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ORIGINAL ARTICLE

Risk factors for and outcomes of patients with POEMS syndrome who experience progression after first-line treatment

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Although clinical improvement is almost universal with therapy in patients with POEMS (an acronym for polyneuropathy, organomegaly, endocrinopathies, monoclonal protein and a variety of skin changes) syndrome, outcomes and management of patients who relapse or progress (R/P) after first-line treatment have not been described. We retrospectively identified 262 patients with POEMS syndrome treated at the Mayo Clinic from 1974 to 2014 and who had follow-up information. The 5-year progression-free survival (PFS) and overall survival (OS) was 58% and 78%, respectively. Median time to R/P was 42 months. Seventy-nine patients (30%) had an R/P, with 52 (19%) experiencing a symptomatic R/P. Eighteen patients relapsed with symptoms or signs that were not documented at diagnosis. Median times to vascular endothelial growth factor, hematologic, radiographic and clinical R/P were 35 months (range, 4–327 months), 72 months (range, 4–327 months), 51 months (range, 4–327 months) and 48 months (range, 6–311 months), respectively. On multivariate analyses, low albumin at diagnosis and failure to achieve a complete hematologic response to first-line therapy were independent risk factors for PFS. Thirty patients had documentation of a second R/P at a median of 26 months from diagnosis of the first R/P. An early R/P was a risk factor for death, but most patients with an R/P had salvageable disease. A majority of patients are still without R/P at 5 years from diagnosis.

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INTRODUCTION

The POEMS (an acronym for polyradiculoneuropathy, organomegaly, endocrinopathies, monoclonal protein and a variety of skin changes) syndrome is a rare paraneoplastic disorder secondary to a plasma cell dyscrasia. However, other important clinical features are not represented in the acronym but are commonly seen in patients and include: PEST (papilledema, extravascular fluid overload resulting in pleural effusions and ascites, sclerotic bone lesions, thrombocytosis), clubbing, pulmonary hypertension, multicentric Castleman disease and fatigue.[1] The goals of treatment are to eradicate the underlying plasma cell clone, reduce plasma vascular endothelial growth factor (VEGF) and control symptoms. This can be achieved either with radiotherapy, if the disease is limited, or systemic chemotherapy in patients with disseminated disease.[2,3]

Very good long-term outcomes have been described in recent cohorts of patients treated with radiotherapy only or autologous stem cell transplantation (ASCT).[4–6] Prior studies have also examined the outcomes of patients after first-line chemotherapy (excluding ASCT) and novel agents.[7–12] Clinical improvement is almost universal with first-line chemotherapy and/or radiation therapy. The incidence of relapse or progression (R/P) and respective outcomes have been described in recent cohorts of patients but these studies were limited by the small number of patients who were included as well as their short follow-up.[4,5,7] These patients are not a representative group as use of ASCT and radiation are surrogates for patients with a better performance status and a lower disease burden respectively. In this study, we describe risk for and outcomes of relapse in the largest cohort of patients with POEMS reported so far.

MATERIALS AND METHODS

Patients

We reviewed patients with POEMS syndrome who were seen at the Mayo Clinic in Rochester, MN, between June 1974 and May 2014. The study was approved by the Mayo Foundation Institutional Review Board, and data were collected in accordance with Minnesota state regulations. POEMS syndrome was defined as previously reported[3,10] as (1) the presence of polyradiculoneuropathy and a monoclonal plasma cell proliferative disorder (with the exception of patients with the Castleman's variant of POEMS in the case of a monoclonal plasma cell disorder); (2) the existence of one of the following other three major criteria: Castleman disease, sclerotic bone lesions or VEGF elevation; and (3) one of six possible minor criteria: organomegaly, extravascular volume overload, endocrinopathy, skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing and white nails), papilledema and either thrombocytosis or polycythemia.

Some patients fulfilled criteria for the diagnosis of Castleman's disease and POEMS syndrome. Of these, only those patients with peripheral neuropathy and a plasma cell clone were classified as standard POEMS syndrome. Without both of these characteristics, patients were classified as the Castleman's disease variant of POEMS provided they had other POEMS features.[1]

A total of 291 patients meeting diagnosis for POEMS syndrome were seen between June 1974 and May 2014. Of these, 29 patients were excluded because detailed follow-up about R/P status within the first 5 years after their diagnosis was not available, leaving 262 patients as the study population (Figure 1).

