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Omar Albanyan
Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA, albanyao@mclaren.org

Samer Alkassis
Department of Internal Medicine, Wayne State University, Detroit, MI, USA

Seongho Kim
Biostatistics Core, Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA

Andrew Kin
Department of Oncology, Blood and Marrow Stem Cell Transplant Program, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA

Asif Alavi
Department of Oncology, Blood and Marrow Stem Cell Transplant Program, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA

See next page for additional authors

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Authors

Omar Albanyan, Samer Alkassis, Seongho Kim, Andrew Kin, Asif Alavi, Lois Ayash, Voravit Ratanatharathorn, Dipenkumar Modi, Joseph P. Uberti, and Abhinav Deol

LETTER TO EDITOR

Impact of Pre-transplant Induction Therapy on Outcomes of Patients Who Undergo Autologous Stem Cell Transplantation for Mantle Cell Lymphoma in First Complete Remission☆

Omar Albanyan [a,*], Samer Alkassis [b], Seongho Kim [c], Andrew Kin [d], Asif Alavi [d], Lois Ayash [d], Voravit Ratanatharathorn [d], Dipenkumar Modi [d], Joseph P. Uberti [d], Abhinav Deol [d]

[a] Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA
[b] Department of Internal Medicine, Wayne State University, Detroit, MI, USA
[c] Biostatistics Core, Department of Oncology, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA
[d] Department of Oncology, Blood and Marrow Stem Cell Transplant Program, Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA

Abstract

Mantle cell lymphoma is a rare subtype of non-Hodgkin's lymphoma with poor prognosis and continue to be challenging to treat. The choice of first line induction regimen remains a topic of debate due paucity of clinical trials. We retrospectively evaluated 66 patients diagnosed with mantle cell lymphoma who achieved first complete response after induction chemotherapy followed by autologous stem cell transplant. Treatment groups were divided into low-intensity versus high-intensity regimens. Our data showed the intensity of induction regimen does not impact posttransplant outcomes of mantle cell lymphoma who underwent autologous stem cell transplant in first complete response.

Keywords: Autologous stem cell transplant (ASCT), Mantle cell lymphoma (MCL), Peripheral blood stem cell transplant (PBSCT)

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma that carries a poor prognosis compared to other subtypes of Non Hodgkin Lymphoma (NHL) with a reported median overall survival (OS) of 4.7 years [1–3]. As of today, there is no standard induction chemotherapy regimen. Most common approaches based on age, performance status and disease status include chemotherapy alone or followed by a consolidative autologous stem cell transplant (ASCT) [4–6].

We conducted a retrospective study of adult patients diagnosed with MCL and achieved first complete response (CR-1) followed by ASCT. Between January 2005 and December 2016, 66 patients underwent ASCT after R-BEAM preparative regimen in CR-1. Patients were divided into two groups based on the induction regimens: low-intensity regimens (R-CHOP, Bendamustine/Rituximab (BR)) versus high-intensity regimens (Hyper-CVAD/Rituximab, Nordic Regimen, R-CHOP alternating with R-DHAP, R-DHAP, and R-EPOCH). The primary objectives were to evaluate relapse-free survival (RFS), OS, nonrelapse mortality (NRM), and relapse rate between patients achieved CR-1 that was followed by ASCT using low-intensity regimens versus the high-intensity

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* Corresponding author at: Department of Oncology, Karmanos Cancer Institute/Wayne State University, 4100 John R, HW04H0, Detroit, MI 48201, USA.
E-mail address: albanyao@mclaren.org (O. Albanyan).

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regimens. Patient baseline characteristics are detailed in Table 1. The median time to platelet engraftment was 12 days and 18 days for low-intensity and high-intensity groups, respectively, ($p = .001$). The median time to neutrophil engraftment was 11 days for both groups. The median follow-up of surviving patients was 4.2 years and 4.9 years for low-intensity and high-intensity groups, respectively. For low-intensity regimen and high-intensity regimen groups, the 3-year OS was 95.7% and 79.1%, respectively (hazard ratio [HR] = 0.77, $p = .59$) and the median OS was 5.9 years (95% confidence interval [CI], 5.75 to not estimable [NE]) and not reached for low-intensity and high-intensity groups, respectively. The 3-year RFS was 83.7% and 66.9% for low-intensity and high-intensity regimens, respectively (HR = 1.05, $p = .88$), and the median RFS was 7.0 years (95% CI, 4.54 to NE) and 5.3 years (95% CI, 3.04 to NE) for low-intensity and high-intensity groups, respectively (Fig. 1A and B). The 3-year cumulative incidence rate of NRM was 4% (95% CI, 0.3–17.4) and 2.7% (95% CI, 0.2–12.3) ($p = .15$) for low-intensity and high-intensity groups, respectively. The 3-year cumulative incidence rate of relapse was 12.4% (95% CI, 3–28.8) and 30.4% (95% CI, 16.2–45.9) for low-intensity and high-intensity groups, respectively ($p = .25$). Multivariable analysis adjusted for the intensity of the regimen, age, Karnofsky performance status (KPS), and duration from diagnosis to transplant showed no differences in OS, RFS, relapse rate, and NRM between low-intensity and high-intensity regimen groups. Older age was associated with worse OS (HR = 1.12; 95% CI, 1.04–1.21; $p = .004$), KPS < 80% was associated with higher NRM (HR = 25.1; 95% CI, 8.51–74.16; $p < .001$) and prolonged duration from diagnosis to transplant was associated with worse RFS (HR = 1.005; 95% CI, 1.001–1.008; $p = .015$).

