POEMS Syndrome: Real World Experience in Diagnosis and Systemic Therapy - 108 Patients Multicenter Analysis

Artur Jurczyszyn,[1] Jorge J. Castillo,[2] Magdalena Olszewska-Szopa,[3] Lalit Kumar,[4] Santiago Thibaud,[5] Joshua Richter,[5] Kari Flicker,[6] Mark Fiala,[7] Ravi Vij,[7] Shuhua Yi,[8] Fang Xu,[9] Rebecca Silbermann,[10] Carmen Montes Gaisan,[11] Enrique M. Ocio,[11] Anna Waszczuk-Gajda,[12] Edvan De Queiroz Crusoe,[13] Aleksander Salomon-Perzyński,[14] Iwona Hus,[14] Julio Davila Valls,[15] Alessandro Gozzetti,[16] Jacek Czepiel,[17] Katarzyna Krzanowska,[18] Aimee Chappell,[19] S.K Chellapuram,[4] Anna Suska,[1] David H. Vesole[19,20]

Abstract

POEMS syndrome, a rare plasma cell disorder, is challenging both in the diagnostic and therapeutic management. We present real word retrospective analysis of 108 cases analyzing clinical features and therapeutic modes. We compare our results with the available literature. This is the first description with such wide use of proteasome inhibitors in first line treatment. POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome is a rare and challenging plasma cell disorder, both in the diagnostic and therapeutic management of the disease. Currently, the literature on POEMS is sparse with most evidence being case reports and small case studies. We present a retrospective real world experience of 108 patients with POEMS. We analyzed the clinical features and therapeutic interventions. Regarding clinical features, our findings demonstrated that skin lesions, thrombocythemia and polycythemia were present less frequently than reported previously. Regarding clinical interventions, this is one of the largest analyses of

[1]Plasma Cell Dyscrasia Center, Department of Hematology Faculty of Medicine, Jagiellonian University Medical College, Cracow, Poland
[2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[3]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland
[4]Department of Medical Oncology, All India Institute of Medical Sciences, New Delhi, India
[5]Mount Sinai Medical Center, New York, NY
[6]Weill Cornell Medical College, New York, NY
[7]Division of Oncology, Section of Bone Marrow Transplant & Leukemia, Washington University School of Medicine, Saint Louis, MO
[8]State Key Laboratory of Experimental Hematology National Clinical Research Center for Blood Diseases Institute of Hematology and Blood Disease Hospital Chinese, Academy of Medical Sciences and Peking Union Medical College Tianjin China
[9]Department of Hematology, Mianyang Central Hospital, Mianyang, Sichuan, People's Republic of China
[10]Division of Hematology and Medical Oncology, Oregon Health and Sciences University, Knight Cancer Institute, Portland
[11]University Hospital Marques de Valdecilla (IDIVAL), University of Cantabria, Santander, Spain
[12]Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Poland
[13]Universidade Federal da Bahia (UFBA), Hospital Universitário Professor Edgard Santos, Salvador, BA, Brazil
[14]Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[15]Complejo Asistencial de Avila, Avila, Spain
[16]Division of Hematology, Department of Medical Science, Surgery and Neuroscience, University of Siena, Siena, Italy
[17]Department of Infectious and Tropical Diseases, Jagiellonian University Medical College, Cracow, Poland
[18]Department of Nephrology, Jagiellonian University Medical College, Kraków, Poland
[19]Department of Hematology/Oncology, Georgetown University Hospital, Washington, DC
[20]John Theurer Cancer Center at Hackensack Meridian School of Medicine, Hackensack, NJ

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Address for correspondence: Artur Jurczyszyn, MD PhD, Department of Hematology, Jagiellonian University Medical College, 17 Kopernika Str. 31-000, Cracow, Poland.
E-mail contact: mmjurczy@cyf-kr.edu.pl

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front line treatment in POEMS and the first one to include frequent utilization of proteasome inhibitors (37%). Bortezomib monotherapy was the most effective therapy achieving complete remission/very good partial remissions (CR/VGPR) in 69% of patients. Thirty percent of patients proceeded to planned autologous stem cell transplant (ASCT) as part of the front-line treatment resulting in statistically superior progression-free (PFS) and overall survival (OS) compared to non-ASCT treated patients ($P = .003$). In multivariate analysis, anemia, thrombocytopenia, and as age over 60 were associated with a negative impact on patient outcomes.

