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LETTER TO THE EDITOR

Outcomes of autologous stem cell transplantation in Waldenström's macroglobulinemia

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Dear Editor,

Waldenström's macroglobulinemia (WM) is a rare lymphoproliferative disease representing 1–2% of all non-Hodgkin lymphomas [1] and is characterized by the presence of IgM monoclonal gammopathy and lymphoplasmacytic lymphoma (LPL) cells in the bone marrow. Due to the indolent and incurable nature of the disease, the clinical course for most patients is marked by multiple relapses and several lines of chemotherapy. Novel drugs, such as proteasome inhibitors and ibrutinib [2, 3], along with autologous hematopoietic stem cell transplantation (auto-HCT) have vastly expanded therapeutic armamentarium for WM patients. However, the role and timing of auto-HCT remain ambiguous in the management of this disease. With the aim of evaluating the role of auto-HCT in WM patients, we present here an updated analysis of our previously published experience [4] with a larger cohort of WM patients who underwent auto-HCT at our institution. The study cohort comprised of 29 patients who underwent high-dose chemotherapy and auto-HCT at MD Anderson Cancer Center (MDACC) between January 1994 and June 2018. The hematologic response was measured as per the IMWG response criteria. The Kaplan–Meier method was used to create survival curves. Overall survival (OS) was defined as the time from the date of transplant to death or the date of the last follow-up in living patients. Progression-free survival (PFS) was defined as the time from the date of transplant to either progressive disease or death, whichever occurred first.

Patient characteristics are described in Table 1. Median age at auto-HCT was 60 (range, 43–75 years). Patients received a median of 2 lines (range 1–6) of therapy before auto-HCT. Eight patients (28%) had concurrent light chain amyloidosis (AL). Of the five patients who had MYD88 testing, 3 were positive for the MYD88 mutation. Additionally, 2 of these 3 patients were also positive for the CXCR4 mutation. The response to induction prior to auto-HCT was complete response (CR) (2/29, 7%), very good partial response (VGPR) (1/29, 3%), partial response (PR) (16/29, 55%), stable disease (SD) (8/29, 28%), and progressive disease (PD) (2/29, 27%). Three patients went on to receive a subsequent allogeneic transplant either after relapse from auto-HCT or due to disease transformation to aggressive lymphoma.

Median time from auto-HCT to the last follow-up for the surviving patients was 5.3 years (range 4–156 months). Twenty-eight patients achieved engraftment with a median time to neutrophil engraftment of 11 days (range, 10–15 days). One patient had primary graft failure due to the progression of the disease and died 84 days after transplant. Non-relapse mortality was 3.4% at 1 year. Sixteen patients were alive at the time of censoring while 13 patients had died. The causes of death include relapsed disease ($n = 5$), chronic graft-versus-host disease from an allogeneic transplant ($n = 1$), primary autologous graft failure secondary to progression of the disease ($n = 1$), secondary malignancy ($n = 2$), and unknown causes ($n = 4$).

All patients were eligible for response evaluation. Overall response rate was 96%: complete response ($n = 8$, 27.6%), very good partial response ($n = 5$, 17.3%), partial response

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Table 1 Patient characteristics for the whole cohort

Patient characteristics ($n = 29$)	
Parameter, median (range)	
Age, years	60 (43–75)
Hemoglobin, g/dL	10.2 (6.6–14.6)
Platelet count, $\times 10^9$/L	263.5 (53–538)
B2 microglobulin	2.98 (1.4–5)
IgM, mg/dL	1704 (347–5130)
CD34 cell counts, $\times 10^6$/kg	5.22 (1–50)
WM-IPSS, *n* (%)	
High	5 (17.2)
Intermediate	9 (31.0)
Low	7 (24.1)
Missing	8 (27.6)
Disease status at auto-HCT, *n* (%)	
First remission consolidation	8 (28%)
Primary refractory	3 (10%)
Relapse	18 (62%)
Induction regimens, *n*	
PI-based	10
Cyclophosphamide-based	5
PI + conventional chemotherapy	6
Cladribine	3
Chlorambucil	1
Revlimid-rituximab	1
Melphalan	1
Others	2
Conditioning regimens, *n*	
Melphalan ± rituximab	20
BEAM ± rituximab	5
Busulfan + melphalan	1
Cyclophosphamide/etoposide/TBI	1
Thiotepa/busulfan/cyclophosphamide	1
Carmustine/thiotepa	1

BEAM, carmustine, etoposide, cytarabine, melphalan; *PI*, proteasome inhibitor; *TBI*, total body irradiation

27 out of 29 patients had received rituximab as a prior therapy either in combination with above induction regimens or alone

($n = 15$, 51.7%), and progressive disease ($n = 1$, 3.4%). Four patients with PR and 3 with SD/PD at auto-HCT upgraded their response to CR after auto-HCT. The median OS from diagnosis was 12.2 years. Seventeen (58%) patients have relapsed at the last follow-up with an estimated 2-yearr and 5-year PFS of 74% and 43.3%, respectively. The 2-year and 5-year OS rates were 89% and 62%, respectively. Median PFS and OS from auto-HCT were 4.1 and 7.3 years, respectively (Fig. 1A). Melphalan ± rituximab was the most common conditioning regimen in our patients. Median PFS and OS in patients receiving that regimen were 4.1 and 7.3 years, respectively, similar to the overall cohort. Among the 18 patients who had auto-HCT for relapsed disease, the median PFS and OS were 3.1 and 4.1 years, respectively. In contrast, median PFS and OS for 8 patients who had auto-HCT in first remission were 4.5 and 12.2 years, respectively.

