

Original Articles**Treatment of Newly Diagnosed POEMS Syndrome: Bortezomib or Lenalidomide? Experience from Two Countries**

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Abstract. Background: POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes) syndrome is a rare plasma cell disorder where treatment selection remains largely empirical. Lenalidomide-based regimens are generally preferred in the first line due to concerns about bortezomib-induced neurotoxicity, despite limited comparative evidence. We aimed to directly compare the real-world efficacy and safety of first-line bortezomib-versus lenalidomide-based regimens.

Methods: In this retrospective multicenter cohort, 26 newly diagnosed POEMS patients between 2005 and 2024 from Türkiye and Italy were included. Nine patients received bortezomib-based therapy and 17 received lenalidomide–dexamethasone. The primary endpoint was overall survival (OS); the secondary endpoint was hematologic response.

Results: Bortezomib-based therapy achieved significantly higher rates of deep response ($\geq$ VGPR, defined as complete response or very good partial response) compared with lenalidomide (88.9% vs 37.5%; $p = 0.013$). Despite a higher prevalence of baseline symptomatic neuropathy in the bortezomib group (77.8% vs 29.4%; $p = 0.038$), no treatment-emergent worsening of neuropathy was observed. Model-based 5-year overall survival was 86.6% with bortezomib and 80.7% with lenalidomide (time ratio [TR] 0.61, 95% CrI 0.04–6.78), indicating no survival difference between the two strategies, with similar autologous transplantation rates and toxicity profiles.

Conclusion: In this multicenter real-world cohort, bortezomib-based first-line therapy was associated with markedly deeper hematologic responses without excess neurotoxicity, and no survival difference could be demonstrated in this small cohort. These findings suggest that bortezomib-based therapy may be an effective upfront option in selected patients and support re-evaluating first-line strategies in prospective studies.

Keywords: POEMS syndrome; Bortezomib; Lenalidomide; Bayesian analysis.

Introduction. POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes) is a rare multisystemic paraneoplastic disorder secondary to an underlying clonal plasma cell disease.^{1,2} Also known as Crow–Fukase syndrome, it presents with a wide spectrum of clinical manifestations involving nearly every organ system, making diagnosis and management particularly challenging.³ A nationwide epidemiological study in Japan estimated the incidence at 0.3 per 100,000 population, underscoring its rarity and the consequent difficulty of conducting large-scale clinical trials.¹ Therefore, current treatment guidelines are primarily based on case series, retrospective analyses, and expert consensus rather than randomized controlled trials.¹⁻⁴

The pathogenesis of POEMS syndrome is closely linked to a clonal plasma cell population that, although typically low-grade, leads to systemic effects through excessive production of various cytokines and growth factors, particularly vascular endothelial growth factor (VEGF).⁵ Markedly elevated VEGF levels are thought to drive many characteristic clinical features of the syndrome and play a key role in the development of peripheral edema, pleural effusion, ascites, organomegaly, and glomeruloid hemangiomas.² The close correlation between serum VEGF levels and disease activity, along with their decline following effective therapy, supports its role as a critical biomarker for both diagnosis and treatment monitoring.^{1,4}

In recent years, the therapeutic paradigm for POEMS syndrome has evolved substantially with the introduction of novel agents originally developed for multiple myeloma. Immunomodulatory drugs (IMiDs) such as lenalidomide have shown promising efficacy with manageable toxicity and are generally recommended as first-line therapy, usually in combination with dexamethasone.^{1,4} Bortezomib, the first-in-class proteasome inhibitor, is a potent anti-plasmacell agent that revolutionized multiple myeloma treatment.⁶ However, the use of bortezomib in POEMS syndrome poses a major clinical dilemma because of the peripheral neuropathy, which is the most common dose-limiting toxicity.⁷ Given that progressive, debilitating polyneuropathy is both a mandatory diagnostic criterion and a major cause of morbidity in POEMS syndrome, the potential of bortezomib to aggravate this pre-existing neurological deficit has raised widespread and justified

concerns.^{1,7} Consequently, bortezomib is not typically recommended as a first-line agent in most treatment guidelines, where lenalidomide is preferred due to its lower neurotoxicity profile.^{1,4}

