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Long Term Survival Outcomes of Allogeneic Haemopoietic Stem Cell Transplantation in Patients with Waldenström's Macroglobulinemia.

Report from the Lymphoma Working Party of The European Society for Blood and Marrow Transplantation (LWP EBMT)

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Waldenström's Macroglobulinemia (WM) is a rare subtype of low-grade B- cell non -Hodgkin lymphoma characterised by bone marrow infiltration with lymphoplasmacytic cells and secretion of clonal IgM paraproteinemia. The major progress in our understanding of the WM biology has enabled advances in the management of the disease. There are multiple treatment options ranging from standard chemo immunotherapies to new targeted therapies that have achieved prolong survivals but there is no cure so far. In the era of the new agents, the role of allogeneic haemopoietic stem cell transplantation (allo-HSCT) as rescue approach is not clear.

This retrospective analysis was focused on the outcomes of allo-HSCT in 330 patients with WM, reported in the EBMT registry between 2000-2021. 117 patients were transplanted between 2000-2010, 125 in 2010-2015 and 88 in 2015-2021. The median age was 55years (IQR: 45 -60), 73% were male and the median time from diagnosis to allo-HSCT was 44 months (IQR: 19-95). Allo-HSCT was used following, 1 prior line of therapy in 11%, 2 prior therapy lines in 20% and ≥ 3 in 68% of the patients. Autologous – HSCT was used in 21% prior to proceeding to the allo-HSCT. Disease status at the allo-HSCT was \geq VGPR in 30%, PR in 45%, relapse or primary refractory (RR) in 26%. Karnofsky was <90 in 25%. Conditioning regimen was TBI based in 61%. Reduced Intensity conditioning (RIC) was administered in 63% and 37% had Myeloablative conditioning (MAC). PB stem cell source was in 89% and 43% had matched related donor, 46% matched unrelated, 9% haploidentical.

With a median follow-up of 8.3years (95%CI: 6.7-9.1) the 2, 5, 10 years estimated OS rates were 62.9%, 54.0% and 47.3%. The PFS at 2, 5 and 10 years were 58.7%, 44.6%, 34.7%. The relapse rates (RR) at the same times were at 21.0%, 31.1% and 37.3% and Non-Relapse Mortality (NRM) at 20.2%, 24.3%, 27.98% respectively. The acute graft versus host disease (aGVHD) grade II-IV incidence was 26.7% (grade III-IV, 12,6%) and the estimated chronic GVHD (cGVHD) incidence was 33.4%, 42.4% and 45.5% at 1, 2 and 5 years with the incidence of extensive cGVHD at these times of 11.4%, 18.2% and 22.8% respectively. On multivariate analysis, patients with Karnofsky performance status >90 ($p= 0.009$, HR:0.59, 95% CI: 0.39-0.87), had better OS, whilst the relapse/refractory/progressive disease status at allo-HSCT had significant impact on OS ($p=0.017$, HR: 1.85, 95% CI: 1.12-3.08), PFS ($p=0.007$, HR: 1.95, 95%CI: 1.20-3.16) and relapse rate ($p=0.023$, HR: 2.04, 95% CI: 1.11-3.76). HLA mismatched HSC donor type was associated with significantly higher incidence of cGVHD ($p=0.029$, HR: 0.26, 95% CI: 0.08-0.87).

In the era of BTK and BCL2 inhibitors, chemo-immunotherapies and forthcoming T cell engagers with bispecific antibodies and CART cell therapies in lymphomas, it is challenging to define the role or timing

for allo-HSCT in WM treatment pathway. This real world European retrospective study showed that, a small group of patients who were transplanted based on local center treatment criteria have achieved prolong OS and PFS survival with acceptable toxicities.