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Key Words: POEMS, standard of care, plasma cell dyscrsia

Introduction

POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome is a rare plasma cell disorder.[1] It is actually a paraneoplastic syndrome caused by an underlying clonal plasma cell disorder which is difficult to recognize, underdiagnosed, and due to the rarity of the disease, outcome analyses are challenging and usually require multicenter cooperation.

The association of the pro-inflammatory cytokine, vascular endothelial growth factor (VEGF) in POEMS is well documented.[1,2] Although VEGF levels decrease with therapeutic intervention, there may not be a direct correlation with clinical response. Treatment approaches are based upon the extent of plasma cell infiltration and end-organ damage utilizing serological parameters, bone marrow evaluation and radiographic findings. In localized disease, radiotherapy is recommended.[1,2] However, this is not considered curative for patients with low burden bone marrow infiltration indicative of systemic disease. The therapeutic objective is to eliminate the underlying – the plasma cell disorder since the depth of hematological response determines PFS[1,2]. Of note, as in amyloidosis, organ response may be extensively delayed compared to hematological responses.[1]

Goals

The aim of this study was to compare the outcomes of front line therapeutic approaches utilizing a real world data set: - alkylating agent – based treatment versus novel agent– based therapy.

Methods

A. Data Review. 108 patients meeting POEMS criteria from 15 hematology centers from 9 countries from the period of 1992 to 2019 were included in the analysis. Patients who did not receive treatment were excluded from the analysis.

Hematologic response criteria were based the International Myeloma Working Group (IMWG) Uniform Response Criteria for multiple myeloma.[3] The study was approved by the individual Institutional Review Boards following the ethical guidelines of the Declaration of Helsinki.

B. Statistical methods: Patients' characteristics are presented using descriptive statistics, median and range for continuous variables and the number and proportion for categorical variables. Comparisons between groups were performed using the Fisher exact test, the Chi square test or the rank sum test, as appropriate. Overall survival was defined as the time between diagnosis and death from any cause or last follow-up. Time to frontline treatment initiation and OS curves was estimated using the Kaplan-Meier method for incomplete observations. *P*-values <.05 were considered statically significant. Calculations and graphics were obtained using STATA (StataCorp, College Station, TX).

Results

Patient characteristics and clinical features are shown in Table 1. The median percentage of bone marrow involvement was 5% (0-50%) including: 33% > 10% plasma cells, 62% < 10% and no identified clonal plasma cells in 5 cases. IgG lambda and IgA lambda M protein were observed with the same frequency, 32% and 34%, respectively. Polycythemia with hemoglobin over 17 g/dL (4 pts-3.7%) was less frequently observed than anemia with hemoglobin below 10 g/dL (8 pts- 7,4%), whereas thrombocythemia >450 K/uL occurred in 30 cases (27.8%). Fifty-eight percent had impaired endocrine function mainly thyroid and gonadal disorders, 34 and 31%, respectively. Castleman disease (23%) was relatively common in our study.

Front line treatments and overall hematologic response to systemic therapy are provided in Table 2. CR/VGPR were observed in 57% (17/30) of patients treated with proteasome inhibitors - (PIs), 44% (17/39) with immunomodulatory agents (IMiDs), and 20% (4/20) with alkylator-based chemotherapy.

High dose chemotherapy with ASCT was incorporated into front line treatment in 25 patients (30%). Fifty-two percent ASCT patients achieved CR/VGPR, compared to 35% in the non-ASCT group ($P = .003$) (Table 2).

Forty two patients received second line treatment with response rates as shown in Table 3. ASCT was implemented in only 7 patients as salvage therapy. Due to low patient numbers, the efficacy evaluation of second line treatment is not statistically significant.

With a median follow up of 2.6 years, the median OS was not reached. The estimated 5-year and 10-year OS was 85% (95% CI 71-92%) and 80% (95% CI 63-90%), respectively (Figure 1). Only 9 out of 104 evaluable patients died. In 4 cases, the death was not related to the disease.

