Long-term outcomes of newly diagnosed POEMS syndrome patients who received first-line lenalidomide-based therapy

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare plasma cell dyscrasia. The long-term outcomes of POEMS syndrome patients after first-line lenalidomide plus dexamethasone (Rd) treatment and the efficacy of lenalidomide maintenance treatment (R-MT) were elusive. This study retrospectively reviewed 141 and 84 newly diagnosed POEMS syndrome patients who received first-line Rd and Rd plus R-MT treatment (Rd+R-MT), respectively. The 5-year progression-free survival and overall survival rates from the first-line treatment (PFS_1 and OS_1) of all patients were 55.1% and 88.8%. Patients who received Rd+R-MT had a significantly longer PFS_1 (median 74.0 *vs*. 63.0 months; *P*=0.035) compared with those who received Rd alone. Sixty patients experienced clinical relapse and fifty-five patients received a second-line treatment. Sixteen (29.1%) patients received bortezomib plus dexamethasone (BD) and twenty-five (45.5%) patients received immunomodulatory drug retreatment as the second-line treatment. After another median follow-up of 40 months, the 3-year OS and PFS rates from the start of the second-line treatment (OS_2 and PFS_2) were 92.8% and 57.4%. In patients with PFS_1 less than 48 months, BD treatment provided a significantly longer PFS_2 compared with immunomodulatory drug retreatment (80.0 *vs*. 26.0 months; *P*=0.012). Lenalidomide-based treatment is highly effective in POEMS syndrome, R-MT after Rd would prolong PFS. The survival after relapse is still promising with efficacious treatments.

First-line treatment with lenalidomide-based regimens has been demonstrated to be highly effective in POEMS syndrome.[1] R-MT had proved to improve outcomes of multiple myeloma patients[2] but had rarely been reported in POEMS syndrome.[3] Moreover, POEMS syndrome is an incurable disease with recurrent remission-and-relapse patterns.[4-9] There is no standard salvage treatment for POEMS syndrome. Several studies have suggested that lenalidomide[5,7] and bortezomib[6,8] could be salvage treatments for relapsed patients. However, due to the rarity of the disease, the scales of previous studies were limited. Therefore, we conducted this retrospective study to evaluate the efficacy of first-line Rd and R-MT, and assess the second-line treatments of those patients.

The medical records of POEMS syndrome patients who met the diagnostic criteria described by Dispenzieri *et al*.[1] and admitted to Peking Union Medical College Hospital between January 2012 and December 2020 were reviewed, and 225 patients were selected. The date of the last follow-up was June 30, 2023. All patients provided informed consent. The study was approved by the Institutional Review Board of Peking Union Medical College Hospital and followed the ethical guidelines of the Declaration of Helsinki.

All patients were treated with Rd as the first-line treatment: lenalidomide 10-25 mg per day on days 1-21, dexamethasone 40 mg on days 1, 8, 15, and 22, one cycle every 28 days for a total of 12 cycles. R-MT was given as 10-25 mg per day on days 1-21, of a 28-day cycle, for nine to 12 cycles. The dosage selection of lenalidomide was based on general appearance and laboratory examinations (e.g., the complete blood count, serum creatinine level) at diagnosis and during follow-up, and dose-related toxicity. Aspirin 100 mg daily was prescribed as a prophylaxis for thrombosis events. None of them received autologous stem cell transplatantion (ASCT) before lenalidomide treatment.

Serum VEGF levels were measured using serum with a human Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA), and serum vascular endothelial growth factor (VEGF) lower than 600 pg/mL was considered normal.[10] Hematological, VEGF, and clinical response criteria were based on current recommendations[1] and the previous clinical trial.[10] CR_H was the complete hematologic remission. CR_V and PR_V were the complete and partial VEGF remission, respectively. Sustained CR_{V1} and CR_{H1} was defined as CR_{V1} and CR_{H1} obtained and sustained for at least 24 months calculated from the start of treatment, respectively. Overall clinical response was defined as the response of any key symptoms without the exacerbation of existing symptoms, and no newly developed symptoms. Clinical relapse was defined as the presence of any new symptom or the reappearance or progression of symptoms attributed to POEMS syndrome (e.g., the deterioration of neurological symptoms (increase of ONLS score), the recurrent extravascular volume overload, the re-emerging skin changes and the progression of organomegaly.). PFS_1 was defined as the time from the start of first-line treatment to the occurrence of first clinical relapse. PFS2 was defined as the time from the start of second-line treatment to the occurrence of second clinical relapse. The OS_1 or the OS_2 was defined as time from the start of the first- or the second-line treatment until the death from any cause, respectively. Survival curves were plotted by the Kaplan-Meier method, the 95% confidence interval (CI) and difference comparison was provided by the log-rank test. Risk factors were analyzed utilizing Cox multivariate models, variates with *P* value <0.1 in univariate analysis and previous reported prognostic factors[4,11] were

