blood advances

TO THE EDITOR:

Outcomes after autologous hematopoietic cell transplantation in POEMS syndrome and comparison with multiple myeloma

Ankit Kansagra,[1] Angela Dispenzieri,[2] Raphael Fraser,[3,4] Noel Estrada-Merly,[4] Surbhi Sidana,[5] Taiga Nishihori,[6] Doris K. Hansen,[6] Larry D. Anderson, Jr.,[1] Rahul Banerjee,[7] Naresh Bumma,[8] Binod Dhakal,[9] Jack Khouri,[10] Heather Landau,[11] Cindy Lee,[12] Hira Mian,[13] Sunita Nathan,[14] Bipin Savani,[15] Shaji Kumar,[16] Muzaffar Qazilbash,[17] Nina Shah,[7] and Anita D'Souza[4]

[1]Department of Medicine, UT Southwestern Medical Center, Blood and Marrow Transplant Program, Dallas, TX; [2]Division of Hematology, Mayo Clinic, Rochester, MN; [3]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI; [4]Department of Medicine, Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI; [5]Department of Medicine, Standford University School of Medicine, Stanford, CA; [6]Department of Blood & Marrow Transplant and Cellular Immunotherapy (BMT CI), Moffitt Cancer Center, Tampa, FL; [7]Division of Hematology-Oncology; University of California San Francisco, San Francisco, CA; [8]Department of Medicine, Ohio State Medical Center, James Cancer Center, Columbus, OH; [9]Division of Hematology/Oncology, Bone Marrow Transplantation and Cellular Therapy, Medical College of Wisconsin, Milwaukee, WI; [10]Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, OH; [11]Bone Marrow Transplant Service, Division of Hematology, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; [12]Royal Adelaide Hospital, Adelaide, SA, Australia; [13]Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada; [14]Section of Bone Marrow Transplant and Cell Therapy, Rush University Medical Center, Chicago, IL; [15]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [16]Mayo Clinic, Rochester, NY; and [17]MD Anderson Cancer Center, Houston, TX

POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome (aka, osteosclerotic myeloma) is a paraneoplastic syndrome associated with an underlying plasma cell neoplasm.[1,2] Effective treatment of POEMS syndrome involves control of the underlying plasma cell clone, which often leads to vascular endothelial growth factor (VEGF) response and improvement in clinical symptoms.[3] Multiple studies of autologous hematopoietic cell transplantation (autoHCT) in POEMS syndrome exist; however, most are single-center experiences without data on long-term toxicity, including the risk of second primary malignancies (SPM).[4-10] We report the outcomes of an international cohort of patients with POEMS syndrome undergoing autoHCT, emphasizing toxicities in comparison with multiple myeloma (MM) along with long-term safety and outcomes.

The Center for International Blood and Marrow Transplant Research (CIBMTR) database is a research collaboration between the Medical College of Wisconsin and The National Marrow Donor Program, comprised of more than 300 centers worldwide. Participating centers report all consecutive transplants consecutively and patients are followed longitudinally. CIBMTR studies comply with federal regulations on protecting human research participants; protected health information is collected and maintained in CIBMTR's capacity as a public health authority under the HIPAA Privacy Rule. All POEMS syndrome patients reported to the CIBMTR aged ≥18 years who underwent autoHCT between 2008-2018 with melphalan conditioning were identified.

Nonrelapse mortality (NRM) was defined as death from any cause within the first 100 days or after that in the absence of relapse or progression. Progression-free survival (PFS) was defined as the time from transplantation to relapse, progression, or death from any cause. Overall survival (OS) was defined as the time from transplantation to death from any cause. Standard definitions for neutrophil and platelet engraftment definitions were used.[11]

Covariates were summarized using descriptive statistics. Probabilities of PFS and OS were calculated using Kaplan-Meier product-limit estimate using the log-rank test. The cumulative incidence of NRM and disease relapse/progression were estimated, accounting for competing risks. We compared outcomes

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The full-text version of this article contains a data supplement.