Definition and evaluation of response

Four types of response were assessed: hematologic, VEGF, fluorodeoxyglucose (FDG) avidity on positron emission tomography (PET) and clinical, as previously described.[4,5]

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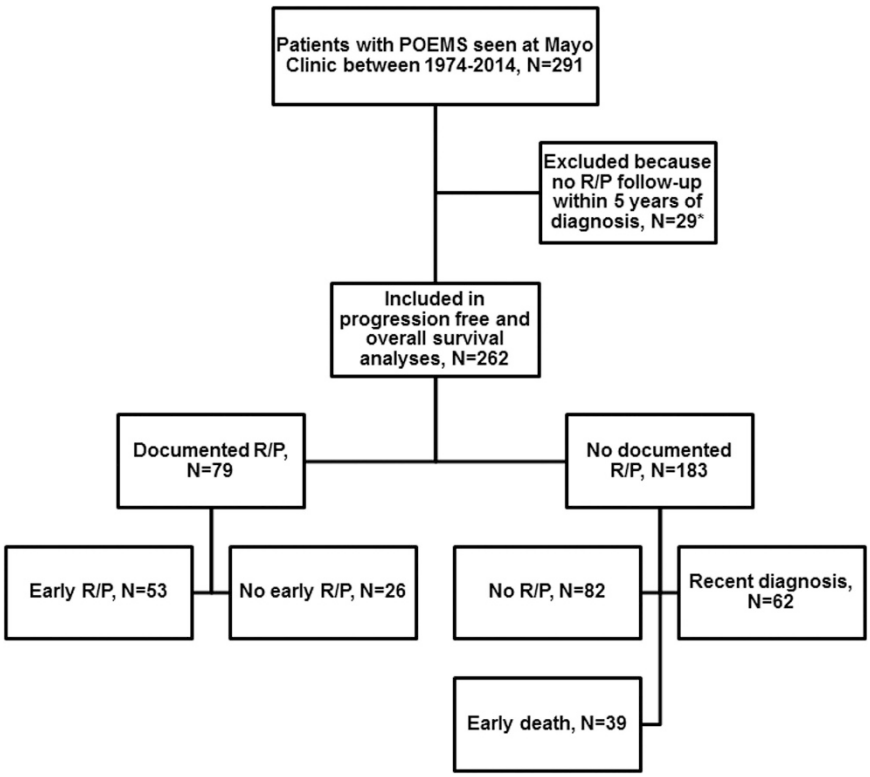

Figure 1. Consort flow diagram of patients. Early: within 5 years of diagnosis; R/P: relapse or progression; Recent diagnosis: within 5 years from end of study. *These patients were all alive at last follow-up.

Hematologic responses were modified from uniform response criteria for multiple myeloma[13] and included complete response (CR): negative bone marrow and negative immunofixation of the serum and urine; very good partial response: 90% reduction in M-protein or immunofixation positive only as long as M-protein was at least 0.5 g/dl at baseline; partial response (PR): 50% reduction in M-protein or immunofixation positive as long as baseline M-protein was at least 1.0 g/dl; no response (NR): did not meet criteria for CR, very good partial response or PR.

PET responses included complete radiologic response, which referred to initial FDG avidity on a baseline PET scan that disappears after treatment; partial radiologic response, which referred to initial FDG avidity that was 50% improved after treatment; and no radiologic response, which referred to all cases that had initial FDG avidity but did not meet criteria for CR or PR.

VEGF responses included CR (normalized VEGF), PR (VEGF improved by at least 50%, assuming baseline was 200 pg/ml) and NR (not meeting either CR or PR). Plasma VEGF levels were performed using plasma samples collected in EDTA tubes by the enzyme-linked immunosorbent assay method. Testing was performed at the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA). Normal values ranged between 31 and 86 pg/ml.

There were four clinical response categories: clinical response, clinical progression, mixed clinical response and clinical stability. Clinical response was considered separately for every organ/system involved. The symptoms and signs eligible for clinical response included peripheral neuropathy, organomegaly, papilledema, erythrocytosis/thrombocytosis, endocrinopathy, extravascular fluid overload (ascites/effusions/edema) and abnormal pulmonary function tests. Peripheral neuropathy was not further quantified in a standardized scale as very few patients had electromyograms or highly detailed functional statuses both before and after therapy, and therefore we had to rely upon qualitative responses for practical purposes. If patients did not meet criteria for a measurable parameter, they were considered nonevaluable for that parameter and noted as such.

Definitions of refractory disease, progression and relapse

Refractory disease was defined as disease requiring change of treatment within 12 months from the start of first-line therapy for reasons other than intolerance to first-line therapy.