Discussion

POEMS is an extremely rare plasma cell disorder which is difficult to diagnose due to the heterogeneous presentation of the disease. The combination of symptoms that prima face do not correspond to one another is easily overlooked, which results in numerous under-

Table 1 Patients Characteristics and Clinical Features

Characteristic	Median (range) or Number (%)
Median age, years	51 (24-90)
Male sex	72 (67%)
Monoclonal component:	
IgA: lambda; kappa; free IgA	***41%:*** 37 (34%); 2(2%); 2(2%)
IgG: lambda; kappa; free IgG	***48%:*** 35 (32%); 10 (9%); 3(3%)
IgM: lambda; kappa; free IgM	***5%:*** 3 (3%); 1(1%); 1(1%)
Free light chains: lambda; kappa	***14%:*** 7 (6%); 7(6%)
Hemoglobin, g/dl	14.0 (7.4-19.6)
Platelet count, K/uL (n = 107)	332 (37-900)
VEGF level, pg/ml (n = 47)	741 (59-8,210)
Bone marrow involvement, % (n = 100)	5% (0-50%)
Neuropathy	
EMG/NCS done (n = 106)	94 (89%)
Demyelination (n = 93)	72 (77%)
Endocrinopathy presence	63 (58%)
Adrenal	15/104 (14%)
Gonadal	32/104 (31%)
Pancreatic	5/58 (9%)
Thyroid	36/106 (34%)
Parathyroid	3/56 (5%)
Organomegaly presence	74 (69%)
Hepatomegaly	50/107 (47%)
Splenomegaly	47/106 (44%)
Lymphadenopathy	49/107 (46%)
Castleman disease	25/107 (23%)
Skin changes presence	74 (69%)
Hyperpigmentation	58 (54%)
Cyanosis	21 (19%)
Hemangioma	22 (20%)
Hypertrichosis	15 (14%)
Volume overload presence	67 (62%)
Ascites	21 (19%)
Pleural effusion	26 (24%)
Pericardial effusion	18 (17%)
Bone lesions presence	79 (73%)
By x-rays	52/84 (62%)
By CT scans	35/54 (65%)
By MRI scans	14/33 (42%)
By PET/CT scans	26/42 (62%)
Pulmonary hypertension	8/83 (10%)
Fatigue	70/104 (67%)
Weight loss	52/103 (50%)
Other features	
Papilledema	37/96 (39%)
Clubbing	43/100 (43%)
Thrombosis	40/106 (38%)
Diarrhea	8/69 (12%)

EMG = electromyography; NCS = nerve conduction study; CT = computed tomography; MRI = magnetic resonance; PET = positron emission tomography; VEGF = vascular endothelial growth factor

Figure 1 Overall survival in POEMS patients
Median follow up 2.6 years (95% CI 2.1-4)
(A) OS probability in the whole POEMS cohort (B) OS probability regarding age
(C) OS probability regarding anemia (D) OS probability regarding thrombocytopenia
(E) OS probability regarding ascites (F) OS probability regarding pleural effusion
OS – overall survival.