Table 1. Characteristics of patients with POEMS syndrome undergoing autoHCT

Characteristic	N = 331 (%)
Median age (range), median (min-max)	51 (18-77)
Sex	
Male (%)	220 (66)
Female (%)	111 (34)
Race, no. (%)	
White	215 (65)
Black or African American	64 (19)
Asian	17 (5)
Native Hawaiian or other Pacific Islander	1 (0)
American Indian or Alaska Native	1 (0)
Missing	33 (10)
Region, no. (%)	
United States	303 (92)
Canada	10 (3)
Asia	9 (3)
Australia/New Zealand	3 (1)
Middle East/Africa	1 (0)
Central/South America	5 (2)
Karnofsky score, no. (%)	
≥90	89 (27)
<90	233 (70)
Missing	9 (3)
HCT-CI, no. (%)	
0	81 (24)
1	38 (11)
2	43 (13)
3	81 (24)
4	41 (12)
5	22 (7)
6+	21 (7)
Missing	4 (1)
Creatinine, mg/dL; no. (%)	
mgdL	319 (96)
mgdL	7 (2)
Missing	5 (2)
Melphalan dose(mg/m), no. (%)	
MEL 140	42 (13)
MEL 200	289 (87)
Organ comorbidity based on HCT-CI: cerebrovascular, no. (%)	18 (5)
Organ involvement based on HCT-CI: hepatic, no. (%)	10 (3)
Organ involvement based on HCT-CI: pulmonary, no. (%)	172 (52)
Mobilization, no. (%)	
G-CSF + plerixafor	94 (28)
G-CSF	72 (22)
G-CSF + chemotherapy	29 (9)
G-CSF + plerixafor + chemotherapy	5 (2)
Chemotherapy	2 (1)
Unknown	129 (39)
Disease status prior to transplant, no. (%)	
sCR/CR	23 (7)
VGPR	22 (7)
PR	79 (24)
SD	87 (26)
PD/relapse	19 (6)
Never treated	72 (22)
Missing	29 (8)
Time from diagnosis to HCT, no. (%)	
mo	132 (40)
6-12 mo	112 (34)
12-24 mo	44 (13)
mo	42 (13)
Missing	1 (0)
Year of transplant, no. (%)	
2008	15 (5)
2009	14 (4)
2010	19 (6)
2011	25 (8)
2012	27 (8)
2013	37 (11)
2014	35 (11)
2015	41 (12)
2016	50 (15)
2017	32 (10)
2018	36 (11)
Follow-up median (range)	48 (3-137)

CR, complete response; sCR, stringent CR; G-CSF, granulocyte colony-stimulating factor; PD, progressive disease; SD, stable disease.

of patients with POEMS syndrome to patients with MM having comprehensive report form (CRF) level data for 2008-2018 (n = 2501) from a published study.[12] Multivariate analysis was conducted using the Cox proportional hazard regression model to understand the association between patient-, disease-, and transplant-related factors with PFS and OS. The variables considered in the stepwise model included age at transplant, sex, race, Karnofsky performance status at transplant (KPS) (≥90% vs <90%), HCT comorbidity index (HCT-CI 0 vs 1 vs 2 vs 3 vs 4 vs ≥5), serum creatinine before transplant (≥2 vs <2 vs missing), organ involvement (pulmonary vs cerebrovascular vs hepatic vs other), VEGF level, disease status at transplant (untreated vs complete response/very good partial response (VGPR)/partial response (PR) vs less than PR vs relapsed/progressed), and time from diagnosis to autoHCT (<6 months vs 6-12 months vs 12-24 months vs >24 months). A P value <.05 was considered significant. The statistical package SAS version 9.4 was used.

Between 2008-2018, 331 patients with POEMS syndrome from 92 centers were identified (Table 1). The median age at transplant was 51 years (range, 18-77), with 66% males and 64 (19%) Black. Most patients (70%) had KPS <90%, and 165 (50%) had an