Nevertheless, accumulating evidence from case reports, earlier and recent retrospective series suggests that bortezomib-based regimens may be highly effective and surprisingly well tolerated in patients with POEMS syndrome.⁸⁻¹¹ Regimens such as bortezomib-cyclophosphamide-dexamethasone (VCD) can induce rapid, profound hematologic responses and significantly reduce VEGF levels.^{9,10} Some studies have even reported neurological improvement following bortezomib therapy, suggesting that disease control may outweigh the risk of drug-related neurotoxicity.¹⁰ Furthermore, strategies such as dose reduction and subcutaneous administration have been successfully implemented to minimize neurotoxicity.^{12,13} No direct comparative data exist between bortezomib and lenalidomide-based regimens as first-line therapy for POEMS syndrome. Balancing the rapid and deep response potential of bortezomib against the perceived lower neurotoxicity risk of lenalidomide is a therapeutic decision challenge.

To address this challenge, we conducted a retrospective study comparing real-world efficacy and outcomes of newly diagnosed POEMS patients treated with first-line bortezomib- versus first-line lenalidomide-based regimens.

Methods

Study Design. This retrospective, multicenter observational cohort study included consecutive patients with POEMS syndrome diagnosed and treated between January 2005 and December 2024. Patients were recruited from a tertiary hematology center in Türkiye and multiple collaborating institutions in Italy. We derived the Italian cases from a previously established multi-institutional cohort and reanalyzed them for the present study.¹⁴ All patients fulfilled established diagnostic criteria for POEMS syndrome² and received first-line treatment with either bortezomib-based regimens (bortezomib-cyclophosphamide-dexamethasone or bortezomib-dexamethasone) or lenalidomide-dexamethasone. Patients treated with alternative systemic therapies, local radiotherapy alone, concurrent hematologic malignancies, or incomplete clinical data were excluded. Data were retrospectively

collected from patient charts and institutional electronic medical records.

Treatment Protocols and Response Assessment. Treatment regimens were administered according to institutional protocols. In the bortezomib group, standard dosing was 1.3 mg/m² administered subcutaneously once weekly (days 1, 8, 15, and 22), with cyclophosphamide 500 mg (days 1, 8, 15, 22 or days 1 and 15) every 28–35 days. In the lenalidomide group, doses of 15–25 mg/day were given for 21-day cycles. Dexamethasone (20–40 mg weekly) was included in all regimens. Treatment responses were evaluated using the International Myeloma Working Group (IMWG) response criteria adapted for POEMS syndrome.²

Safety and Toxicity. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Hematologic toxicities and non-hematologic toxicities were recorded separately.

Peripheral neuropathy severity and progression were evaluated retrospectively based on serial clinical neurological examinations and documented patient symptoms, graded according to the CTCAE version 5.0. Worsening of neuropathy was defined as an increase by ≥ 1 CTCAE grade from baseline or the emergence of new sensory/motor deficits leading to treatment modification. Objective neurophysiologic studies (EMG/NCS) were performed when clinically indicated rather than as routine screening.

Follow-up and Survival Analysis. Follow-up duration was calculated from diagnosis and from treatment initiation to the last follow-up or death. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Time to relapse was calculated from the date of initial response to disease relapse in patients who achieved a response.

Ethical Considerations. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethics committee of the participating centers. Detailed ethics approvals are provided in the Supplementary Appendix.

Statistical Analysis. Continuous variables were assessed as mean $\pm$ standard deviation or median (range), as appropriate. Categorical variables are presented as frequencies and percentages. Group comparisons were performed using the Mann–Whitney U test for non-parametric continuous variables and Pearson's chi-square or Fisher's exact tests for categorical variables, as appropriate.