included in multivariate analysis, and $P<0.05$ were considered statistically significant.

The baseline demographic and clinical data of the 225 patients are summarized in Table 1. All patients received Rd as the first-line treatment, among them 84 (37.3%) patients received Rd+R-MT. Ninety-two (45.3%) of the 203 patients evaluable of hematological response achieved CR_{H1}, and the median time to CR_{H1} was 15.0 months (95% CI: 12.5-17.5). A total of 118 (64.5%) and 51 (27.8%) of the 183 patients evaluable for VEGF response achieved CR_{V1} and PR_{V1}, respectively. The overall VEGF response rate was 92.3%. The median time to CR_{V1} was 9.0 months (95% CI: 6.63-11.4). The overall clinical response rate was 94.2%. Patients who received Rd+R-MT had a tendency of higher sustained CR_{V1} rate than patients who did not (69.4% *vs*. 53.8%; P=0.074), whereas there was no significant difference in the rate of sustained CR_{H1} (45.6% *vs*. 42.7%; P=0.726) (*Online Supplementary Table S1)*.

In the Rd group, one patient had grade 4 thrombocytopenia and discontinued Rd treatment. Two patients had grade 3 neutropenia, and two patients had grade 3-4 anemia. Two patients discontinued Rd treatment due to ischemic

Table 1. Baseline characteristics of patients.

Baseline characteristics	All patients, N=225	Rd group, N=141	Rd+R-MT group, N=84	*P*
Male, N (%)	133 (59.1)	80 (56.7)	53 (63.1)	0.348
Age in years, median (range)	51 (21-76)	51 (21-73)	51 (28-76)	0.664
Polyneuropathy ONLS >4, N (%)	59 (26.2)	42 (29.8)	17 (20.2)	0.115
Organomegaly, N (%)				
Hepatomegaly	68/218 (31.2)	48/136 (35.3)	20/82 (24.4)	0.092
Splenomegaly	121/220 (55.0)	70/137 (51.1)	51/83 (61.4)	0.135
Lymphadenopathy	130/214 (60.7)	89/136 (65.4)	41/78 (52.6)	0.063
Castleman disease, N (%)	28/38* (73.7)	18/21* (85.7)	10/17* (58.8)	0.078
VEGF pg/mL, median (range)	4,646 (322-23,728), 202 evaluated	4,746 (322-23,728), 131 evaluated	4,498 (445-12,586), 71 evaluated	0.244
VEGF <600 pg/mL at baseline, N (%)	6/202 (3.0)	4/131 (3.1)	2/71 (2.8)	-
M protein				
SPE g/L, median (range)	1.0 (0-18.3), 193 evaluated	0.825 (0-18.3), 122 evaluated	1.3 (0-10.9), 71 evaluated	0.320
IgA type heavy chain, N (%)	149/216** (69.0)	89/133**(66.9)	60/83** (72.3)	0.406
Serum IFE negative[a], N (%)	9 (4.0)	8 (5.7)	1 (1.2)	-
BMPC ≥10%, N (%)	3/179 (1.7)	2/121 (1.7)	1/58 (1.7)	-
Osteosclerosis, N (%)	110/121*** (90.9)	69/75*** (92.0)	41/46*** (89.1)	0.746
Angioma, N (%)	143/216 (66.2)	95/133 (71.4)	48/83 (57.8)	0.040
Hyperpigmentation, N (%)	192/219 (87.7)	124/137 (90.5)	68/82 (82.9)	0.098
Edema, N (%)	183/221 (82.8)	117/138 (84.8)	66/83 (79.5)	0.315
Pleural effusion, N (%)	102/211 (48.3)	69/136 (50.7)	33/75 (44.0)	0.349
Ascites, N (%)	87/201 (43.3)	56/131 (42.7)	31/70 (44.3)	0.834
Pericardial effusion, N (%)	134/191 (70.2)	95/128 (74.2)	39/63 (61.9)	0.080
Pulmonary dysfunction				
sPAP >50 mmHg, N (%)	31/175 (17.7)	21/122 (17.2)	10/53 (18.9)	0.792
DLCO <40% predicted, N (%)	22/105 (21.0)	17/78 (21.8)	5/27 (18.5)	0.718
Papilledema, N (%)	72/114 (63.2)	54/84 (64.3)	18/30 (60.0)	0.676
Stroke, N (%)	16/162 (9.9)	12/116 (10.3)	4/46 (8.7)	1.000
Serum albumin <30 g/L, N (%)	17/200 (8.5)	11/129 (8.5)	6/71 (8.5)	0.985
eGFR <30 mL/min/1.73 m^2, N (%)	12/203 (5.9)	9/132 (6.8)	3/71 (4.2)	0.547
Polycythemia[b], N (%)	28/204 (13.7)	17/131 (13.0)	11/73 (15.1)	0.677
Thrombocytosis[c], N (%)	33/204 (16.2)	23/131 (17.6)	10/73 (13.7)	0.473
Prominent weight loss, N (%)	170/206 (82.5)	109/130 (83.8)	61/76 (80.3)	0.513
Fatigue, N (%)	175/206 (85.0)	112/130 (86.2)	63/76 (82.9)	0.528
Diarrhea, N (%)	46/206 (22.3)	28/120 (23.3)	18/76 (23.7)	0.721
Fever, N (%)	24/206 (11.7)	17/130 (13.1)	7/76 (9.2)	0.404