Eight patients (28%) also had concurrent AL amyloidosis. The median overall survival for patients with concurrent AL ($n = 8$) was 12 years, longer than the full cohort. On univariate analyses, the number of chemotherapy regimens before transplant (≤ 2 vs > 2 lines) was the strongest predictor of PFS (HR 0.24; CI, 0.07–0.85; $p = 0.001$ log-rank) and OS (HR 0.3; CI, 0.09–0.9; $p = 0.03$ log-rank). The median PFS in patients with ≤ 2 lines and > 2 lines of therapy was 5.9 years versus 1.6 years, respectively (Fig. 1B). The median OS in patients with ≤ 2 lines and > 2 lines of therapy was 8.1 years versus 3 years, respectively.

There is heterogeneity in survival outcomes in WM patients as shown by the International Prognostic Staging System (WM-IPSS), with 5-year OS in low and high risk-group patients at 87% and 36%, respectively [5]. Patients in the high-risk group may benefit from an early auto-HCT,

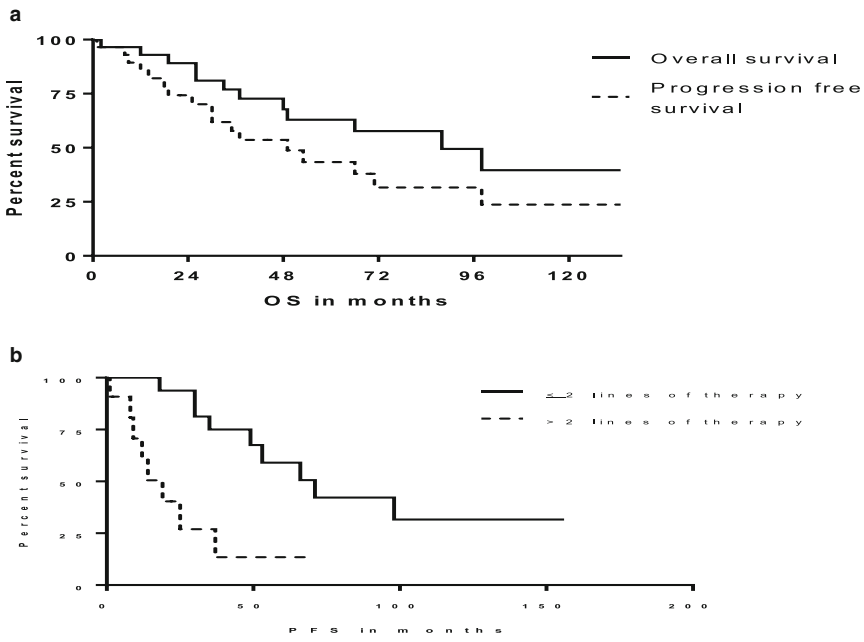

Fig. 1 **a** Kaplan-Meier curve demonstrating OS and PFS for the cohort. **b** Kaplan-Meier curve demonstrating PFS stratified according to the number of previous lines of therapy

which can provide a durable chemotherapy-free remission of > 4 years as shown in this analysis. In a previously published EBMT registry study involving 158 WM patients, auto-HCT was associated with a 5-year PFS and OS of 40% and 68%, respectively [6]. In that study, chemorefractory disease and at least three lines of therapy before transplant were the most important independent prognostic factors for a significantly shorter PFS. As corroborated by other studies [6–8], our data also suggests that utilizing auto-HCT early in the course of disease than at a later stage, when the disease might be chemorefractory, may be more beneficial.

Recently, the ibrutinib-rituximab combination showed durable remission (82% PFS at 30 months) in the iNNOVATE trial [3]. With the emergence of several effective novel therapies, including ibrutinib and rituximab [9], and the relatively infrequent use of auto-HCT in WM, its role and timing in WM remains unclear. However, our data and previous registry reports underscore the safety, feasibility, and effectiveness of auto-HCT in selected patients with WM. We believe that auto-HCT may be considered in WM patients after they fail 1–2 lines of therapy, as it is still associated with durable remisison. In conclusion, given the safety, high response rate and durable remission with auto-HCT in WM, it can be utilized in selected patients with high-risk or relapsed disease.

Compliance with ethical standards

Conflict of interest Authors do not have any relevant conflict of interest to declare.

Ethical approval This was a retrospective evaluation of patient's chart data and approval was obtained from the Institutional Research Board at MD Anderson Cancer Center. The study was conducted in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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