



CORRESPONDENCE

Autologous and Allogeneic Stem-Cell Transplantation for Transformed Waldenström Macroglobulinemia

Eric Durot¹ | Lukshe Kanagaratnam² | Saurabh Zanwar³ | Adrienne Kaufman⁴ | Shirley D'Sa⁵ | Elise Toussaint⁶ | Damien Roos-Weil⁷ | Miguel Alcoceba⁸ | Josephine M. I. Vos⁹ | Anne-Sophie Michallet¹⁰ | Dipti Talaulikar^{11,12} | Efsthios Kastiris¹³ | Jahanzaib Khwaja⁵ | Steven P. Treon¹⁴ | Ramon Garcia-Sanz⁸ | Pierre Morel¹⁵ | Javier Munoz⁴ | Jorge J. Castillo¹⁴ | Prashant Kapoor³ | Alain Delmer¹

¹Department of Hematology, University Hospital of Reims and UFR Médecine, Reims, France | ²Department of Research and Public Health, University Hospital of Reims, and UR 3797, Vieillessement, Fragilité (VieFra), Faculty of Medicine, University of Reims Champagne-Ardenne, Reims, France | ³Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA | ⁴Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, Arizona, USA | ⁵University College London Hospitals (UCLH) Centre for Waldenström Macroglobulinemia and Related Conditions, University College London Hospitals NHS Foundation Trust, London, UK | ⁶Department of Hematology, Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France | ⁷Sorbonne Université, Hematology, Pitié-Salpêtrière Hospital, Paris, France | ⁸Department of Hematology, University Hospital of Salamanca, CIBERONC and Research Biomedical Institute of Salamanca (IBSAL), Salamanca, Spain | ⁹Department of Hematology, Amsterdam University Medical Center (UMC), University of Amsterdam, Amsterdam, The Netherlands | ¹⁰Department of Hematology, Léon Bérard Center, Lyon, France | ¹¹Department of Hematology, ACT Pathology, Canberra Hospital, Canberra, Australia | ¹²College of Health and Medicine, Australian National University, Canberra, Australia | ¹³Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece | ¹⁴Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA | ¹⁵Department of Hematology, University Hospital of Amiens, Amiens, France

Correspondence: Eric Durot (edurot@chu-reims.fr)

Received: 4 September 2024 | **Revised:** 13 November 2024 | **Accepted:** 18 November 2024

Keywords: diffuse large B-cell lymphoma | histological transformation | IgM lymphoplasmacytic lymphoma

To the Editor,

Waldenström macroglobulinemia (WM) is characterized by a clonal proliferation of plasmacytoid B-cells in the bone marrow and monoclonal IgM gammopathy, that ultimately require treatment in symptomatic patients. Moreover, a small subset of patients undergoes histological transformation (HT) [1], mainly in the form of diffuse large B-cell lymphoma (DLBCL). They usually present with high-risk features, such as extranodal involvement, advanced stage, and elevated serum lactate dehydrogenase (LDH) [2]. Immunochemotherapy (ICT) using anti-CD20 antibodies is commonly used for HT-WM patients, in line with the treatment paradigm for DLBCL. However, the response rates remain low for patients with HT-WM, and the median survival after HT is short (1.5–2.7 years). The role of hematopoietic stem-cell transplantation (HSCT) as consolidation therapy in HT-WM for fit patients is unknown. Data regarding the use of auto and allo-HSCT in transformed indolent lymphomas is limited to retrospective studies of small patient series with heterogeneous populations in terms of the antecedent histologies

(predominantly transformed follicular lymphoma), the timing of HSCT (upfront or salvage), or the conditioning regimen. No dedicated study has specifically examined the outcome of patients with HT-WM who received HSCT.

In this context, results of a large, retrospective, multicenter, international study investigating the clinical course of patients with HT-WM who underwent autologous (auto-HSCT) or allogeneic (allo-HSCT) transplantation are reported here.

The database collected, comprising 283 patients with HT-WM, treated between January 1995 and December 2021, was compiled through a retrospective investigation of relevant cases in 20 French centers and 9 from other countries. The study protocol was conducted according to the Declaration of Helsinki.