[a]Negative serum IFE results in 9 patients, among which 5 patients had urine IFE λ^+, and 3 patients had a free light chain ratio (κ/λ <0.26), 1 patient had extramedullary plasmacytoma with restrictive λ expression. [b]Polycythemia: hemoglobin b (Hgb) >160 g/L for females, Hgb>165 g/L for males. [c]Thrombocytosis: platelet count >450×10^9/L. ASCT: autologous stem cell transplantation; eGFR: estimated glomerular filtration rate; ONLS: overall neuropathy limitations scale; BMPC: bone marrow plasma cells; SPE: serum protein electrophoresis; IFE: immunofixation electrophoresis; VEGF: vascular endothelial growth factor; sPAP: systolic pulmonary artery pressure; DLCO: diffusion capacity of lung for carbon monoxide; Rd: lenalidomide plus dexamethasone; R-MT: lenalidomide maintenance treatment; Tdex: thalidomide plus dexamethasone; *with lymph node biopsy; **detectable; ***with bone lesions.

strokes. One patient had liver cancer and another patient had meningioma in the Rd group during follow-up. No grade 3-4 neutropenia, anemia, or thrombocytopenia, and no secondary malignancy was observed yet in the R-MT group. After a median follow-up of 41 months (range, 1-127 months), 60 patients had relapsed disease and 18 patients died before receiving second-line treatment (*Online Supplementary Figure S1*). The median PFS_1 was 68.0 months (range, 1-116 months; 95% CI: 56.4-79.6). The estimated 3-year and 5-year PFS1 rates were 75.4% and 55.1%, respectively. The median OS_1 was not reached, the estimated 3-year and 5-year OS_1 rates were 90% and 88.8%, respectively. Rd+R-MT group had significantly longer PFS_1 (median 74.0 *vs*. 63.0 months; *P*=0.035) and OS_1 (median not reached in both groups; *P*=0.017) compared with Rd group. In multivariate Cox analysis, Rd+R-MT treatment is an independently predictor for a superior PFS_1 (hazard ratio [HR]= 0.423, 95% CI: 0.212-0.878; *P*=0.020) and OS_1 (HR=0.119, 95% CI: 0.016-0.894, *P*=0.039) (Figure 1; *Online Supplementary Table S2*). Fifty-five patients who received a second-line treatment were included in further analysis. Seven (12.7%), 16 (29.1%), and seven (12.7%) patients received ASCT, BD, and melphalan plus dexamethasone (MDex) regimen as the second-line treatment, respectively. Notably, 25 (45.5%) patients were re-treated with immunomodulatory drugs (i.e., 23 and two patients received lenalidomide- and thalidomide-based therapy, respectively). Patients were classified into the immunomodulatory drug group (who received Rd, thalidomide and dexamesthasone), BD group, and other treatments group (who received MDex or ASCT) according to their second-line treatment.

