Received: 4 December 2023 | Accepted: 6 March 2024

DOI: 10.1111/bjh.19409

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

SHORT REPORT

Haematological Malignancy – Clinical

Long-term results of Waldenström macroglobulinaemia treatment by bendamustine and rituximab: A study on behalf of the French Innovative Leukemia Organization (FILO)

Kamel Laribi[1] | **Stéphanie Poulain**[2] | **Lise Willems**[3] | **Fatiha Merabet**[4] | **Charles Herbaux**[5] | **Damien Roos-Weil**[6] | **Inès Laribi de Materre**[7] | **Xavier Roussel**[8] | **Morgane Nudel**[9] | **Sabine Tricot**[10] | **Jehan Dupuis**[11] | **Ronan Le Calloch**[12] | **Benoit Bareau**[13] | **Véronique Leblond**[6]

[1]Haematology Department, Le Mans Hospital, Le Mans, France

[2]Cellular Haematology, Biology and Pathology Center, Lille Regional and University Hospital and INSERM UMR 1172, IRCL, Lille, France

[3]Haematology Clinic, Cochin Hospital, APHP, Paris, France

[4]Haematology and Oncology Clinic, André Mignot Hospital, Versailles Hospital, Versailles, France

[5]Haematology Clinic, Montpellier University Hospital, Montpellier, France

[6]Haematology Department, APHP, Sorbonne University, University Hospital La Pitié Salpêtrière-Charles Foix, Paris, France

[7]Paris Centre University, Paris, France

[8]Haematology Department, University of Franche-Comté, INSERM UMR 1098, Besançon University Hospital, Besançon, France

[9]Haematology Department, Lille Regional and University Hospital, Lille, France

[10]Haematology Clinic, Valenciennes Hospital, Valenciennes, France

[11]Lymphoid Malignancies Unit, APHP, Henri Mondor-Albert Chennevier Hospital, Créteil, France

[12]Internal Medicine, Infectiology and Blood Diseases, Cornouaille Hospital Center, Quimper, France

[13]Haematology and Internal Medicine Clinic, Sévigné Vivalto Santé Private Hospital, Cesson-Sévigné, France

Correspondence
Kamel Laribi, Haematology Department, Le Mans Hospital, 194 Avenue Rubillard, 72037 Le Mans, France.
Email: klaribi@ch-lemans.fr

Summary

The bendamustine–rituximab (BR) schedule is an efficient first-line therapy in Waldenström macroglobulinaemia (WM). A previous analysis of 69 patients who received this treatment confirmed a high response rate and good progression-free (PFS) and overall survival (OS). With a median follow-up of 76.1 months (95% confidence interval [CI] 69.9–80.6), 5-year outcome is still excellent at 66.63% (95% CI 56.09–79.17) for PFS and 80.01% (95% CI 70.82–90.41) for OS. The rate of secondary cancers is 17.66% (IQR 7.99–27.64) at 66 months. Relapsed patients who received ibrutinib as second-line clearly benefited from this schedule. This confirms current recommendations suggesting BR long-term efficacy as first-line option in WM.

KEYWORDS
antibody therapy, chemotherapy, Waldenström macroglobulinaemia

The use of bendamustine in Waldenström macroglobulinaemia (WM) treatment was first evoked by Treon in 2009[1] on the basis of an abstract reporting 41 patients included in a larger cohort of indolent lymphomas. A study of first-line treatment, comparing R-CHOP (rituximab–cyclophosphamide, doxorubicin, vincristine and prednisone) to bendamustine + rituximab (BR) was published a few years later.[2] The BR combination then appeared in recommendations from the International Workshop on Waldenström macroglobulinaemia

(IWWM) as the best choice for first-line therapy in 2014 in both front-line and relapsed settings.[3] This strategy was applied by the French Innovative Leukemia Organization (FILO) from January 2013 to December 2017 for 69 treatment-naïve WM patients in 13 centres of the group. The first results of this study were published in 2018.[4] Patient characteristics are recalled in Table S1. The main conclusion was that this regimen had been highly efficient with a cumulative incidence of overall response rate of 97% at 18 months including 19% of complete responses.