Response rates were based on positron emission tomography (PET)-scan, according to the Lugano 2014 classification, as addressed by the treating physician (or computed tomography if a

PET-scan was not performed). The primary endpoint was overall survival (OS), calculated from the date of HSCT until death from any cause or last follow-up (FU). Progression-free survival (PFS) was calculated from the date of HSCT to relapse, progression, death, or last FU. Other secondary endpoints were the rates of relapse/progression and non-relapse mortality (NRM). PFS and OS probabilities were calculated using Kaplan–Meier estimates and compared using log-rank test. Univariate and multivariate analyses were performed for the cohort of patients who received auto-HSCT fitting Cox proportional-hazard regression models for OS and PFS.

To study the added utility of auto-HSCT after a complete response (CR) to initial ICT, a cohort of 34 patients younger than 70 years, in CR after first-line therapy for HT-WM without HSCT was used. In this comparison, PFS and OS were calculated from the date of HT-WM diagnosis.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Characteristics are summarized in Table S1 for the three HT-WM groups of patients without ($n=227$), with auto- ($n=46$) and with ($n=10$) allo-HSCT, respectively. The median OS from transformation (Figure S1) was respectively of 1.3 year (95% confidence interval [95% CI], 1–1.7), 11 years (95% CI, 2.6—not reached [NR]) and 3.2 years (0.4—NR) for the non-HSCT, auto-HSCT and allo-HSCT groups ($p<0.001$).

In the auto-HSCT group, the median age was 63 years (range, 31–75) at the time of transplantation with more than half of them being over 60 years old (63%). *MYD88^{L265P}* mutation was detected at WM diagnosis in 11 of 23 tested patients (48%). Four patients underwent HSCT while progressing (PD), and 14 were in partial response (PR); 27 (59%) were in CR. Conditioning was mostly a BEAM (BCNU, etoposide, cytarabine and melphalan)-based regimen.

The ten patients who received an allo-HSCT (matched related donor: $n=6$, mismatched related donor: $n=1$, matched unrelated donor: $n=2$, unknown: $n=1$) had a median age of 51 years (range, 43–70), with only 2 patients being over 60 at the time of transplant. *MYD88^{L265P}* mutation was detected in 2 of 3 tested patients. Five were in CR, 3 in PR and 1 in PD (unknown: $n=1$) at the time of transplant. Seven patients received a reduced-intensity conditioning regimen.

After auto-HSCT, 76% of the patients reached CR (Table S1). A total of eight patients among the 14 in PR before auto-HSCT and 1 among 4 in PD had a deepening of response to CR (9/18, 50%) after auto-HSCT. Median FU was 5.5 years for alive patients (95% CI, 2.8–7.2). Estimations at 3-years (Figure 1) were of 44% (95% CI, 31%–62%) for PFS, 57% (95% CI, 44%–74%) for OS, 54% (95% CI, 38%–68%) for cumulative incidence of relapse (CIR) and 2% (95% CI, 0.2%–10%) for NRM. The size of this cohort allowed to investigate prognostic factors further. As shown in Table S2, univariate analyses disclosed a statistically significant favorable impact of being in CR at the time of auto-HSCT with a 3-year PFS rate of 62% (95% CI, 45%–84%) versus 21% (95% CI, 8%–53%, $p=0.0009$), and a 3-year OS rate of 81% (95% CI, 68%–98%) versus 23% (95% CI, 9%–58%, $p=0.001$). A single previous line of

therapy for HT-WM also provided a better 3-year OS prognosis (75%, [95% CI, 60%–95%] vs 36% [95% CI, 19%–67%], $p=0.01$). In multivariate analysis (Table S2 and Figure 1), being in CR at the time of auto-HSCT remained a favorable prognostic marker both for PFS (hazard ratio [HR] 0.27, 95% CI, 0.12–0.64, $p=0.003$) and OS (HR 0.27, 95% CI, 0.10–0.73, $p=0.01$). The median duration of response for the patients in CR was 6.3 years (95% CI, 2–7.3).