Because the disease is rare and the sample size is limited, we performed survival analyses using Bayesian

parametric survival models and Bayesian Cox models. Survival analyses were performed using a Bayesian log-normal accelerated failure time model, with the treatment effect reported as a TR with 95% credible intervals; hazard-scale estimates were obtained from a separate univariable Bayesian Cox model with results reported as hazard ratios (HRs) with 95% credible intervals (CrIs). Additional statistical details are provided in the Supplementary Appendix.

Results. A total of 26 patients with POEMS syndrome were included in the study. Nine patients received bortezomib-containing regimens as first-line treatment, whereas 17 were treated with lenalidomide-based therapy. The majority of patients were male (73.1%), and the median age at diagnosis was 53 years (**Table 1**). There were no significant differences between treatment groups in terms of sex distribution or age at diagnosis ($p = 0.999$ and $p = 0.387$, respectively). All patients in the bortezomib group were treated at the Turkish center, whereas 76.5% of patients in the lenalidomide group were from Italian centers. All patients met the mandatory diagnostic criterion of documented polyneuropathy; however, peripheral neuropathy as the primary presenting symptom was significantly more frequent in the bortezomib group than in the lenalidomide group (77.8% vs. 29.4%, $p = 0.038$). When initial clinical features were evaluated, hepatosplenomegaly (61.5%), skin manifestations (61.5%), and sclerotic bone lesions (57.7%) were the most frequently observed findings (**Table 2**). Among laboratory parameters, baseline serum VEGF levels were available in only 3 patients in the bortezomib group and were therefore excluded from formal statistical comparison.

Monoclonal protein analysis showed lambda light-chain restriction in the majority of patients, while rare kappa-restricted cases were also identified; all kappa-restricted patients fulfilled standard diagnostic criteria with documented osteosclerotic lesions and elevated VEGF levels.

The treatment groups did not differ significantly in the frequency of these baseline characteristics. The duration of first-line therapy differed markedly between the two regimens. Patients in the bortezomib group received a fixed-duration induction ranging from 4 to 8 cycles (median 4 cycles). In contrast, the number of cycles in the lenalidomide group ranged from 1 to 118 cycles (median 7 cycles), reflecting the continuous nature of the lenalidomide regimen. Treatment response data were unavailable for one patient, so response rates were evaluated in 25 patients; the deep response rate [$\geq$ VGPR, defined as VGPR or complete response (CR)] was 88.9% in the bortezomib group compared with 37.5% in the lenalidomide group. No cases of stable disease or progressive disease were observed in the bortezomib group, whereas five patients (31.2%) had

Table 1. Baseline demographic characteristics, presenting symptoms, and laboratory findings in patients with POEMS syndrome according to first-line treatment.

