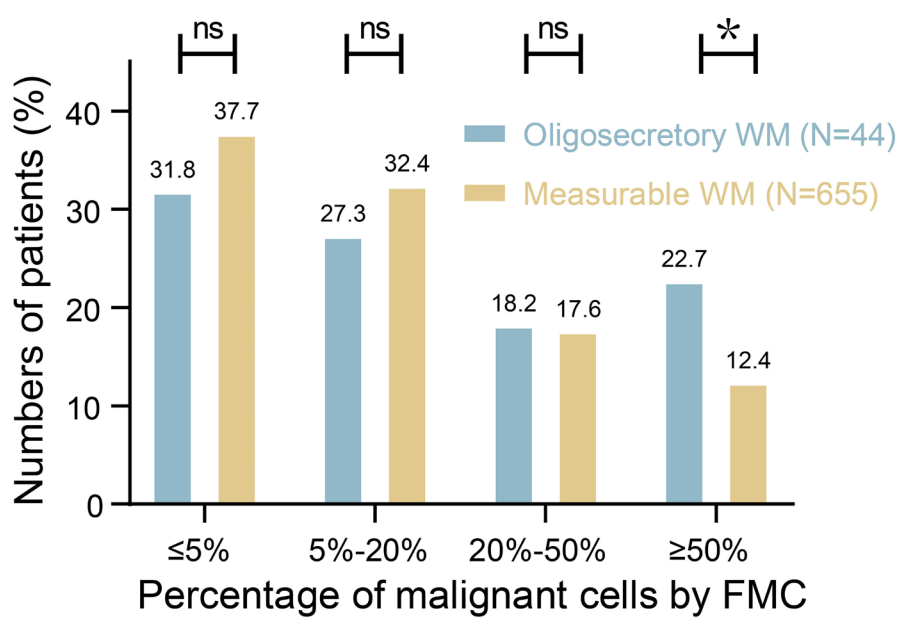

Figure 1. The percentage of malignant cells in bone marrow by flow cytometry. WM: Waldenstrom macroglobulinemia; FCM: flow cytometry; ns: not significant.