For the smaller group of allo-HSCT recipients (Figure S2), the median FU was 12.6 years (95% CI, 2.7–14.4). Estimations at 3-years were 50% (95% CI, 27%–93%) for PFS, 50% (95% CI, 27%–93%) for OS, 30% (95% CI, 6%–60%) for CIR, and 20% (95% CI, 3%–49%) for NRM.

To appreciate the benefit of CR in patients undergoing auto-HSCT as upfront therapy for HT-WM, 18 of these patients were compared to 34 who did not receive HSCT, younger than 70 years and in CR after first-line therapy for HT-WM. As shown in Table S3, a higher proportion of patients in the non-HSCT group was older than 60 years (44% vs. 17%, $p=0.04$) but they were less frequently treated for WM and displayed less frequently high-risk clinical features (IPI, advanced stage, extranodal involvement) as compared to the auto-HSCT group. The 3-year PFS rate was 66% (95% CI, 48%–92%) in the auto-HSCT group versus 66% (95% CI, 52%–85%) ($p=0.96$) (Figure S3). Of 9 patients who relapsed after auto-HSCT, this involved the underlying WM without DLBCL in 6, whereas all but one (14/15) relapses/progressions were due to DLBCL in the non-HSCT group. The 3- and 5-year OS rates were 83% (95% CI, 68%–100%) and 83% (95% CI, 68%–100%) in the auto-HSCT group and 78% (95% CI, 65%–94%) and 65% (95% CI, 50%–84%) in the non-HSCT group, ($p=0.08$) (Figure S3).

This multicenter retrospective study shows that durable remission can be achieved with auto- or allo-HSCT in HT-WM, especially for patients in CR before auto-HSCT.

Limited data about DLBCL transformation in hematological malignancies is available, usually coming, as here, from retrospective studies. In Richter transformation (RT), Cwynarski et al. [3] reported poorer results after allo-HSCT compared with auto-HSCT, but already identified the benefit of being in CR at the time of transplantation. More recently, Herrera et al. [4], also in RT, observed comparable outcomes between patients who received allo- ($n=118$) or auto-HSCT ($n=53$), at respectively 43%/48% for PFS and 52%/57% for OS. These rates are in the same range as those observed in the present HT-WM cohort. In the cohort of transformed indolent B-cell lymphoma examined by Chin et al. [5], which included only one case of HT-WM, the 15% of patients who received auto-HSCT had a better 4-year PFS than those who did not, a characteristic confirmed in a propensity-matched cohort of 98 patients.

The efficacy of auto-HSCT in non-transformed WM patients has previously been reported with 3-year PFS and OS rates of 62% and 78% respectively [6]. These results are comparable to the series reported here, where patients had, however, a more severe (transformed) disease yet received HSCT in a more recent period.

This study has limitations, including the lack of information on comorbidities, potential selection bias, and heterogeneous