Variable	Overall (n=26)	Bortezomib based regimen (n=9)	Lenalidomide (n=17)	p value
Gender				
Male	19 (73.1)	7 (77.8)	12 (70.6)	0.999*
Female	7 (26.9)	2 (22.2)	5 (29.4)	0.999*
Age at diagnosis, year	53.0 [39.0–66.0]	51.0 [39.0–61.0]	53.0 [40.0–66.0]	0.387**
Time from symptom onset to diagnosis, month	17.5 [1.0–244.0]	61.0 [1.0–244.0]	11.0 [2.0–180.0]	0.161**
Patient cohort				
Türkiye	13 (50.0)	9 (100.0)	4 (23.5)	<0.001*
Italy	13 (50.0)	0 (0.0)	13 (76.5)	<0.001*
Electrophysiologically confirmed polyneuropathy		17 (100.0)	-	-
Presenting symptoms				
Symptomatic neuropathy	12 (46.2)	7 (77.8)	5 (29.4)	0.038*
Pain	6 (23.1)	2 (22.2)	4 (23.5)	0.999*
Edema	3 (11.5)	2 (22.2)	1 (5.9)	0.268*
Fatigue	3 (11.5)	1 (11.1)	2 (11.8)	0.999*
Weight loss	2 (7.7)	0 (0.0)	2 (11.8)	0.529*
Skin findings	2 (7.7)	1 (11.1)	1 (5.9)	0.999*
Lymphadenopathy	2 (7.7)	0 (0.0)	2 (11.8)	0.529*
Laboratory findings				
Hemoglobin, g/dL	13.5 [9.7–17.4]	13.5 [11.0–15.7]	13.7 [9.7–17.4]	0.850**
Platelets, /μL	337,000 [136,000–669,000]	394,000 [136,000–480,000]	333,500 [186,000–669,000]	0.925**
VEGF, pg/mL	1,415.0 [31.0–6,620.0]	113.0 [31.0–559.0]	2,035.5 [120.0–6,620.0]	-
Bone marrow plasma cells, %	7.0 [0.0–20.0]	7.0 [0.0–20.0]	6.5 [2.0–10.0]	0.876**
Monoclonal protein type				
IgG/ λ	10 (38.5)	6 (66.7)	4 (23.5)	0.370*
IgA/ λ	6 (23.1)	2 (22.2)	4 (23.5)	0.370*
λ light chain	4 (15.4)	1 (11.1)	3 (17.6)	0.370*
IgG/ κ	3 (11.5)	0 (0.0)	3 (17.6)	0.370*
IgA/ κ	2 (7.7)	0 (0.0)	2 (11.8)	0.370*
κ light chain	1 (3.8)	0 (0.0)	1 (5.9)	0.370*

Data are presented as n (%) or median (range). * Fisher's exact or Fisher–Freeman–Halton test. ** Mann–Whitney U test. Bold p values indicate statistical significance ($p \leq 0.05$). (κ : kappa; λ : lambda; VEGF: vascular endothelial growth factor).

stable disease and two patients (12.5%) had progressive disease in the lenalidomide group. When the ordinal nature of response categories was taken into account, the linear-by-linear association test demonstrated a significant difference in favor of bortezomib ($p = 0.013$).

ASCT rates were similar between the two groups (55.6% vs 56.2%; $p = 0.999$).

At the time of last follow-up, 88.9% of patients in the bortezomib group and 76.5% in the lenalidomide group were alive. In time-to-event analysis, overall survival did

Table 2. Clinical features, treatment characteristics, and outcomes in patients with POEMS syndrome according to first-line treatment.

Variable	Overall (n=26)	Bortezomib based regimen (n=9)	Lenalidomide (n=17)	p value
Hepatosplenomegaly	16 (61.5)	4 (44.4)	12 (70.6)	0.234*
Skin findings	16 (61.5)	5 (55.6)	11 (64.7)	0.692*
Sclerotic bone lesions	15 (57.7)	4 (44.4)	11 (64.7)	0.419*
Edema, effusions	11 (44.0)	6 (66.7)	5 (31.2)	0.115*
Lymphadenopathy	9 (34.6)	4 (44.4)	5 (29.4)	0.667*
Elevated pulmonary artery pressure	9 (36.0)	5 (55.6)	4 (25.0)	0.200*
Papilledema	5 (20.8)	3 (33.3)	2 (13.3)	0.616*
Castleman disease	4 (15.4)	0 (0.0)	4 (23.5)	0.263*
Treatment and response				
Number of treatment courses, median	6.0 [1.0–118.0]	4.0 [4.0–8.0]	7.0 [1.0–118.0]	0.106**
Hematologic response				
≥VGPR	14 (56.0)	8 (88.9)	6 (37.5)	
PR	4 (16.0)	1 (11.1)	3 (18.8)	0.013*
Stable disease	5 (20.0)	0 (0.0)	5 (31.2)	
Progressive disease	2 (8.0)	0 (0.0)	2 (12.5)	
ASCT	14 (56.0)	5 (55.6)	9 (56.2)	0.999*
Hematologic toxicity	1 (4.3)	0 (0.0)	1 (7.1)	0.999*
Non-hematologic toxicity	4 (17.4)	0 (0.0)	4 (28.6)	0.127*
Time to relapse, months	44.0 [15.0–118.0]	15.0 [15.0–15.0]	81.0 [44.0–118.0]	0.667**
Follow-up from diagnosis, months	54.1 [5.0–232.6]	38.0 [5.0–136.0]	57.9 [11.0–232.6]	0.634**
Follow-up from treatment initiation, months	47.7 [5.0–230.7]	38.0 [5.0–133.0]	48.8 [11.0–230.7]	0.711**
Survival				
Alive	21 (80.8)	8 (88.9)	13 (76.5)	0.649 ‡
Deceased	5 (19.2)	1 (11.1)	4 (23.5)	0.649 ‡