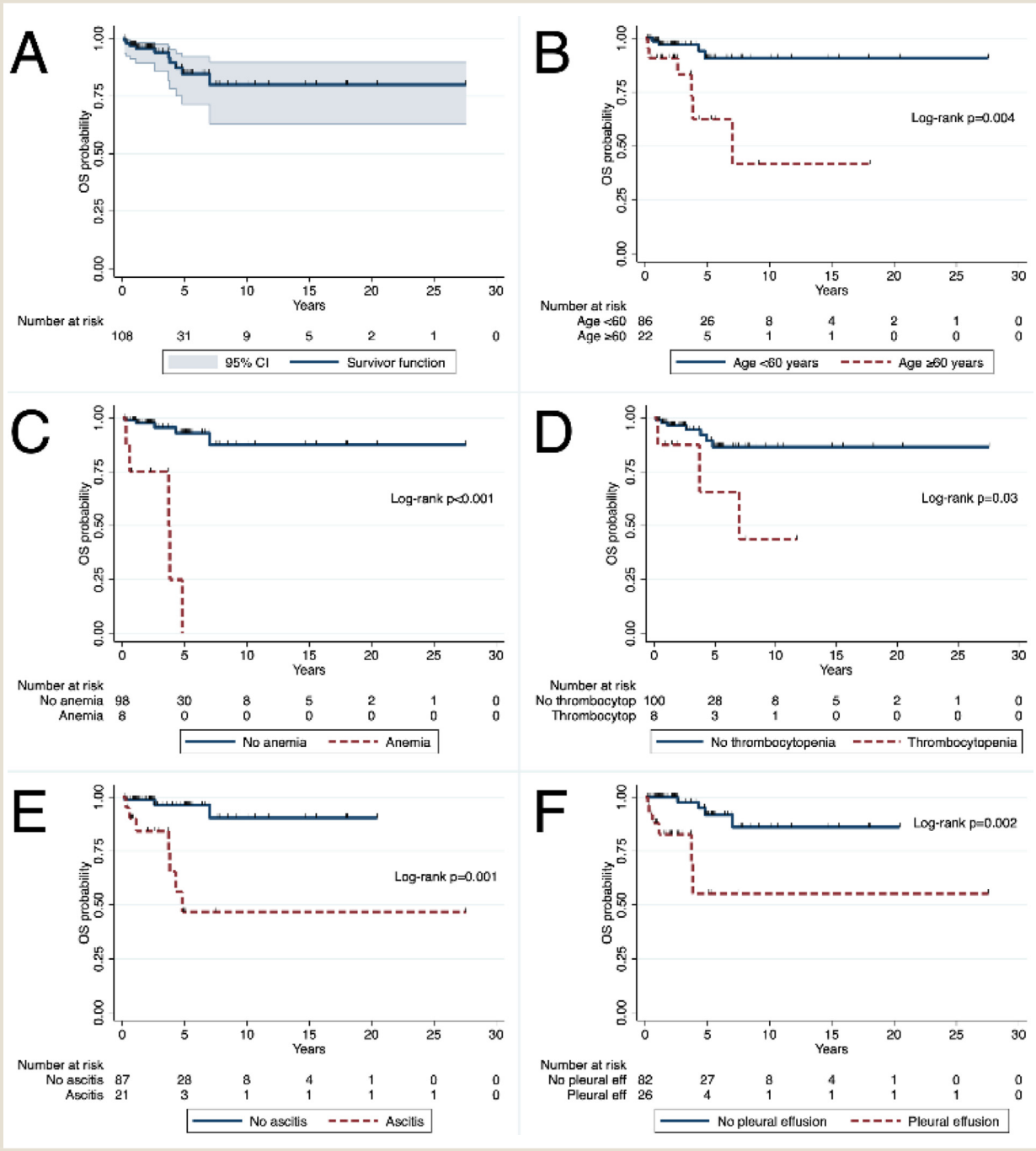

Table 2 Frontline Therapy in POEMS Patients and Response to Frontline Systemic Therapy (n = 82; Fisher's exact $P = .075$).

Therapy	N (%)	Agent			N (%)
Chemo	35 (43%)	Melphalan			20 (57%)
		Cyclophosphamide			13 (37%)
		VAD/CVAD			2 (6%)
PI	30 (37%)	Bortezomib			29 (97%)
		Carfilzomib			1 (3%)
IMID	39 (48%)	Lenalidomide			34 (87%)
		Thalidomide			5 (13%)
Regimen +/- ASCT	**N (%)**	**CR/VGPR**	**PR**	**SD**	**PD**
Chemo only	20 (24%)	4 (20%)	11 (55%)	4 (20%)	1 (5%)
PI based	23 (28%)	14 (61%)	8 (35%)	1 (4%)	0 (0%)
IMID based	32 (39%)	14 (44%)	8 (25%)	8 (25%)	2 (6%)
PI-IMID containing	7 (9%)	3 (60%)	3 (20%)	0 (0%)	1 (20%)
Total	82 (100%)	35 (43%)	30 (37%)	13 (16%)	4 (5%)
ASCT	**N (%)**	**CR/VGPR**	**PR**	**SD**	**PD**
No	57 (70%)	22 (35%)	20 (35%)	13 (23%)	2 (4%)
Yes	25 (30%)	13 (52%)	10 (40%)	1 (4%)	1 (4%)

Chemo = chemotherapy; IMID = immunomodulating drug; PI = proteasome inhibitor; CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone; VAD = vincristine, doxorubicin, dexamethasone, ASCT = autologous stem cell transplantation; Chemo = chemotherapy; IMID = immunomodulating drug; PI = proteasome inhibitor; CR = complete remission, VGPR = very good partial remission, PR = partial remission, SD = stable disease, PD = progressive disease.