The overall clinical response rate was 94.1%. Fourteen (36.8%) of the 38 patients evaluable for hematological response achieved CR_{H2}. Of 38 patients evaluable for VEGF response, 23 (60.5%) patients achieved CR_{V2}. The CR_{H2} rates were 31.3% (5 of 16 patients evaluable), 38.5% (5 of 13 patients evaluable), and 44.4% (4 of 9 patients evaluable) of the immunomodulatory drug group, BD group, and the other treatment group, respectively (*P*=0.797). The CR_{V2} rates were 64.7% (11 of 17 patients evaluable), 50.0% (6 of 12 patients evaluable), and 66.7% (6 of 9 patients evaluable) of the three groups, respectively (*P*=0.693).

The median follow-up time calculated from the second-line treatment was 40 months (range, 1-89 months). Three patients died due to events related to disease progression or disease-related comorbidities. One patient was refractory to the second-line treatment (MDex) and was excluded from PFS analysis. A total of 20 patients had further relapses and received a third-line treatment. The median OS_2 was not reached. The median PFS_2 was 43 months (range 1-80, 95% CI: 16.2-69.8). The 3-year OS_2 and PFS_2 rate was 92.8% and 57.4%, respectively (Figure 2A, B). The median PFS_2 was 32 months, 80 months, and 41 months in the immunomodulatory drug group, BD group, and the other treatment group, respectively. The median OS_2 was not reached in the three groups. There were no significant differences in PFS_2 and OS_2 among the different second-line treatment groups (*P*=0.236 and *P*=0.93, respectively) (Figure 2A, B). However, in patients who had PFS_1 less than 48 months, those retreated with immunomodulatory drug had a sig-