Data are presented as n (%) or median (range). Response comparisons were performed among patients with available response data (evaluable n = 25). * Pearson chi-square, Fisher's exact, or Fisher–Freeman–Halton test. ** Mann–Whitney U test. ‡ Log-rank test for overall survival. Bold p-values indicate statistical significance ($p \leq 0.05$). (ASCT: autologous stem cell transplantation; PR: partial response; ≥VGPR: complete response or very good partial response).

not differ significantly between the two groups (log-rank $p = 0.649$).

Adverse event data were limited, precluding formal statistical analysis. Notably, although baseline peripheral neuropathy was more common in the bortezomib group (77.8% vs. 29.4%, $p = 0.038$), no worsening of preexisting neuropathy was observed during follow-up. Furthermore, no patient in the bortezomib group required dose reduction, schedule modification, or permanent discontinuation due to peripheral neuropathy. In contrast, two patients in the lenalidomide group experienced documented worsening of neurological symptoms during treatment.

Bayesian Survival Analysis. In the Bayesian log-normal AFT model (**Table 3**), the estimated TR for lenalidomide

relative to bortezomib was 0.61 (95% CrI 0.04–6.78), with a 67.3% posterior probability of shorter survival in the lenalidomide group (two-sided p-like value = 0.654). Although the posterior probability of shorter survival with lenalidomide was 67%, the credible interval was wide and fully compatible with no difference. On the hazard scale, the univariable Bayesian Cox model yielded a hazard ratio of 1.74 (95% CrI 0.24–21.77; P ($HR > 1$) = 0.70). Both Bayesian survival models yielded concordant findings, showing no statistically discernible difference in overall survival between lenalidomide and bortezomib. Given the low number of events, posterior estimates were accompanied by wide credible intervals, which fully encompass the null hypothesis of equal survival. Model-based 5-year overall survival was 86.6% (95% CrI 57.9%–98.5%) with bortezomib and 80.7%

Table 3. Bayesian log-normal accelerated failure time (AFT) analysis of overall survival by first-line treatment in patients with POEMS syndrome.

Measure	Estimate	95% Credible Interval
Time ratio (<i>lenalidomide/bortezomib</i>)	0.61	0.04–6.78
P(TR < 1): shorter survival with lenalidomide	67.3%	—
P(TR > 1): longer survival with lenalidomide	31.9%	—
Bayesian two-sided p-like value	0.654	—
Model-based 5-year OS — bortezomib	86.6%	57.9%–98.5%
Model-based 5-year OS — lenalidomide	80.7%	59.7%–93.7%

CrI: credible interval; OS: overall survival; TR: time ratio. The time ratio is the ratio of model-estimated median survival times (lenalidomide/bortezomib). A TR < 1 indicates shorter estimated survival in the lenalidomide group. Hazard-scale estimates and prior sensitivity analyses are provided in Supplementary Tables S1–S2. Overall survival was measured from diagnosis. Model-based 5-year OS corresponds to survival probability at 60 months. Events: 5 deaths (bortezomib 1/9; lenalidomide 4/17).