Here, data are presented from the same cohort with a median follow-up (reverse Kaplan–Meier) of 76.1 months (95% confidence interval [CI] 69.9–80.6) post BR. Five-year progression-free (PFS) and event-free survival are, respectively, of 66.63% (95% CI 56.09–79.17) and 62.26% (95% CI 51.52–75.24). Five-year overall survival (OS) is of 80.01% (95% CI 70.82–90.41) (Figure 1).

Nineteen patients died, six from progression (including one aggressive B-cell transformation and two AL amyloidosis), two from an acute myeloid leukaemia and five from solid tumours (lung, oesophagus, stomach [$n=2$], pancreas). The last six patients died from other causes (brain haemorrhage [$n=2$], cardiac failure, organ failure, lung fibrosis or flu [one of each]).

Sixteen patients have relapsed with a median time, from the end of first treatment to initiation of second treatment, of 35.3 months (interquartile range [IQR] 22.8–52.07 months). Second-line therapy included ibrutinib with or without rituximab ($n=8$), DRC (dexamethasone, rituximab, cyclophosphamide, $n=3$), rituximab alone ($n=1$), RVCD (lenalidomide, bortezomib, cyclophosphamide, dexamethasone, $n=1$), PAD (bortezomib, doxorubicin and dexamethasone) followed by autologous haematopoietic stem cell transplantation ($n=1$). Two patients received palliative support. Ibrutinib-based therapy proved to be more efficient than other approaches, yielding a median PFS2 of 45 months (IQR 9.13–NR) while it was 21 months (IQR 8.97–NR) for the whole cohort of relapsed patients.

Persistent toxicity was mostly characterized by long-lasting post-treatment cytopenias, which were observed in 35 (51%) patients. They were, respectively, neutropenia (38%), anaemia (25%) and thrombocytopenia (16%). The median duration of these cytopenias was of 9 months for both neutrophils (range 3–24 months) and platelets (range 3–36 months), and 6 months for anaemia (range 3–36 months). Second malignancies occurred in 12 patients, including nine solid tumours (pancreas $n=2$, stomach $n=2$, colon $n=1$, breast $n=1$, skin $n=1$) and three haematological malignancies (one myelodysplasia and two AML). The cumulative incidence of second malignancies is thus of 17.66% (IQR 7.99–27.64) at 66 months. Of note, although all occurred more than 1 year after the end of treatment, this rate is not negligible and could be related to therapy.

Univariate analyses (Table S2; Figure S1) were meaningful in this cohort and identified age at diagnosis and IPSSWM as factors significantly influencing PFS (respectively, HR 1.04 [95% CI 1.00–1.08] $p=0.04$ and HR 0.25 [95% CI 0.007–0.92], $p=0.037$, for younger age and high vs. favourable IPSSWM). For OS, age at diagnosis, age at first treatment, IgM level, IPSSWM and number of cycles all had a significant impact. However, in multivariate analysis, no variable remained significant.

The mutational status of $MYD88^{L265P}$ and *CXCR4* was available for 51 and 44 patients, respectively, with 45 (88%) and 11 (25%) mutated patients (62% of non-sense CXCR4 mutations). These mutations were investigated on bone marrow samples by allele-specific polymerase chain reaction or capture high-throughput sequencing with a sensitivity of 0.1%–1% as recommended.[5] Although a lower OS was observed for the six patients without *MYD88* mutation (5-year OS of negative patients, 66.7% [95% CI 37.9–100] vs. 83.5% [95% CI 73.0–95.5]), this was not statistically significant with a *p*-value of 0.09, likely owing to lack of power. Similarly, while *CXCR4*-mutated patients fared less well (5-year OS of negative patients, 87.2% [95% CI 76.3–99.8] vs. 80.8% [95% CI 60.0–100]), this did not reach statistical significance with a *p*-value of 0.45. These data are comparable to those reported by Zanwar et al.[6] for 116 *MYD88*-mutated and 12 *CXCR4*-mutated patients whose PFS did not differ significantly from that of wild-type patients ($p=0.05$). In spite of the fact that the study was underpowered, the possible absence of impact of *MYD88* status has already been reported by Paludo et al.[7] Finally, of the 34 patients for whom *TP53* alteration had been investigated, only one had a partial del(17p). This patient had a low IPSSWM, reached and maintained a very good partial response, experienced 17 months of neutropenia and died 8 years after entering the protocol, at age 77, from cardiac failure. However, in this context, the prognostic impact of *TP53* alterations during rituximab–bendamustine treatment could not be evaluated.