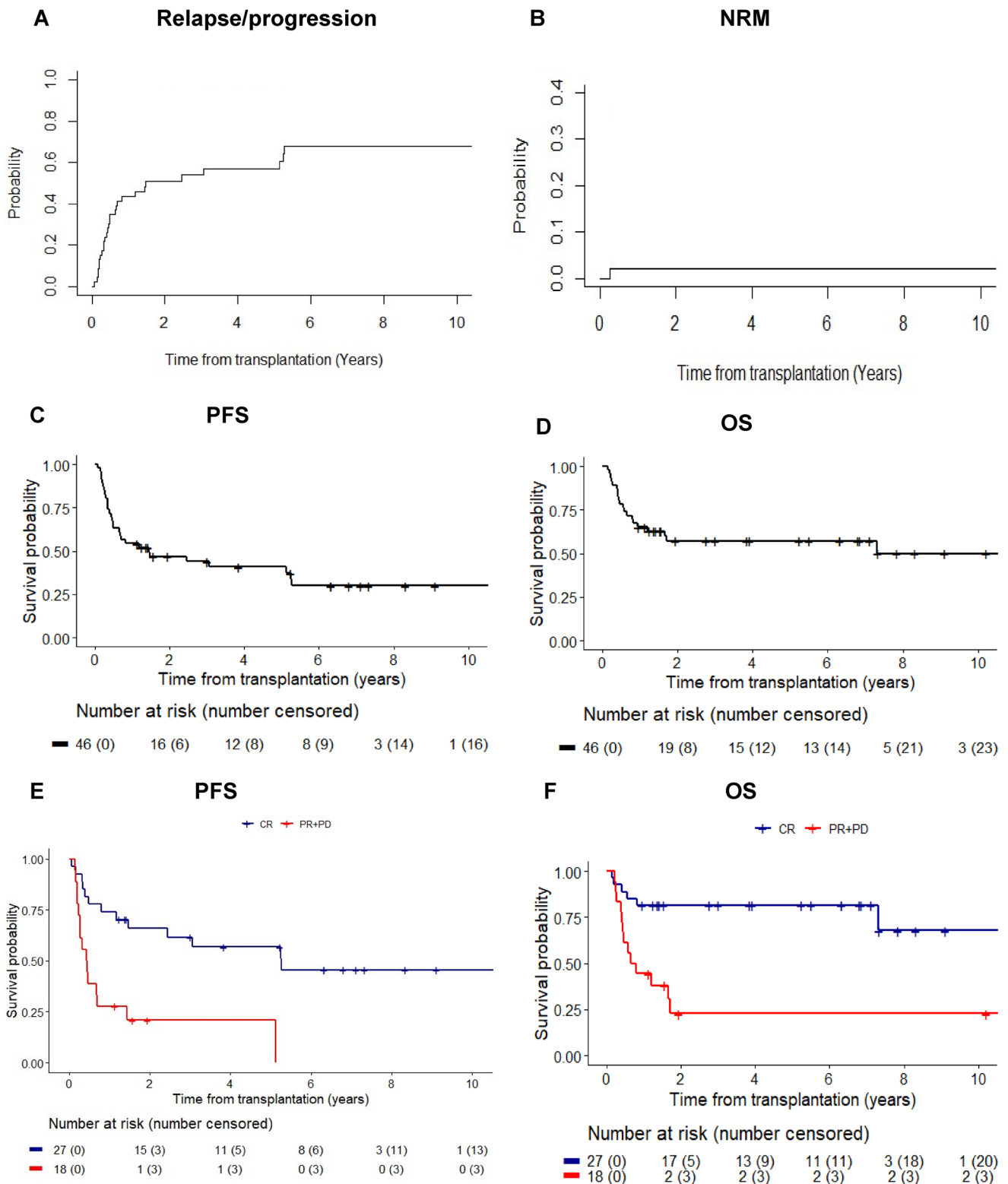


FIGURE 1 | Outcomes after auto-HSCT in HT-WM. (A) Relapse/progression; (B) NRM; (C) PFS; (D) OS; (E) PFS according to disease status at HSCT; (F) OS according to disease status at HSCT.

center-specific transplantation practices. Moreover, owing to the period considered, no information about clonal relationship between the initial WM and HT-WM is available.

In conclusion, HSCT has thus long been established as a valid therapeutic option for patients with transformed DLBCL-like

lymphoma. This was confirmed here in the less frequent context of HT-WM, highlighting that auto-HSCT performed in patients having reached CR appears to be the best option. The control group of patients with not transplanted HT-WM was not ideal for comparison with patients who received auto-HSCT. It nonetheless allowed to demonstrate identical PFS and a trend

towards better OS in the auto-HSCT group. This could be explained by the higher rate of WM relapses without DLBCL in the auto-HSCT group.

Auto-HSCT thus appears to be a feasible and effective approach, associated with durable remission in HT-WM patients, particularly if performed as a consolidative approach for patients in CR.

Acknowledgments

Medical writing for this manuscript was assisted by MPIYP (MC Béné), Paris, France. The authors would like to acknowledge the following people who participated in the study: Bénédicte Hivert (Lille), Caroline Protin (Toulouse), Jithma P. Abeykoon (Rochester), Jehan Dupuis (Créteil), Stéphane Leprière (Rouen), Xavier Roussel (Besançon), and Caroline Regny (Grenoble).