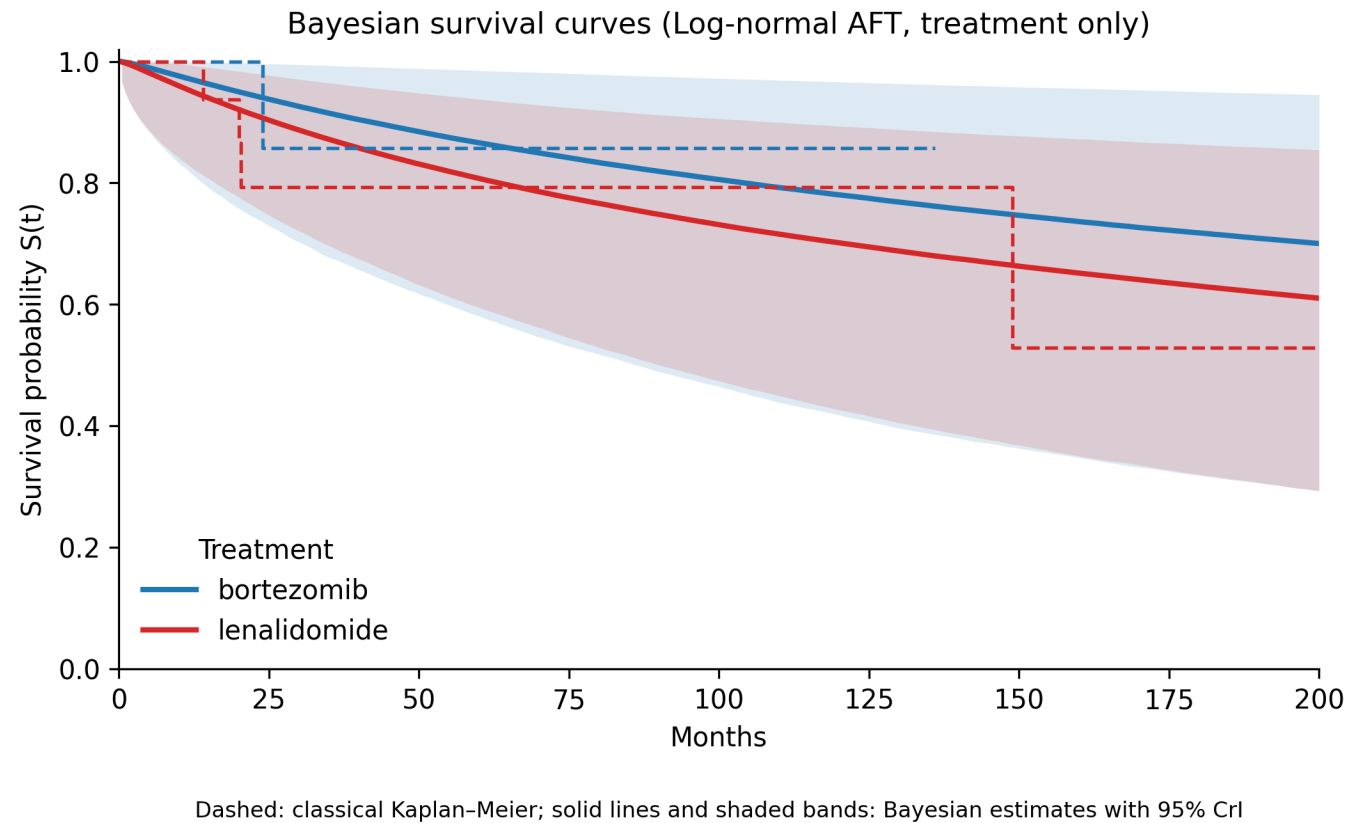


Figure 1. Estimated survival curves for patients with POEMS syndrome receiving bortezomib-containing regimens and lenalidomide, derived from a Bayesian parametric survival model. Dashed lines represent empirical Kaplan–Meier curves, solid lines represent median survival estimates obtained from a Bayesian log-normal accelerated failure time (AFT) model, and shaded areas indicate 95% credible intervals. The number of patients at risk over time is provided in **Supplementary Table S3**. Blue denotes the bortezomib group (n = 9), and red denotes the lenalidomide group (n = 17). Similar survival patterns were observed between the two treatment groups, with no statistically meaningful difference between the curves (Bayesian p-like value = 0.654).