MCL remains challenging to treat because of the disease rarity and paucity of evidence from

Table 1. Patient Baseline Characteristics.

	Low intensity ($N = 25$)	High intensity ($N = 41$)	All ($N = 66$)	p
Age at transplant, median (range)	58 (42,70)	55 (38,75)	56 (38,75)	0.183
Sex, *n* (%)				0.269
Female	10 (40)	10 (24)	20 (30)	
Male	15 (60)	31 (76)	46 (70)	
Race, *n* (%)				>0.99
Non-Caucasian	2 (8)	4 (10)	6 (9)	
Caucasian	23 (92)	37 (90)	60 (91)	
Induction therapy, *n* (%)				<0.001
R-CHOP	21 (84)	0 (0)	21 (32)	
Hyper-CVAD	0 (0)	28 (68)	28 (42)	
Nordic regimen	0 (0)	9 (22)	9 (14)	
R-EPOCH	0 (0)	1 (2)	1 (2)	
BR	4 (16)	0 (0)	4 (6)	
RCHOP/RDHAP	0 (0)	1 (2)	1 (2)	
Hyper-CV/B.R.	0 (0)	1 (2)	1 (2)	
Hyper-CVAD/R- CHOP/R-CVP	0 (0)	1 (2)	1 (2)	
Stage at diagnosis, *n* (%)				>0.99
II	1 (4)	1 (2)	2 (3)	
III	1 (4)	1 (2)	2 (3)	
IV	23 (92)	39 (95)	62 (94)	
Bone marrow involvement, *n* (%)				0.465
No	4 (16)	4 (10)	8 (12)	
Yes	21 (84)	37 (90)	58 (88)	
Priming agents, *n* (%)				0.102
G-CSF + CY	4 (16)	2 (5)	6 (9)	
G-CSF	17 (68)	25 (61)	42 (64)	
G-CSF + plerixafor	3 (12)	13 (32)	16 (24)	
Missing	1 (4)	1 (2)	2 (3)	
Infused CD34, median (range)	4.22 (1.48–9.34)	3.36 (1.8–9.6)	3.55 (1.48–9.6)	0.054
Admit KPS, median (range)	80 (60–90)	80 (70–100)	80 (60–100)	0.989
Days from diagnosis to transplant, median (range)	213 (167–953)	202 (138–589)	206.5 (138–953)	0.108

*Note.*R-CHOP= Rituxima, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone; R-EPOCH= Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin; BR= Bendamustine and Rituximab; G-CSF = granulocyte-colony-stimulating factor; CY= Cyclophosphamide KPS = Karnofsky performance status.