Progression was defined as follows: hematologic progression, increase in the M-component (serum or urine) by 25% from the lowest value; PET progression, definite increase in size or FDG avidity of existing plasmacytomas on PET scan; VEGF progression, persistent increase in plasma VEGF level >200 pg/ml on at least 2 occasions. Similarly, relapse was defined as: hematologic relapse, reappearance of serum/urine M-protein by electrophoresis/immunofixation; radiographic (PET) relapse, new bone/soft tissue plasmacytomas; VEGF relapse, rising plasma VEGF level >200 pg/ml on at least 2 occasions. Clinical relapse and clinical progression were considered together as new or progressive symptoms attributable to POEMS syndrome.

Patient follow-up

Median follow-up for overall survival (OS) and progression-free survival (PFS) for the entire cohort was 68 months (range, 0–378 months) and 67 months (range, 0–349 months), respectively. Complete follow-up for progression was defined as detailed clinical follow-up within 12 months from the end of study enrollment and was available for 161 (61%) patients (Figure 1, Supplementary Table 1). Of the remaining 101 (39%) patients, 62 patients had <5 years of follow-up for R/P because of a recent diagnosis (that is, within 5 years of the end of study enrollment) and 39 died within 5 years of diagnosis (cause of death was unknown in 34 and unrelated to POEMS in 5 patients). As the assignation of 'no R/P' is limited by the quality of follow-up in this retrospective study, all deaths were considered events for PFS analyses except where stated otherwise. If a patient's cause of death was known to be secondary to POEMS syndrome, then this was counted as an R/P event for progression analyses in addition to death event for survival analyses.

Early R/P was defined as an R/P documented within 5 years of diagnosis. The 5-year cutoff was chosen because both the median time to relapse, excluding refractory patients, and our median follow-up for R/P were ~ 5 years.

Statistical analyses

Statistical analyses were performed using JMP statistical software (SAS, Carey, NC, USA). Fisher's exact and Kruskal–Wallis tests were used to define differences among categorical and continuous variables, respectively.

OS and PFS were calculated from diagnosis and were estimated using the method of Kaplan–Meier. For PFS analyses, death or progression were considered as events.

RESULTS

Baseline characteristics

Of the 262 patients in this study, 176 (67%) were male and their median age was 51 (19–82) years. Ninety (34%) patients achieved a hematologic CR with first-line therapy, 67 (26%) less than CR and in 105 (40%) patients hematologic response to first-line therapy was not available. Seventy-nine (30%) patients experienced a documented R/P. Of these, 53 (20%) had an early R/P, that is, within 5 years of diagnosis, and 26 (10%) a late R/P, that is, 5 years after diagnosis (Figure 1). The 39 patients who died without a documented R/P within the first 5 years were counted as R/P events for the purpose of comparing baseline characteristics (Table 1). Patients with early death or R/P had higher dFLC levels (that is, the difference between involved and uninvolved free light chains) and lower serum albumin levels. They were less likely to have received an ASCT and more likely to have received standard-dose cytotoxic chemotherapy.

POEMS syndrome progression

The 5-year PFS for the whole group was 58% (Figure 2a). Among patients with an R/P, the median time to relapse was 42 months (range, 3–327 months). The 5-year PFS for patients receiving ASCT vs radiation vs chemotherapy/novel agents was 72% vs 62% vs 45%, respectively ($P = 0.001$; Figure 2b). The 5-year PFS for patients achieving a hematologic CR to first-line therapy vs achieving less than CR vs not evaluated for a hematologic response was 88% vs 50% vs 37%, respectively ($P < 0.0001$; Figure 2c).

On univariate and multivariate analyses, albumin level at diagnosis and failure to achieve a hematologic CR to first-therapy were identified as significant risk factors for PFS (Table 2). When performing univariate and multivariate landmark analyses at 12 months, achieving a hematologic CR was the only independent risk factor associated with PFS ($P < 0.0001$, data not shown). Although patients receiving radiation or ASCT fared better than those receiving chemotherapy or novel agents on univariate analysis, this did not persist on multivariate analysis. Because patients included this study spanned a 40-year period, we dichotomized them according to diagnosis period (before and after June of 2003). Diagnosis period was not predictive of PFS in our univariate analyses.