Table 3 Second Line Therapy in POEMS Patients (N 42) and Response to Second Line Therapy

Therapy	N (%)	Agent			N (%)
Chemo	18 (50%)	Melphalan			8 (44%)
		Cyclophosphamide			9 (50%)
		Doxorubicin			3 (17%)
PI	8 (22%)	Bortezomib			6 (75%)
		Carfilzomib			2 (25%)
IMiD	15 (42%)	Lenalidomide			10 (67%)
		Thalidomide			5 (33%)
Others	3 (8%)	Rituximab			1 (33%)
		Daratumumab			1 (33%)
		Bevacizumab			1 (33%)
Regimen +/- ASCT	**N (%)**	**CR/VGPR**	**PR**	**SD**	**PD**
Chemo only	14 (41%)	6/43%)	3 (21%)	4 (29%)	1 (7%)
PI based	4 (10%)	0 (0%)	3 (75%)	0 (0%)	1 (25%)
IMiD based	10 (24%)	1 (10%)	6 (60%)	1 (10%)	2 (20%)
PI-IMiD containing	3 (6%)	2 (67%)	1 (33%)	0 (0%)	0 (0%)
Other	3 (9%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)

ASCT = autologous stem cell transplantation; Chemo = chemotherapy; IMID – immunomodulating drug; PI = proteasome inhibitor; CR = complete remission, VGPR = very good partial remission, PR = partial remission, SD = stable disease, PD = progressive disease.

diagnosed cases. The literature is largely limited to small retrospective analyses and case reports.

We evaluated the clinical features of 108 cases finding the majority of them consistent with the description in the existing literature. However, we observed some unique differences: the proportion of patients with plasma cell infiltration >10% and the number of patients suffering from fatigue was significantly higher than in published data.[1,4] The percentage of patients presenting with skin lesions, thrombocythemia or polycythemia was lower than described previously (69% vs. 68%-89%, 28% vs. 54%-88% and 7% vs. 12%-19%, respectively).[1] The incidence of Castleman disease (23%) was comparable to that reported in the literature

Table 4 Clinical Characteristic According to Current Data, A. Dispenzieri metaanalysis and Zhao Analysis

Feature	Current analysis	Dispenzieri 2019[17]	Zhao 2019[4]	Wang 2017[9]	Li 2011[16]
Number of patients	101	metaanalysis	347	362	99
Age	median – 51 years	-	>50 y - 40%	>50y -40%	median – 45 years
Male sex (%)	72	-	65,7	62	59
Polycythemia (%)	3,7	12-19	-	15	9
Thrombocytosis (%)	27,8	54-88	-	51	54
BMPC >10% (%)	33	-	3,7	3	2
Castleman disease (%)	23	11-25	61,5	64	25
Splenomegaly (%) Hepatomegaly (%) Splenomegaly (%)	44 47 46	22-70 24-78 26-74	59 38 64	67 47 65	47 70 74
Any endocrinopathy (%)	58	67-84	-	>68	>89
Bone lesions present (%)	73	27-97	-	=>55	27
Skin lesions (%)	14	68-89	-	>87	89
Volume overload (%)	10	29-87	84%	>87	87
Weight loss (%)	38	37	-		1
Fatigue (%)	67	31	-		1

BMPC – bone marrow plasma cells

(11%-25%).[1] In contrast, Zhao et al. reported an incidence exceeding 60%.[4] Thus, our observations confirm the extensive heterogeneity of signs and/or symptoms of POEMS at presentation (Table 4).

Since hematological response in POEMS is directly correlated to PFS/OS, we focused our analysis on front line therapy.[5] Treatment options have changed substantially over the course of the study period of the current report (1992-2019). Publications with more than 30 POEMS patients on upfront therapy including modern agents and or ASCT are listed in Table 5.

Classic chemotherapy is still utilized in POEMS but with decreasing frequency over time; 24% of analyzed patients received alkylator-based therapy, predominantly melphalan. In our study, classic chemotherapy was the least effective therapy with only a 20% CR/VGPR rate. The largest study (n = 31) using alkylator-based therapy was reported by Li et al using melphalan-based treatment resulting in a 39% CR rate.[6] Given the small numbers of patients, hematologic responses between the two studies are comparable.

Over the past 15 years, most treatments have included PIs and IMiDs. Upfront therapy with PIs, predominantly bortezomib achieved a 69% CR/VGPR rate, which was the most efficacious treatment reported. Although bortezomib may be associated with peripheral neuropathy, particularly in the setting of individuals with documented pre-existing polyneuropathy, the potential benefits of PIs appears to overcome the risk of bortezomib-associated neuropathy. No patient in our study discontinued bortezomib due to adverse effects. The literature regarding bortezomib front line therapy is sparse: Pramanik et al. reported bortezomib as part of induction therapy in 7 out of 10 POEMS patients who underwent ASCT. All the patients achieved PR and no neurologic toxicities were reported.[7] Therefore, based on our study and the short series and case reports in the literature, the utilization of bortezomib as front line therapy appears to be tolerated and highly effective.