Overall, this study confirms the excellent results of a BR schedule as first-line therapy in WM. Indeed, similar results have been reported for a 48-month follow-up in a subset of WM by Rummel et al.[2] More relevantly, a 10-year follow-up for WM patients was published by Castillo et al.,[8] yet with rituximab maintenance.

In the study reported here, toxicity was acceptable, mostly haematological on the long term, yet lasting less than 1 year for patients now followed for a median of almost 6 years (with some patients reaching nearly 9 years of follow-up). The 23% rate of relapse, over the whole period, seems acceptable, especially since only two patients were not eligible to second treatment while salvage therapy could be applied successfully to others. Similarly, the death rate, at 27.5%, in a population with a 71-year-old median age at treatment initiation, can be considered satisfactory and witness of rather low toxicity. Owing to the relative rarity of WM, no significant clinical trials are available to compare with. However, recommendations have steadily pointed out the efficacy of a BR approach.[9,10] This long-term evaluation of the efficacy of a first-line BR regimen in patients with BM strongly suggests that this approach, with manageable toxicity and side effects, could still be considered besides targeted therapies if needed.

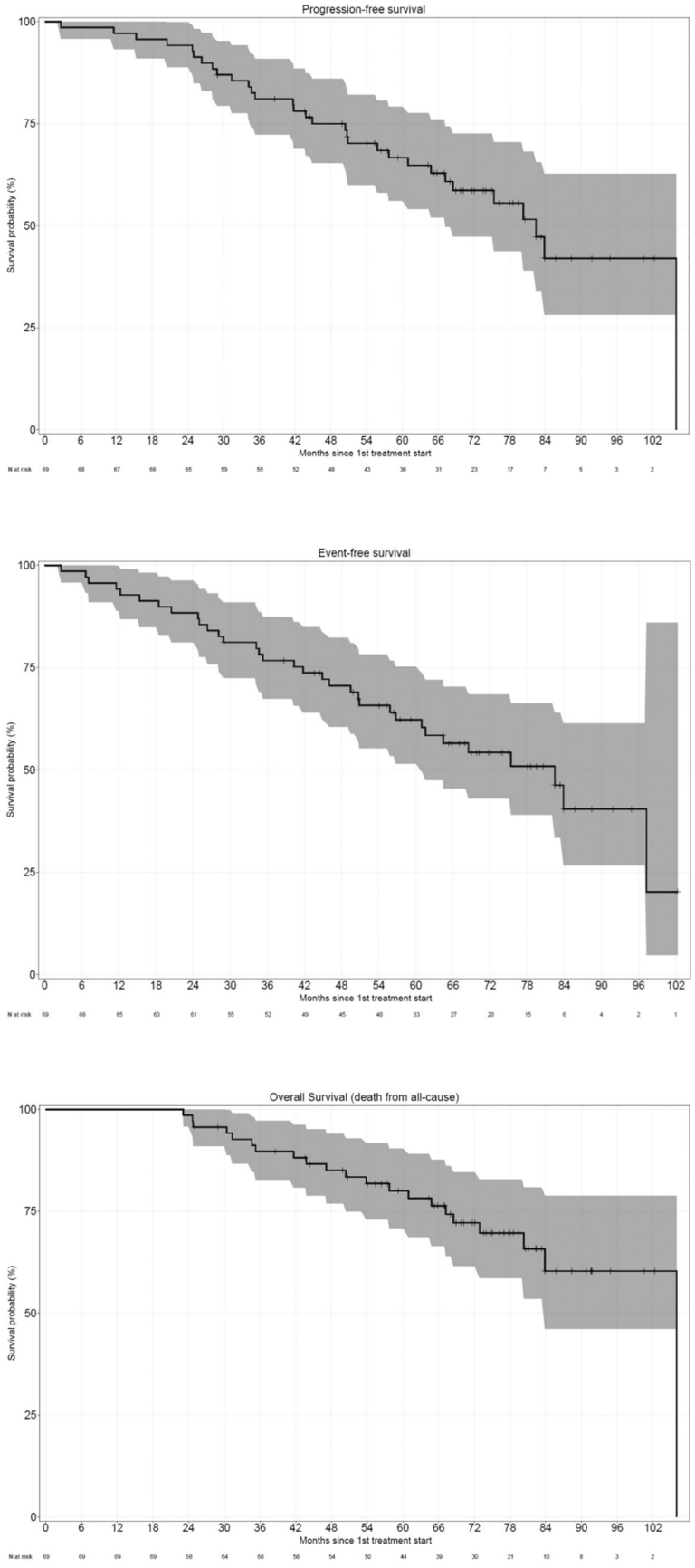

FIGURE 1 Progression-free (A), event-free (B) and overall (C) survivals.

AUTHOR CONTRIBUTIONS

KL and VL designed the study, all authors except SP enrolled patients, SP performed NGS analysis, KL and VL wrote the paper. All authors read and approved the final version of the manuscript for submission.

ACKNOWLEDGEMENTS

Medical writing for this manuscript was assisted by MPIYP (MC Béné), Paris, France.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

More data available upon reasonable request from the corresponding author.

ETHICS STATEMENT

The study was approved by the local ethics committee.

PATIENT CONSENT STATEMENT

All patients provided informed consent.

ORCID

Kamel Laribi https://orcid.org/0000-0002-4389-6164
Charles Herbaux https://orcid.org/0000-0003-4910-476X
Damien Roos-Weil https://orcid.org/0000-0002-7767-755X