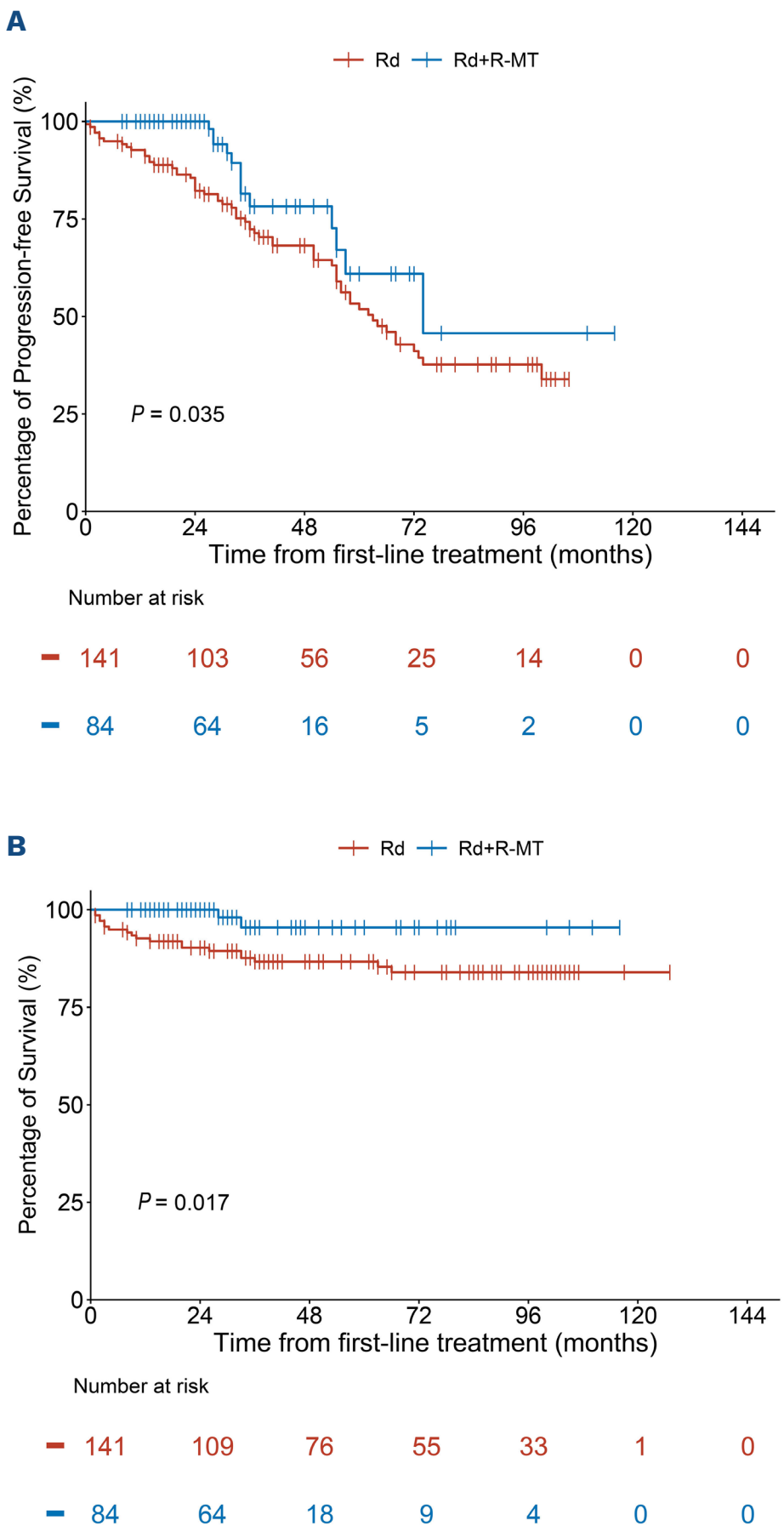

Figure 1. Kaplan-Meier curve for progression-free survival and overall survival (PFS_1 and OS_1) of 225 patients according to the first-line treatment (Rd and Rd+R-MT). (A) Kaplan-Meier curve for progression-free survival from first-line treatment (PFS_1). (B) Kaplan-Meier curve for overall survival from first-line treatment (OS_1). Rd: lenalidomide plus dexamethasone; R-MT: lenalidomide maintenance treatment.