Although utilized in small numbers of patients, IMID based therapy resulted in a 44% (n = 14) CR/VGPR rate and in combination with a PI, 60% (n = 3). A prospective study of upfront IMID based therapy in 42 patients resulted in a 46% hematologic CR.[8] A retrospective study by Zhao et al also demonstrated therapeutic efficacy of MiDs with 49,7% CR rate in Lendex arm.[4] Lenalidomide based therapy was the most commonly used in Wang analysis but no data on hematological response is available according to our knowledge.[9] Dispenzieri et al. reported a small cohort of 1 newly diagnosed and 8 relapsed/refractory POEMS patients treated with ixazomib, lenalidomide, dexamethasone combination. Tolerability was shown and the authors reported hematologic response in 1 of 3 patients.[10] Although the numbers in the our study are small, it is important to investigate whether a PI-IMID combination is more effective a single agent.

In our study 30% of patients underwent ASCT as part of front line therapy. The differences in CR/VGPR rates were superior in the ASCT versus non-ASCT cohorts: 52% versus 35%, respectively; $P = 0.003$). In contrast, Zhao et al reported similar CR rates in both lenalidomide and/or dexamethasone versus ASCT treated patients (50% vs. 48%). He noted a trend towards better PFS and OS in the ASCT group. Of note, there is an inherent bias to his report at baseline characteristics of the ASCT cohort were more favorable.[4] Ohwada et al observed a 64% hematological CR after ASCT in 36 POEMS patients, with 5 year OS exceeding 91%.[11] d'Souza et al. reported a 57% CR in 59 patient report.[12] Cook et al described 84.5% of CR after ASCT with 5 year OS 91% in 127 patients retrospective analysis.[13] Finally, Kourelis et al reported a 90% 10 year OS after ASCT.[14]

In salvage therapy settting, classic chemotherapy and IMIDs were the most commonly used agents (41 and 38% respectively) 21% received a PI. In individual situations immunotherapy for example,

Table 5 Publications With More Than 30 POEMS Patients on Upfront Therapy Including Modern Agents and or ASCT

Author, journal, year, character of analysis	No of pts	Therapy mode	ASCT	Response hematologic	m follow up	OS	Relapse rate
Dispenzieri A et al. EJH 2008 Retrospective[15]	30	0-7 lines of therapy mainly CTX, IMIDs	Y Mel140 (10) Mel200 (19) BEAM (1)	CR/PR 90%	19	NG	3,33%
Li et al. Ann Hemat 2011 Retrospective[6]	75	Mdex, traditional Chinese medicine	Y - 20% Mel200	NG	NG	2y OS not reached	NG
D'Souza A et al. Blood 2012 Retrospective[12]	59	47% (28), eg: CTX (14), Mel-based (2), IMID (9)	Y, Mel200 (41) Mel140 (17) BEAM (1)	CR 57% VGPR 3% PR 19%	45	5 y 94%	23,7%
Cook G et al. Haematologica 2017 Retrospective[13]	127	NG	Y 123 Mel200 TBI (1)	CR 84,5% PR 20,8	48	5 y OS 89%	16,5%
Wang et al. Leukemia 2017 Retrospective [9]	362	Mel-based (83), novel drugs 29%: Len-based (95), Tal-based (5), Bort-based (4)	Y 36% (133)	NG	30	5 y OS 84%	NG
Li et al. EJH 2018 Prospective[8]	41	Ldex 100%	N	CR 46%	34	3y OS 90%	17%
Zhao et al. Leukemia 2019 Retrospective[4]	347	Ldex, Mdex	Y - 47% Mel140/Mel200	CR: ASCT 49,7%, Ldex 47,5% Mdex 37,7%	45	3y OS: 94.4% ASCT vs. 90.7% Ldex vs. 83.1% Mdex,	14,7%
Pramanik et al. Clin Lymph 2019 Retrospective[7]	49	Mdex (25) Bort-based (19)	Y (10) Mel140	CR 37,5% ASCT 100%	NG	m OS not reached	NG

CTX = cyclophosphamide; IMIDs = immunomodulating drugs; ASCT = autologous stem cell transplantation; Bort = bortezomib; Ldex = lenalidomide plus dexamethasone; Len = lenalidomide; Mdex = melphalan plus dexamethasone; NG = not given; Y = yes; N = No.

rituximab or daratumumab have been reported. However, due to very small numbers of individual regimens applied, it is not possible to determine an efficacy endpoint.