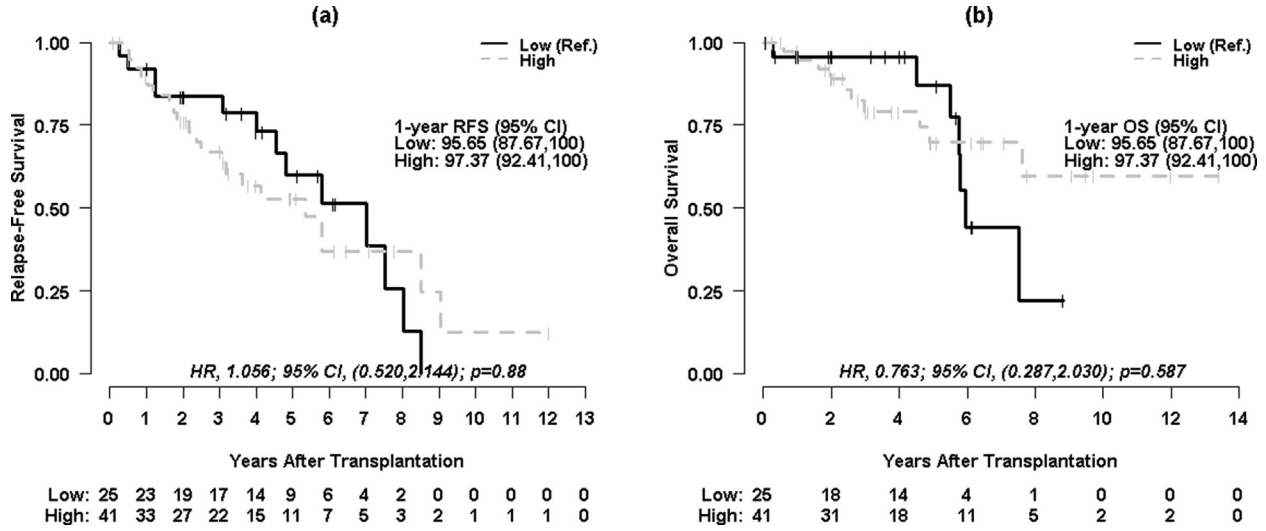

Fig. 1. Kaplan–Meier plots for relapse-free survival (RFS) and overall survival (OS) by intensity (Group 2: High vs. Group 1: Low, Group 1 as reference). (A) The median RFS is 7.00 years (95% confidence interval [CI], 4.54 to NE) and 5.34 years (95% CI, 3.04 to NE) for Group 1 and Group 2, respectively. The median follow-up time of RFS is 5.71 years (95% CI, 4.02 to NE) and 5.11 years (95% CI, 3.79 to NE) for Group 1 and Group 2, respectively. (B) The median OS is 5.96 years (95% CI, 5.75 to NE) and not reached for Group 1 and Group 2, respectively. The median follow-up time of OS is 4.18 years (95% CI, 3.21 to NE) and 4.93 years (95% CI, 3.10 to 6.48) for Group 1 and Group 2, respectively. The follow-up time was calculated using the reverse Kaplan–Meier estimate. Note. HR = hazard ratio; NE = not estimable.

randomized clinical trials. Despite the advancement in understanding the disease's biology and the development of new therapeutic approaches, it continues to carry a poor prognosis [3,4]. We reported no significant difference in OS, RFS, NRM, and relapse rate for patients who achieved a complete response after either low-intensity regimen or high-intensity regimen followed by ASCT. One approach based on age and performance status is to treat fit patients with aggressive chemotherapy followed by ASCT [7–10]. Hermine et al. showed the addition of high dose cytarabine improved time to treatment failure but with increase in grades 3 and 4 hematological toxicity [9]. The only randomized trial showing the benefit of ASCT was conducted by Dreyling et al. [11], comparing consolidative ASCT with interferon (IFN)-α maintenance after induction with CHOP (cyclophosphamide, hydroxydaunorobicin, oncovin, prednisone or prednisolone)-like regimen showed a significant improvement in PFS with a median PFS of 39 months compared with 17 months, respectively (p = .0108). Our study showed a better outcome in both low intensity and high intensity than what was reported, and this can be attributable to the addition of rituximab to the induction regimen [11]. In a retrospective analysis by Gerson et al. [12] reported in the rituximab era, consolidative ASCT is associated with improvement in PFS with only a trend of improvement in OS in a subset of patients treated with CHOP-like regimen, high MIPI (Mantle Cell Lymphoma International Prognostic Index) score, blasted or pleomorphic variant. Similar to our finding, Ng et al. [13] reported that the choice of chemoimmunotherapy induction regimen had no significant impact on OS, overall response rate, and PFS. Our study showed more patients required granulocyte colony stimulating factor (G-CSF) plus plerixafor for stem cell collection in the high-intensity group compared with the low-intensity group, and patients who received high-intensity chemotherapy were able to mobilize a lower number of CD34 + ve cells. This finding raises the concern for difficulty in stem cell mobilization as seen in the SWOG S1106 trial, where BR was compared to HyperCVAD, and the trial had to be terminated early because of high mobilization failure in the HyperCVAD arm [14].

Our finding needs to be interpreted with caution because of several limitation factors, such as small sample size, potential bias in assigning patients to low-intensity versus high-intensity regimen at diagnosis with the retrospective nature of our study. The majority of the patients were diagnosed and received induction chemotherapy at outside facilities and were referred for transplant to our center; thus, we could not reliably obtain data regarding Ki67, MIPI score at the time of diagnosis, or post-transplant maintenance rituximab. We were not able to obtain information for patients who were not referred for ASCT evaluation.

In conclusion, our data showed no significant difference in transplant outcomes based on the

induction regimen for patients who undergo ASCT in CR-1. To some degree, this provides reassurance for patient who achieves CR-1 prior to transplant regardless of induction chemotherapy used. More information will be provided by the Eastern Cooperative Oncology Group (ECOG) clinical trial NCT03267433 looking at minimal residual disease negative patients who were treated with either low-intensity or high-intensity regimen followed by ASCT versus rituximab maintenance alone.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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