Table 1. Baseline characteristics and first-line treatments of patients

	Neither documented early R/P nor early death,[a] N = *170*	*Either documented early R/P or early death,*[a] N = *92*	P-*value*
Characteristic			
Male, *N* (%)	111 (65%)	65 (71%)	NS
Age, years, median (range)	50 (19–82)	52 (28–81)	NS
Seen at Mayo within 90 days of diagnosis	118 (70%)	59 (65%)	NS
Diagnosed after June 2003[b]	96 (56%)	42 (46%)	NS
Polyneuropathy	170 (100%)	92 (100%)	NS
Hepatomegaly/splenomegaly	69 (41%)	37 (40%)	NS
Lymphadenopathy	52 (31%)	31 (34%)	NS
Castleman's variant	15 (9%)	13 (14%)	NS
Endocrinopathy	113 (68%)	66 (73%)	NS
Skin changes	110 (65%)	56 (62%)	NS
Extravascular fluid overload (edema/effusions/ascites)	89 (54%)	56 (62%)	NS
Erythrocytosis or thrombocytosis	97 (57%)	51 (55%)	NS
Abnormal lung function[c]	71 (43%)	28 (31%)	NS
Papilledema[d]	37 (22%)	25 (27%)	NS
Bone lesions	138 (81%)	74 (80%)	NS
Plasma VEGF, pg/ml[e]	236 (31–3764)	643 (187–4802)	NS
Serum albumin, g/dl	3.4 (2.4–4.5)	2.9 (2.2–4.2)	< 0.0001
Serum M-spike size, g/dl	1.3 (0.5–2.6)	1.2 (0.5–2.8)	NS
M-spike type			
Lambda	163 (96%)	86 (94%)	NS
IgG	73 (45%)	35 (38%)	NS
IgA	71 (44%)	48 (52%)	NS
IgM	5 (3%)	1(1%)	NS
No heavy chain	13 (8%)	8 (9%)	NS
Lambda restricted	163 (96%)	86 (93%)	NS
dFLC, mg/dl	1.9 (0.01–19.89)	3.2 (0.5–105)	< 0.01
FLC ratio	0.58 (0.04–8.6)	0.4 (0.08–1.6)	< 0.01
Treatment			
ASCT	62 (37%)	18 (20%)	< 0.01
Radiation	57 (34%)	26 (28%)	NS
Chemotherapy	34 (20%)	32 (35%)	< 0.01
Novel agents[f]	6 (4%)	5 (5%)	NS
Unknown/best supportive care	11 (6%)	11 (12%)	NS

Abbreviations: ASCT, autologous stem cell transplantation; dFLC, difference between involved and uninvolved free light chain; FLC, free light chain; NS, nonsignificant; R/P, experiencing relapse or progression; VEGF, vascular endothelial growth factor. [a]Early relapse and early death are defined as event within 5 years of diagnosis. [b]The median diagnosis date. [c]Fifty-one patients were not evaluated for lung function abnormalities and were not included in the denominator. [d]Forty-six patients were not evaluated for papilledema and were not included in the denominator. [e]VEGF levels were available only for 56 patients at diagnosis. [f]Novel agents included lenalidomide ($n = 8$), bortezomib ($n = 1$) and thalidomide ($n = 3$).