Ethics Statement

The study protocol was conducted according to the Declaration of Helsinki.

Consent

All patients gave their informed consent to have their medical charts reviewed for medical research.

Conflicts of Interest

S.D. reports advisory boards from BeiGene, Sanofi, Hillstar Bio and Cellectar, and research funding and congress expenses from BeiGene. E.T.: COI: BeiGene, AstraZeneca, Roche, and Janssen. J.M.I.V. has received consultancy and advisory board honoraria from Sanofi and Janssen, research support from BeiGene and Abbvie/Genmab, and participated in the speakers' bureau for BMS, Sanofi, and Amgen. All honoraria were directed to the institution. D.T. reports research funds, honoraria and consulting fees from Janssen, Roche, BeiGene, Amgen, CSL Behring, EUSA, Takeda, Novartis, and Antengene. R.G.S. reports honoraria and consulting fees from Janssen, BeiGene, Amgen, Takeda, Incyte, and Astellas. J.M.: Consulting: Pharmacyclics/Abbvie, Bayer, Gilead/Kite, BeiGene, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosunkite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genentech/Roche, ADC Therapeutics, Epizyme, BeiGene, Novartis, Morphosys/Incyte, MEI, T.G. Therapeutics, AstraZeneca, Eli Lilly; Research funding: Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis, BeiGene. Honoraria: Targeted Oncology, OncView, Curio, Physicians' Education Resource, and Seattle Genetics. J.J.C. reports research funds and/or consulting fees from AbbVie, AstraZeneca, BeiGene, Cellectar, Janssen, Kite, LOXO, Mustang Bio, and Pharmacyclics. P.K. reports research funds and/or consulting fees from AbbVie, Sanofi, BMS, Amgen, Ichnos, Karyopharm, AstraZeneca, BeiGene, Cellectar, Janssen, Mustang Bio, and Pharmacyclics.

Data Availability Statement

Data are available upon reasonable requests. Requests for data review should be submitted to the corresponding author.

References

1. D. Talaulikar, C. Tomowiak, E. Toussaint, et al., "Evaluation and Management of Disease Transformation in Waldenström Macroglobulinemia," *Hematology/Oncology Clinics of North America* 37 (2023): 787–799.

2. E. Durot, C. Tomowiak, A. S. Michallet, et al., "Transformed Waldenström Macroglobulinaemia: Clinical Presentation and Outcome. A Multi-Institutional Retrospective Study of 77 Cases From the French Innovative Leukemia Organization (FILO)," *British Journal of Haematology* 179 (2017): 439–448.

3. K. Cwynarski, A. van Biezen, L. de Wreede, et al., "Autologous and Allogeneic Stem-Cell Transplantation for Transformed Chronic Lymphocytic Leukemia (Richter's Syndrome): A Retrospective Analysis From the Chronic Lymphocytic Leukemia Subcommittee of the Chronic Leukemia Working Party and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation," *Journal of Clinical Oncology* 30 (2012): 2211–2217.

4. A. F. Herrera, K. W. Ahn, C. Litovich, et al., "Autologous and Allogeneic Hematopoietic Cell Transplantation for Diffuse Large B-Cell Lymphoma-Type Richter Syndrome," *Blood Advances* 5 (2021): 3528–3539.

5. C. K. Chin, K. J. Lim, K. Lewis, et al., "Autologous Stem Cell Transplantation for Untreated Transformed Indolent B-Cell Lymphoma in First Remission: An International, Multi-Centre Propensity-Score-Matched Study," *British Journal of Haematology* 191 (2020): 806–815.

6. C. Kyriakou, C. Canals, D. Sibon, et al., "High-Dose Therapy and Autologous Stem-Cell Transplantation in Waldenström Macroglobulinemia: The Lymphoma Working Party of the European Group for Blood and Marrow Transplantation," *Journal of Clinical Oncology* 28 (2010): 2227–2232.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.