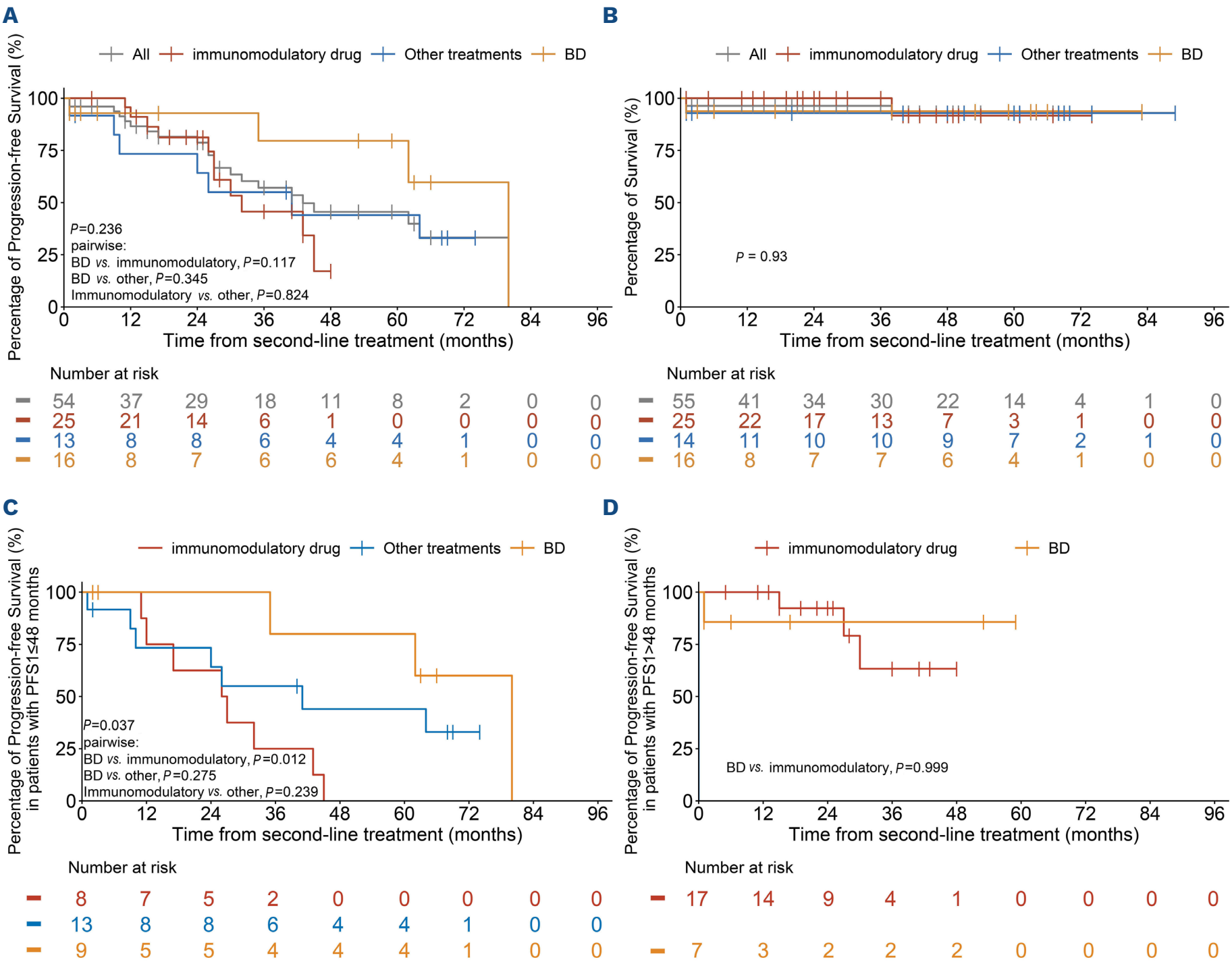

Figure 2. Kaplan-Meier curve of progression-free survival and overall survival (PFS_2 and OS_2) according to the second-line treatment groups. (A) Kaplan-Meier curve of progression-free survival from second-line treatment (PFS_2). (B) Kaplan-Meier curve of overall survival from second-line treatment (OS_2). (C) Kaplan-Meier curve of PFS_2 for patients who have PFS_1 shorter than 48 months according to the second-line treatment group. (D) Kaplan-Meier curve of PFS_2 for patients who have PFS_1 longer than 48 months according to the second-line treatment group. BD: bortezomib plus dexamethasone.

nificantly shorter PFS_2 compared with BD treatment (PFS_2 26.0 months *vs*. 80.0 months; *P*=0.012). In patients who had PFS_1 longer than 48 months, there was no significant difference in PFS_2 between the two groups (median PFS_2 not reached; *P*=0.999) (Figure 2C, D).

This study demonstrated that Rd treatment is a highly effective front-line treatment in POEMS syndrome, provided a CR_{H1} and CR_{V1} rate comparable to ASCT, melphalan- and bortezomib-based treatment,[12,13] and had also been proved by previous studies.[14,15] Moreover, our study suggested that compared with patients who received Rd alone, patients who received Rd+R-MT had significant longer PFS and OS. Thus, Rd+R-MT treatment might be a better strategy than Rd alone. Change of the backbone of a regimen is a common mode when choosing a salvage treatment. Briani *et al.* reported two successfully treated cases that switched to bortezomib-based treatment from front-line Rd after relapse,[6] however, sizes of previous studies were very limited. Our study demonstrated that BD salvage treatment provided patients with the longest PFS_2 after front-line Rd. However, due to neuropathy side effects, BD should be used with close observation. Notably, nearly half of our patients received immunomodulatory drugs again as a salvage treatment. The immunomodulatory drug group had a significantly shorter PFS_2 than the BD group in patients with PFS_1 less than 4 years, whereas no significant difference in PFS_2 between the two groups in patients with PFS_1 more than 4 years. There was no significant difference in OS among the three groups. Considering the OS, retreatment with immunomodulatory drugs is an alternative for