(95% CrI 59.7%–93.7%) with lenalidomide, consistent with the crude proportions of patients alive (88.9% and 76.5%) and with the log-rank test ($p = 0.649$). Estimates did not change under informative priors or when survival was measured from treatment initiation (**Supplementary Table S1**). Given the small number of events, no multivariable model was fitted; exploratory univariable analyses of ASCT and age are provided in **Supplementary Table S2**, and none showed a robust

association with survival. Bayesian survival estimates alongside empirical Kaplan–Meier curves are presented in **Figure 1**.

Discussion. In this study, first-line bortezomib-containing regimens achieved significantly higher deep hematologic response rates ($\geq$ VGPR) than lenalidomide-based therapy (88.9% vs 37.5%; $p = 0.013$) without compromising overall survival. The lack of a discernible

OS difference is expected given the generally indolent course of POEMS syndrome, high rates of subsequent consolidation with ASCT, and limited statistical power due to the small number of events.

The deep hematologic response rates achieved with bortezomib-based therapies in our cohort were consistent with studies evaluating the efficacy of the frontline VCD regimen in a similar patient population.⁹ These investigators reported that 75% of patients receiving the VCD regimen achieved VGPR or better response and that rapid and marked reductions in VEGF levels were observed. Similarly, in a multicenter analysis of 108 patients, bortezomib-based regimens were shown to stand out with high response rates and an acceptable toxicity profile.¹¹ These data suggest that the strong anti-plasma cell activity of bortezomib, proven in multiple myeloma, is also preserved in POEMS syndrome.^{15,16} Our findings highlight a clinically relevant paradox. The higher prevalence of neuropathy at presentation in the bortezomib group suggests that clinicians may have preferred a rapidly acting agent in patients with more aggressive disease. Although the incidence of bortezomib-associated peripheral neuropathy is reported to be relatively high in patients with multiple myeloma,¹⁷ accumulating evidence, together with our findings, suggests that this risk may be relatively lower in POEMS syndrome.^{12,13} Despite a higher prevalence of neuropathy at presentation in our bortezomib group (77.8% vs 29.4%), no neuropathy progression was observed during treatment, which may be attributed to our choice of weekly and subcutaneous administration of bortezomib. Consistent with our findings, the literature also reports cases of neuropathy improvement during bortezomib treatment.⁸

Lenalidomide-based therapies are widely used in POEMS syndrome and are recommended as first choice in major guidelines.¹ In the prospective phase II study with lenalidomide, hematologic response was achieved in 81% of patients receiving the lenalidomide-dexamethasone combination, and the median progression-free survival (PFS) was reported as 28 months.¹⁸ The lower response rates observed in the lenalidomide group in our study may, at least in part, reflect the study's retrospective design, which naturally entails heterogeneity in patient selection, dose intensity, and treatment duration. Nevertheless, the similar survival rates in both treatment groups suggest that both approaches are valid for long-term outcomes. Thrombosis is a common adverse event of lenalidomide, but in the lenalidomide arm of the current study, none of the patients experienced thrombotic events.

ASCT is considered one of the most effective treatment modalities for POEMS syndrome in eligible patients. In our study, ASCT was performed in 56% of patients in both groups, which may have masked the impact of different initial treatments on long-term

survival. Prior studies have reported a 5-year PFS rate of 74% after ASCT, with favorable outcomes regardless of the induction therapy administered before transplantation.^{14,19}