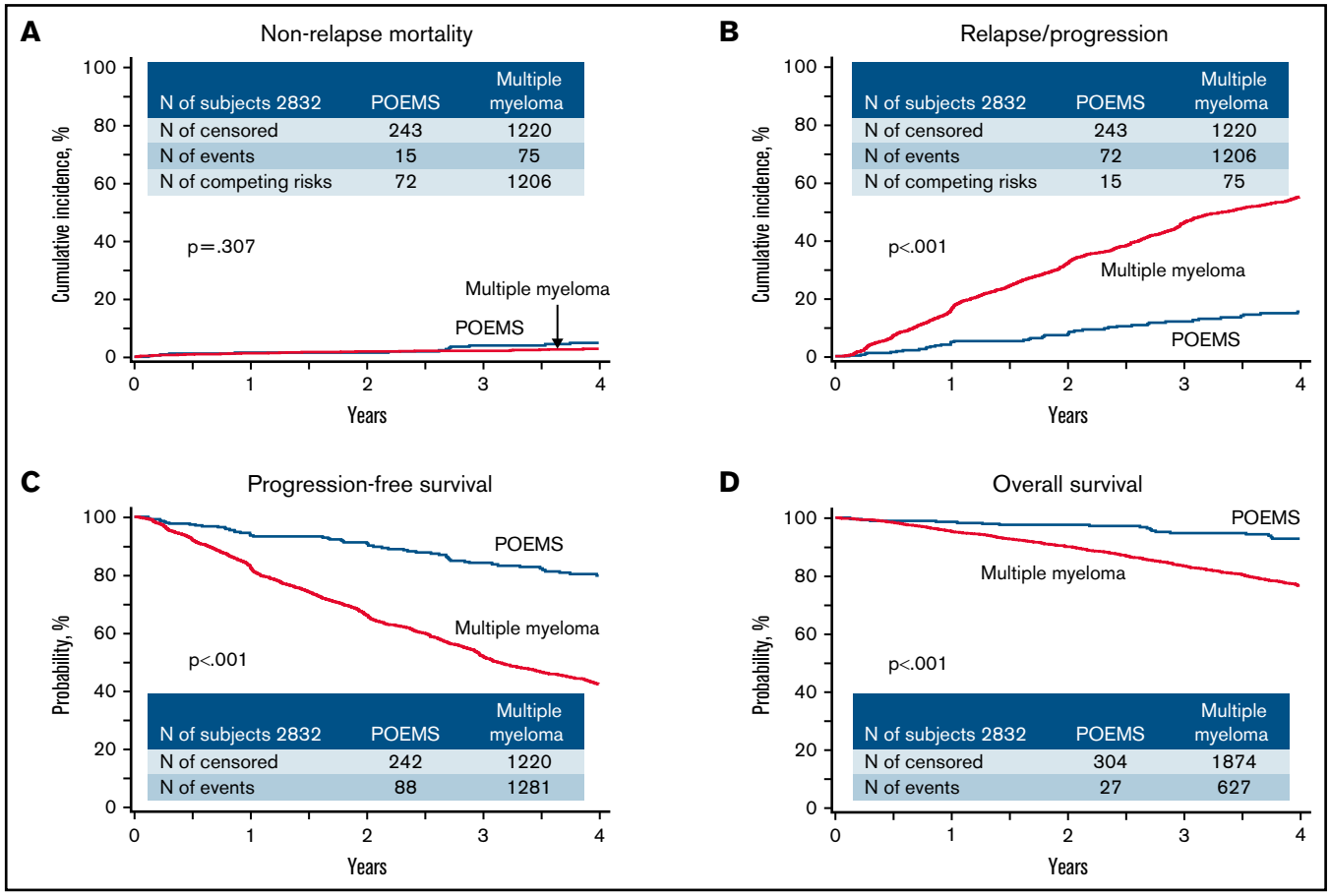

Figure 1. Outcomes of patients with POEMS syndrome and Multiple Myeloma after autoHCT.

HCT-CI of ≥3. Pulmonary comorbidities were present in 172 (52%) patients, followed by the cerebrovascular system in 18 (5%) and hepatic in 10 (3%). Pre-HCT hematological disease response included 45 (14%) in VGPR or better, 79 (24%) in PR, 87 (26%) with stable disease, and 19 (6%) patients with progressive disease. Median time to autoHCT was 7 months. Mobilization strategies included G-CSF alone in 72 (22%) patients, in combination with plerixafor for 94 (28%) patients, and with chemotherapy in 29 (9%) patients. Eighty-seven percent received 200 mg/m^2 of melphalan as conditioning chemotherapy. The median follow-up of survivors was 48 months (range, 3-137 months). In the CRF cohort (n = 47), we identified engraftment rate of 15%, with most of them needing corticosteroid treatment. The majority of patients (n = 39) had hospitalization of <21 days. The median time from autoHCT to neutrophil engraftment was 13 days and platelet engraftment of 18 days, respectively.