patients who had PFS_1 longer than 4 years after front-line lenalidomide treatment.
Although this study had the largest sample size until now, there may still be some bias due to its retrospective, single-center design. Further research is needed to identify the best candidates for early salvage treatment at biochemical relapse without clinical relapse.
In conclusion, our study demonstrated that R-MT after first-line Rd treatment would provide additional benefits for POEMS syndrome patients. Bortezomib might be the best choice for front-line lenalidomide-treated patients with PFS_1 less than 4 years, whereas for patients with PFS_1 longer than 4 years, retreatment with immunomodulatory drugs still exhibit good survival.

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Disclosures

No conflicts of interest to disclose.

Contributions

X-MG was involved in the study design, analyzed the data, and wrote the manuscript. A-AL, HZ, and K-NS participated in patient recruitment. JL designed the study, recruited the patients, analyzed the data, and wrote and critically revised the manuscript. All authors have approved the final manuscript.

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Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Dispenzieri A. POEMS syndrome: 2021 Update on diagnosis, risk-stratification, and management. Am J Hematol. 2021;96(7):872-888.
2. Alonso R, Cedena MT, Wong S, et al. Prolonged lenalidomide maintenance therapy improves the depth of response in multiple myeloma. Blood Adv. 2020;4(10):2163-2171.
3. Yu Y, Gao X, Zhao H, et al. Maintenance therapy with single-agent lenalidomide for POEMS syndrome. Blood. 2022;140(Suppl 1):10118-10119.
4. Kourelis TV, Buadi FK, Gertz MA, et al. Risk factors for and outcomes of patients with POEMS syndrome who experience progression after first-line treatment. Leukemia. 2016;30(5):1079-1085.
5. Cai Q-Q, Wang C, Cao X-X, Cai H, Zhou D-B, Li J. Efficacy and safety of low-dose lenalidomide plus dexamethasone in patients with relapsed or refractory POEMS syndrome. Eur J Haematol. 2015;95(4):325-330.
6. Riva M, Lessi F, Berno T, et al. Bortezomib-based regimens in patients with POEMS syndrome: a case series in newly diagnosed and relapsed patients. Leuk Lymphoma. 2019:60(8):2067-2070.
7. Vannata B, Laurenti L, Chiusolo P, et al. Efficacy of lenalidomide plus dexamethasone for POEMS syndrome relapsed after autologous peripheral stem-cell transplantation. Am J Hematol. 2012;87(6):641-642.
8. Warsame R, Kohut IE, Dispenzieri A. Successful use of cyclophosphamide, bortezomib, and dexamethasone to treat a case of relapsed POEMS. Eur J Haematol. 2012;88(6):549-550.
9. Kawajiri-Manako C, Sakaida E, Ohwada C, et al. Efficacy and long-term outcomes of autologous stem cell transplantation in POEMS syndrome: a nationwide survey in Japan. Biol Blood Marrow Transplant. 2018;24(6):1180-1186.
10. Li J, Zhang W, Jiao L, et al. Combination of melphalan and dexamethasone for patients with newly diagnosed POEMS syndrome. Blood. 2011;117(24):6445-6449.
11. Wang C, Huang XF, Cai QQ, et al. Prognostic study for overall survival in patients with newly diagnosed POEMS syndrome. Leukemia. 2017;31(1):100-106.
12. Zhao H, Huang XF, Gao XM, et al. What is the best first-line treatment for POEMS syndrome: autologous transplantation, melphalan and dexamethasone, or lenalidomide and dexamethasone? Leukemia. 2019;33(4):1023-1029.
13. Gao XM, Yu YY, Zhao H, et al. Bortezomib plus dexamethasone as first-line therapy for patients with POEMS syndrome. Ann Hematol. 2021;100(11):2755-2761.
14. Li J, Huang XF, Cai QQ, et al. A prospective phase II study of low dose lenalidomide plus dexamethasone in patients with newly diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Am J Hematol. 2018;93(6):803-809.
15. Nozza A, Terenghi F, Gallia F, et al. Lenalidomide and dexamethasone in patients with POEMS syndrome: results of a prospective, open-label trial. Br J Haematol. 2017;179(5):748-755.