The central role of VEGF in POEMS pathogenesis is well established, and it is widely used for diagnosis and to evaluate treatment response.^{5,20} Bortezomib is known to downregulate VEGF gene expression and consequently inhibits VEGF secretion.²¹ However, in our study, VEGF measurements were not consistently available in patients from Türkiye (3 out of 9 patients), and the lack of inter-laboratory standardization precluded a reliable comparison of VEGF levels between the two countries; therefore, no statistical analysis was performed regarding VEGF levels. Besides VEGF, alternative cytokines such as IL-6 may play a role in POEMS diagnosis and treatment evaluation. In a pilot study evaluating IL-6 alongside VEGF, IL-6 correlated well with VEGF during the active disease state and the immediate peri-transplant period, reflecting rapid cytoreduction. However, this concordance was lost during long-term follow-up due to confounding comorbidities, late relapses, or coexisting Castleman disease.²²

Our study has several important limitations. Most notably, treatment allocation was profoundly confounded by the participating country and center. All patients in the bortezomib cohort were treated at the Turkish center, whereas most lenalidomide-treated patients (13 of 17) were from the Italian cohort ($p < 0.001$). Consequently, this study essentially compares not only two distinct pharmacological regimens, but also center- and country-specific treatment strategies. Discrepancies in patient selection, diagnostic workup, response-assessment intervals, supportive care practices, indications for consolidation ASCT, and local management traditions cannot be fully disentangled from true pharmacological treatment effects. While clinicians across all centers aimed to follow established international diagnostic and therapeutic guidelines, this adherence does not eliminate structural confounding. Therefore, a definitive causal superiority of bortezomib over lenalidomide cannot be established from this observational dataset.

Additionally, neuropathy assessment relied on clinical documentation and physician reporting of CTCAE grading rather than standardized objective clinical scales or tests, which may have limited the detection and definition of minor neurological changes. We acknowledge that standardized neuropathy assessment in plasma cell dyscrasias is critical for correctly interpreting treatment-related toxicity.¹⁷ Finally, the extended inclusion period (2005–2024) may introduce treatment-era bias. Over this extended timeframe, clinical practice has evolved substantially: earlier disease recognition, routine and more sensitive

assessment of disease activity, transition from intravenous to subcutaneous bortezomib with reduced neurotoxicity, refined anti-thrombotic prophylaxis protocols for lenalidomide, and general improvements in multidisciplinary supportive care. Furthermore, patients diagnosed in more recent years may have benefited from more effective second-line therapies upon relapse. Although comparative analyses across distinct time intervals were limited by cohort size, this era-dependent heterogeneity in supportive and subsequent management must be considered when interpreting our long-term efficacy and safety outcomes.

The disease's extreme rarity makes large-scale randomized controlled trials practically impossible. Therefore, real-world evidence plays an important role in clinical decision-making. In a bibliometric analysis, it was emphasized that although research on POEMS syndrome has increased in recent years, high-quality comparative studies remain lacking.²³ International collaborations and prospective registries are critical to developing evidence-based treatment algorithms for this rare disease. Additionally, cost-effectiveness analyses may help guide treatment selection.

Future research should evaluate next-generation proteasome inhibitors and monoclonal antibodies in POEMS syndrome. Recently, successful use of agents such as carfilzomib and daratumumab has been reported

in relapsed or refractory disease.^{24,25} These novel treatment options appear promising.

Conclusions. In patients with POEMS syndrome, first-line bortezomib-based therapy achieved significantly higher rates of deep hematologic responses compared with lenalidomide-based regimens in this cohort. Although this superior depth of response did not translate into an overall survival advantage, no clinically documented worsening of neuropathy was observed in this small retrospective cohort using weekly subcutaneous bortezomib, despite a higher prevalence of baseline symptomatic neuropathy. However, because POEMS syndrome is a multisystem disorder and systematic data on organ and VEGF responses were limited, deeper hematologic responses alone cannot be equated with globally superior clinical efficacy. Furthermore, given the profound confounding between participating centers and treatment allocation, this observational dataset cannot establish definitive causal superiority of bortezomib over lenalidomide. Nonetheless, our findings challenge the prevailing reluctance to use bortezomib due to neurotoxicity concerns, suggesting that upfront bortezomib-containing regimens represent an effective, viable therapeutic option for selected patients with POEMS syndrome.

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