Ronan Le Calloch https://orcid.org/0000-0001-5883-1825

REFERENCES

1. Treon SP. How I treat Waldenström macroglobulinemia. Blood. 2009;114(12):2375–85.
2. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, et al. Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
3. Dimopoulos MA, Kastritis E, Owen RG, Kyle RA, Landgren O, Morra E, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood. 2014;124(9):1404–11.
4. Laribi K, Poulain S, Willems L, Le Calloch R, Eveillard JR, Herbaux C, et al. Bendamustine plus rituximab in newly-diagnosed Waldenström macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). Br J Haematol. 2019;186(1):146–9.
5. García-Sanz R, Hunter ZR, Poulain S, Varettoni M, Owen RG. New developments in the diagnosis and characterization of Waldenström's macroglobulinemia. Expert Rev Hematol. 2023;16(11):835–47.
6. Zanwar S, Abeykoon J, Castillo J, Durot E, Kastritis E, Uppal E. P1159: a multicenter, international collaborative study evaluating frontline therapy with bendamustine rituximab for Waldenström macroglobulinemia. HemaSphere. 2022;6(Suppl):1046–7.
7. Paludo J, Abeykoon JP, Shreders A, Ansell SM, Kumar S, Ailawadhi S, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. Ann Hematol. 2018;97(8):1417–25.
8. Castillo JJ, Gustine JN, Meid K, Dubeau TE, Severns P, Xu L, et al. Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenström macroglobulinaemia. Br J Haematol. 2018;181(1):77–85.
9. Castillo JJ, Advani RH, Branagan AR, Buske C, Dimopoulos MA, D'Sa S, et al. Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia. Lancet Haematol. 2020;7(11):e827–e837.
10. Buske C, Castillo JJ, Abeykoon JP, Advani R, Arulogun SO, Branagan AR, et al. Report of consensus panel 1 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on management of symptomatic, treatment-naïve patients. Semin Hematol. 2023;60(2):73–9.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Laribi K, Poulain S, Willems L, Merabet F, Herbaux C, Roos-Weil D, et al. Long-term results of Waldenström macroglobulinaemia treatment by bendamustine and rituximab: A study on behalf of the French Innovative Leukemia Organization (FILO). Br J Haematol. 2024;00:1–4. https://doi.org/10.1111/bjh.19409