In summary, although there were many clinical variables and treatment modalities compared to the number of patients, we attempted to evaluate the effect of baseline clinical characteristics on POEMS response, as shown in Table 6.

In multivariate analysis, anemia, thrombocytopenia and age over 60 had a negative impact on patient outcomes. We did not find any other unfavorable prognostic factors among clinical and laboratory markers of the disease including VEGF levels or response. Two deaths from stroke may be related to the underlying disease as POEMS is associated with an increased risk of thrombosis, although both were at least partially responding when they died.

Limitations of the study include the retrospective design, the wide time span of the data collection (1992-2019) during which time treatment options have markedly changed, the heterogeneity of the patient population, the availability of novel agents (USA vs. non-USA sites), and the small number of patients in the various examined cohorts.

In conclusion: This is one of the largest analyses of front line treatment efficacy in POEMS and the first one with such a wide upfront use of proteasome inhibitors. Proteasome inhibitors as single agents, the combination of a PI/IMiD and ASCT all demonstrate high responses and should be considered standard options for a newly diagnosed POEMS patient.

Clinical Practice Points

- The data on POEMS diagnosis and therapy mainly consists of small series or case reports. This group is still not well characterized and has no clear recommendations concerning the management. This manuscript describes the real-life data on clinical picture, systemic therapy and outcome of POEMS patients. Based on our and systemic review data, observations concerning the treatment of this group of patients are presented in this manuscript.
- As we know, this is one of the largest series analyzing systemic therapy in this group with novel agents. We focused on hematological response since we know that achieving HCR (hematological complete remission) is essential for further clinical outcome.

Table 6 The Impact of Baseline Features on Clinical Outcomes of POEMS Patients

Clinical Presentation	N	HR (95% CI)	*P*-Value
Age >60 years	108	6.52 (1.83-23.2)	.004
Male sex	108	2.10 (0.61-7.30)	.24
Anemia	106	20.6 (5.36-78.8)	<.001
Thrombocytopenia	108	4.56 (1.16-17.8)	.03
Thrombocytosis	108	0.42 (0.09-1.98)	.27
Adrenal insufficiency	104	0.86 (0.11-6.95)	.89
Gonadal insufficiency	104	0.28 (0.04-2.25)	.23
Pancreatic insufficiency	58	UTC*	
Thyroid insufficiency	106	2.92 (0.78-11.0)	.11
Parathyroid insufficiency	56	1.03 (0.24-17.1)	.51
Hepatomegaly	107	1.75 (0.49-6.23)	.39
Splenomegaly	106	0.88 (0.25-3.15)	.85
Lymphadenopathy	107	1.90 (0.53-6.73)	.32
Castleman disease	107	0.75 (0.16-3.54)	.72
Hyperpigmentation	108	0.94 (0.27-3.24)	.92
Cyanosis	108	0.27 (0.03-2.19)	.22
Hemangioma	108	0.20 (0.02-1.62)	.13
Hypertrichosis	108	0.40 (0.05-3.19)	.39
Edema	108	2.86 (0.61-13.5)	.18
Ascitis	108	10.3 (2.63-40.0)	.001
Pleural effusion	108	7.90 (2.18-28.6)	.002
Pericardial effusion	108	3.70 (0.92-14.8)	.06
Papilledema	96	0.99 (0.24-3.90)	.99
Clubbing	100	0.45 (0.09-2.17)	.32
Thrombosis	106	0.50 (0.10-2.39)	.38
Diarrhea	69	0.96 (0.12-7.85)	.97

HR: Hazard ratio; N: number; UTC: Unable to calculate
* None of the patients who presented with pancreatic insufficiency has died

According to our observation real world proteasome inhibitor (PI) use in the first line treatment is surprisingly wide. PI efficacy in monotherapy as well as in combinations is higher than immunomodulating drugs (IMIDs) and much higher than classic chemotherapy. We think that these results require further clinical studies inter alia to assess safety issues.

- We also made some observations on clinical picture heterogeneity of POEMS.
- We think that both, the sample size and the systematic review performance allow us to provide novel and reliable information regarding POEMS.

Disclosure

The authors have stated that they have no conflicts of interest.

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