Univariate analysis of outcomes showed that day 100 NRM was 0.9% (95% confidence interval [CI], 0.2% to 2.2%); 1-year NRM was 1.5% (95% CI, 0.5% to 3.1%), and 4-year NRM was 4.9% (95% CI, 2.6-7.9). The 4-year PFS was 79.7% (95% CI, 74.5% to 84.3%), and the 4-year OS was 92.7% (95% CI, 89.2% to 95.6%). On comparison of outcomes with those of MM patients, no difference in NRM at 100 days (P = .623), 1 year (P = .706) or 4 years (P = .128) was seen. Five-year outcomes were superior among patients with POEMS syndrome compared with MM: 5-year PFS (72.2% vs 34.5%; P = .001) and 5-year OS (90.9% vs 71%; P = .001), Figure 1. On multivariable analysis, the only factor significant for worse OS included age of >60 years (hazard ratio, 2.6; 95% CI, 1.2-5.6; P = .0148) at autoHCT. There were no significant predictors for relapse, NRM, and PFS.

Our database analysis is the largest study to date on outcomes of patients with POEMS syndrome undergoing autoHCT. Although therapies including lenalidomide, bortezomib, and daratumumab[13,14] have shown good hematologic disease control in POEMS syndrome, autoHCT remains an effective therapy in this disease.[15] With 50% of patients having a HCT-CI index of ≥3 and 70% with KPS <90, our study elucidates the safety of autoHCT in patients with POEMS syndrome and multiple underlying comorbidities.[16-19]

We describe the practice patterns and multicenter autoHCT clinical experience in POEMS syndrome, such as induction therapy and mobilization strategies. Induction therapy available in the 14% of patients (n = 47) with comprehensive research data included bortezomib and lenalidomide with dexamethasone in 45% of those patients. Pre-HCT disease status had no impact on posttransplant outcomes, though this can be hard to assess given that patients often have low M-spikes to follow. These findings contrast with light chain amyloidosis, where induction therapy has shown benefit.[20] Although the ideal mobilization strategy is not defined in POEMS

syndrome, a small study suggested that cyclophosphamide with G-CSF may reduce the incidence of engraftment syndrome.[21] We identified G-CSF plus or minus plerixafor as the predominant strategy in 50%, with only 12% getting chemotherapy mobilization. We identified an engraftment syndrome rate of 15%, in range with published literature describing rates between 6% to 37%.[5,8,10]

Finally, comparison of outcomes of POEMS syndrome with MM outcomes did not identify a difference in short- or long-term NRM. Patients with POEMS syndrome had superior PFS/OS compared with MM at 5 years, consistent with known data. Our multivariate analysis only identified older age compared with younger age as a correlate to worse OS, but our data lack comparison of outcomes with POEMS syndrome patients not undergoing autoHCT. Understanding the risk of SPM is crucial for a disease with excellent long-term survival. Of 331 patients, 16 (5%) patients developed SPM, including 4 (1.2%) myeloid malignancies and 12 (3.6%) new solid tumors, comparable to MM with hematologic SPM of 2.8% and solid tumor SPM of 4.2% in patients not receiving maintenance lenalidomide after autoHCT.[22]

Our study was limited in assessing important clinical factors seen with POEMS syndrome. We included all patients, with only 14% cases with CRF data. Supplemental data on VEGF, lung function, and imaging characteristics from 8 high volume centers was collected but was also limited by missing data. Thus, our data are unable to specify clinical or VEGF responses. Due to these issues, we decided to use hematological progression as a marker of PFS given that this was well captured in the CIBMTR database. Another limitation is ascertaining time to next therapy as patients with biochemical progression may not consistently go on to the next line of treatment until clinical symptoms or signs. Like many published studies[4,5,23] we were limited to using hematological progression as a marker of PFS given that was well captured in the CIBMTR database with understanding of its clinical implication. To conclude, this is a global cohort, the largest to date, providing safety and long-term outcomes that serve as a benchmark for studies and help provide decision-making tools in peri-autoHCT for patients and physicians of this rare disease.

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ORCID profiles: A.K., 0000-0001-6901-0782; A.D., 0000-0001-8780-9512; S.S., 0000-0003-3288-7614; T.N., 0000-0002-2621-7924; L.D.A., 0000-0002-6531-9595; R.B., 0000-0003-3781-5441; B.D., 0000-0002-4377-9742; J.K., 0000-0002-2473-6528; H.L., 0000-0002-3152-1189; S.K., 0000-0001-5392-9284.

Correspondence: Anita D'Souza, Center for International Blood and Marrow Transplant Research (CIBMTR), Department of Medicine, Medical College of Wisconsin. Ste 5500, 9200 W Wisconsin Ave, Milwaukee, WI 53226; e-mail: andsouza@mcw.edu.

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