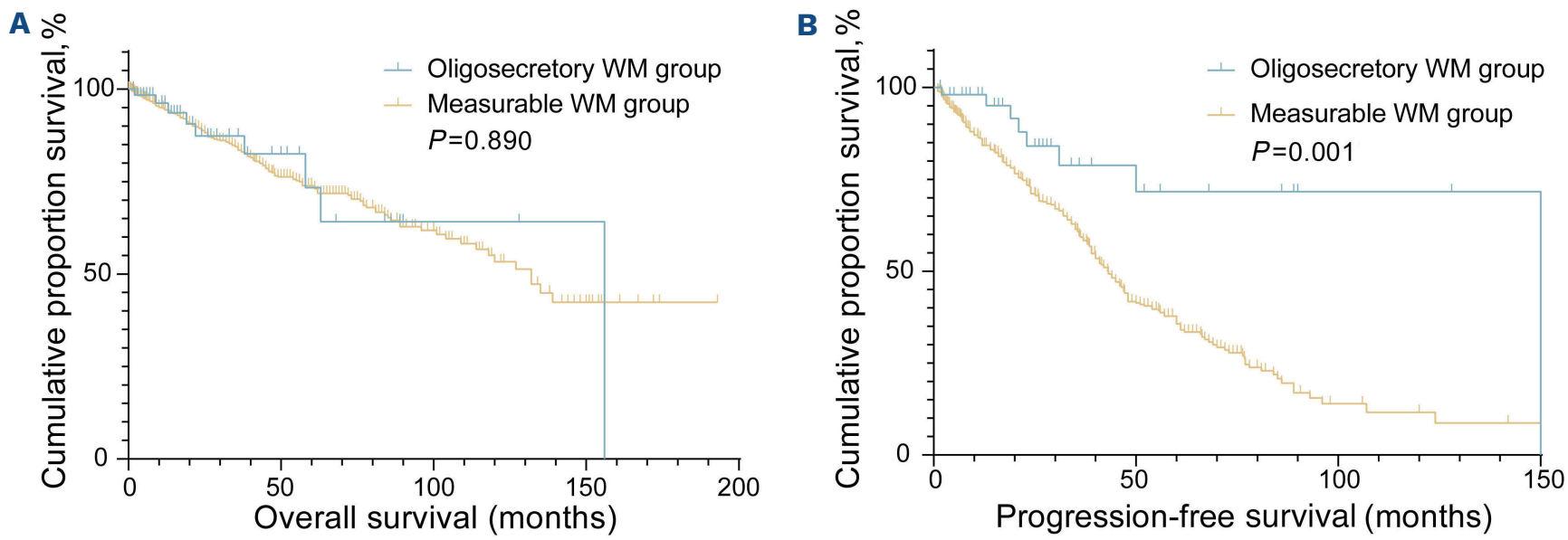

Figure 2. Kaplan-Meier curves for survival of oligosecretory Waldenstrom macroglobulinemia patients and measurable Waldenstrom macroglobulinemia patients. (A) Overall and (B) progression-free survival of the two groups.

uximab-based regimens (R-based), bortezomib-based regimens (B-based), BTK inhibitors, and traditional cytotoxic drug regimens. The treatment regimens were comparable between the two groups (*Online Supplementary Table S1*). Thirty-four (42.5%) oligosecretory WM patients had a post-treatment BM biopsy, which could evaluate the treatment response, while treatment response was evaluated in 559 patients (46.8%) in the measurable group.

At a median follow-up of 21.1 months, 8 patients had died in the oligosecretory WM group and 173 in the measurable WM group. Overall, the 3-year overall survival (OS) rates in the oligosecretory WM group and measurable WM group were 83.4% and 87.3%, respectively (P=0.890) (Figure 2A). Interesting, the CR rate and 3-year PFS rate were both higher in the oligosecretory group, but with highly heterogeneous treatments used in both groups. Among the 34 evaluable oligosecretory patients, 21 (61.8%) achieved ≥PR, and 8 (23.5%) achieved <PR. Overall response rates were 85.3% and 76.0% in the oligosecretory and measurable group (CR 5.4%, ≥PR 57.1%, minor response 13.6%), respectively. Importantly, 5 oligosecretory WM patients achieved CR, which was significantly higher than the measurable WM group (14.7% *vs.* 5.4%, P=0.043). During the follow-up period, 8 patients in the oligosecretory WM group and 286 patients in the measurable WM group experienced disease progression. The 3-year PFS rate was 59.6% in the measurable WM group and 78.8% in the oligosecretory WM group (P=0.001) (Figure 2B). Subsequently, we validated the predictive performance of the IPSSWM for survival in oligosecretory WM patients. The IPSSWM had a prognostic role for PFS (P=0.070) but not for OS (P=0.280) in oligosecretory WM (*Online Supplementary Figure S1*).

This study is the first to study the characteristics and survival of a large cohort of patients with very low IgM levels. Treon *et al.*[12] have defined 10 g/L as the cut-off value for low IgM WM. We found that WM patients with IgM levels lower than 10 g/L also showed better PFS with no significant differences found (*Online Supplementary Figure S2*). We believe that initial IgM status lower than two times the ULN was a reasonable and clinically useful threshold. Interestingly, we found that patients with oligosecretory WM had different clinical characteristics. Although oligosecretory WM had low IgM, the tumor load was actually not low. Importantly, this group of patients had a good treatment response and PFS.

However, the study has some limitations. Firstly, the retrospective design may lead to potential bias. Secondly, the number of patients available for treatment regimens and efficacy was limited, so we could not perform a subgroup analysis of different treatment responses and meta-regression analyses of the PFS of oligosecretory WM patients. Lastly, the follow-up period was not long enough to evaluate long-term survival outcomes, which may be one of the causes for the negligible differences in OS between two groups. In the future, we will expand the cohort and extend the follow-up time for more detailed subgroup analysis. Previous studies have shown that Chinese WM patients have unique genetic characteristics.[13,14] We also expect that genetic information such as gene mutations, chromosome karyotypes, and IGHV gene repertoire will further deepen our knowledge of this rare entity.

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Contributions

SY conceptualized the study. WX, YYu, CS, JD and ZC analyzed data, performed statistical analyses, and wrote the manuscript. ZW, XCa, YYa, JC, YH, ZJ, HW, TN, GY, HX, BL, HH, ZL, QL, FL, OB, MM, RF, LiW, CL, XCh, LL, YD, LuW, JL, YW and RC acquired data and managed patients. LQ, JL and SY revised the manuscript critically and approved the final version.

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Data-sharing statement

Data are available from the corresponding author on reasonable request.

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