

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)

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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 2009¹ 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.

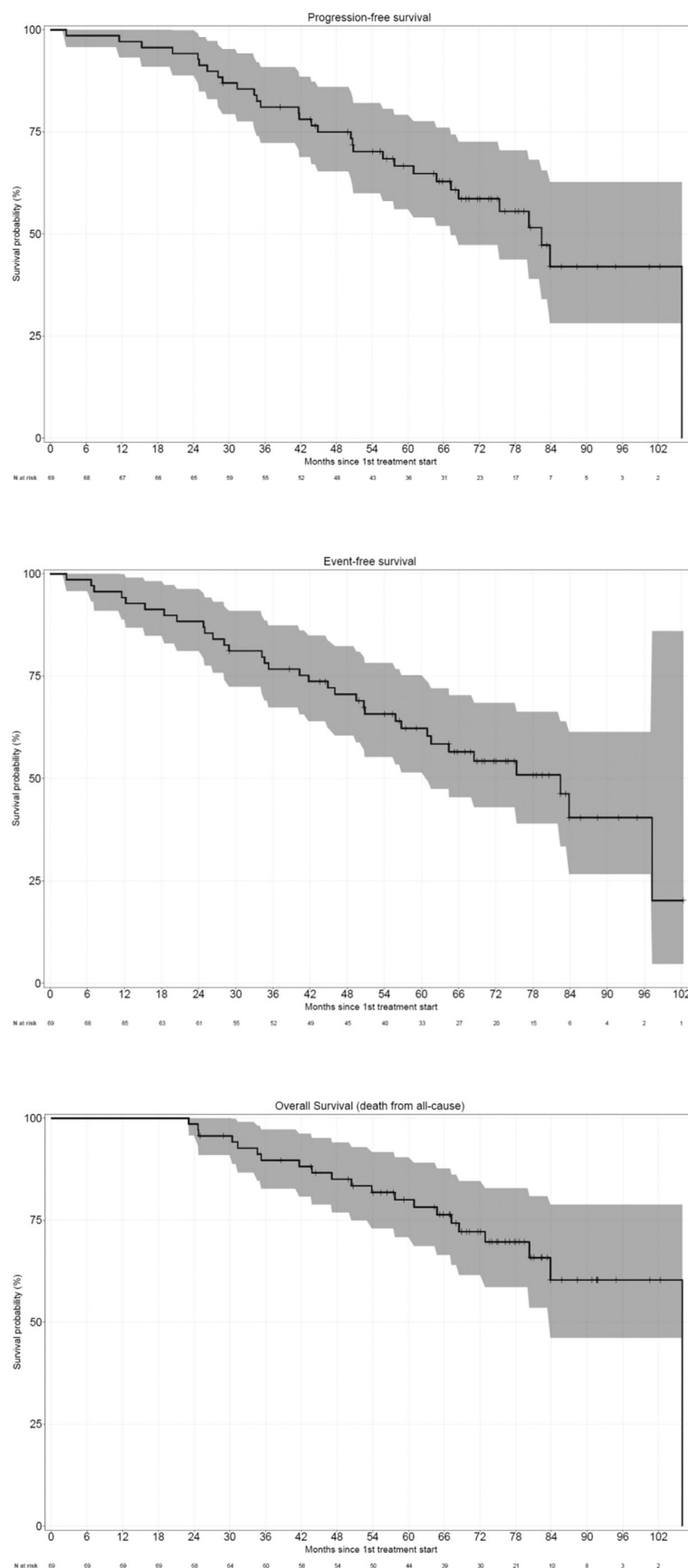


FIGURE 1 Progression-free (A), event-free (B) and overall (C) survivals.

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.

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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.

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SUPPORTING INFORMATION

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

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