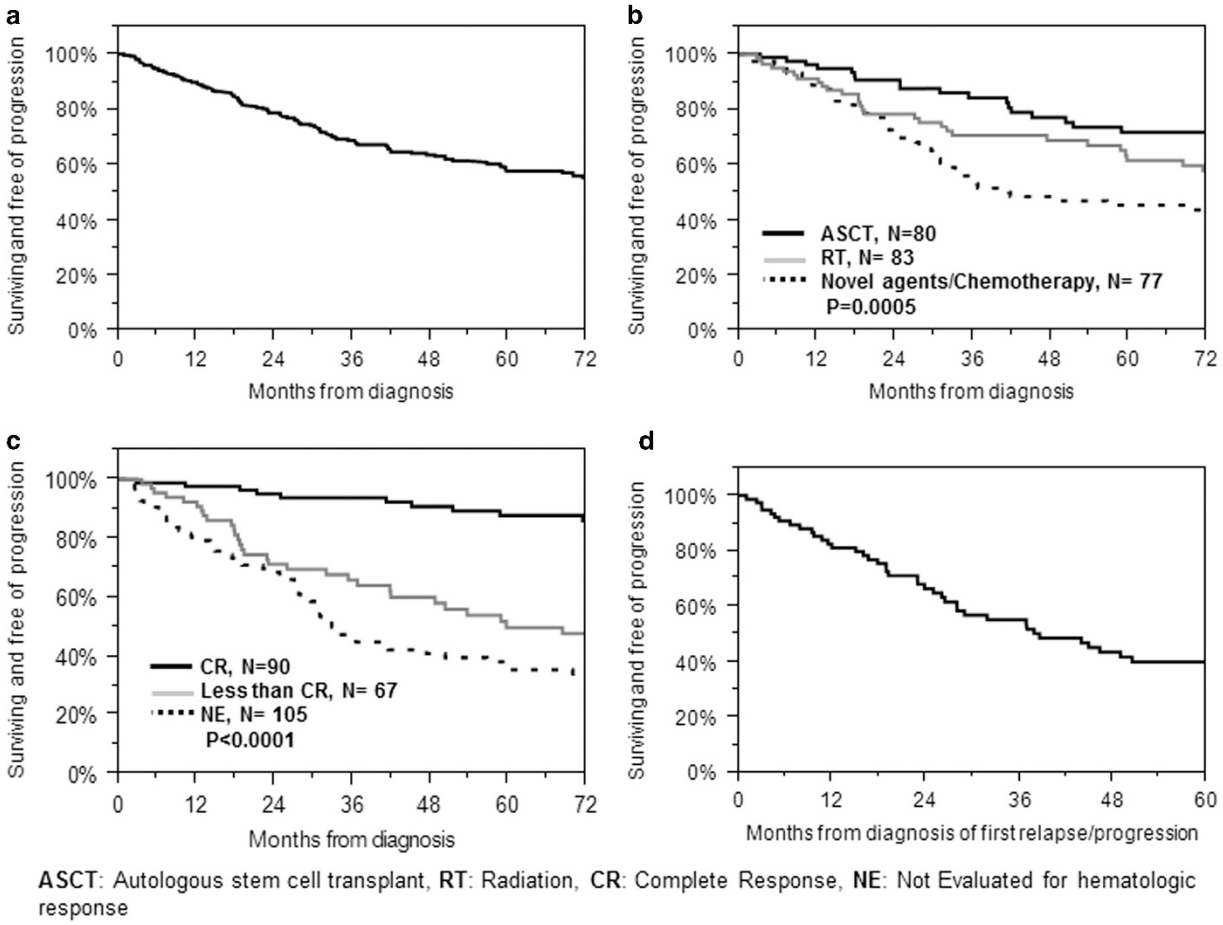

Figure 2. (**a**) PFS of 262 patients. (**b**) PFS according to first-line treatment. (**c**) PFS according to hematologic response to first-line treatment. (**d**) PFS from time of first relapse/progression of 79 patients.

Table 2. Analysis of risk factors predictive of progression-free survival

Prognostic factor	*Univariate*		*Multivariate*	
	Risk ratio (95% CI)	P-*value*	*Risk ratio (95% CI)*	P-*value*
Age	1.02 (0.99–1.03)	NS	Not included	
dFLC >2.2[a]	2.1 (0.98–4.9)	NS	Not included	
Albumin >3.2[a]	0.28 (0.16–0.49)	0.004	0.6 (0.4–0.97)	<0.05
Bone lesions	0.7 (0.47–1.09)	NS	Not included	
Castleman's variant	0.86 (0.54–1.47)	NS	Not included	
Erythrocytosis or thrombocytosis	0.85 (0.6–1.2)	NS	Not included	
Extravascular fluid overload	1.52 (1.05–2.2)	0.02	1.5 (0.95–2.58)	NS
Diagnosed after June 2003[b]	0.92 (0.62–1.3)	NS	Not included	
First-line therapy				
Radiation vs chemotherapy/novel agents	0.59 (0.4–0.9)	0.01	1.02 (0.6–1.75)	NS
ASCT vs chemotherapy/novel agents	0.42 (0.25–0.67)	0.0003	0.64 (0.3–1.17)	NS
Radiation vs ASCT	1.4 (0.85–2.4)	NS	Not included	
Hematologic response to first-line therapy				
CR vs NE	0.21 (0.13–0.33)	<0.0001	0.2 (0.1–0.4)	<0.0001
CR vs less than CR	0.31 (0.19–0.5)	<0.0001	0.3 (0.2–0.6)	<0.001
NE vs less than CR	1.5 (0.99–2.18)	NS	Not included	

Abbreviations: ASCT, autologous stem cell transplantation; CI, confidence interval; CR, complete hematologic response; dFLC, difference between involved and uninvolved free light chain; NE, not evaluated; NS, nonsignificant. [a]The median value. [b]The median diagnosis date.

For the 79 patients with R/P, median PFS from time of first R/P was 39 months (range, 27–79 months) (Figure 2d), and it was not different among patients presenting with a symptomatic R/P versus patients presenting with an asymptomatic R/P.

POEMS syndrome OS

For the 92 patients who died during the study period, causes of death were as follows: POEMS syndrome-related complications in 17 (19%) patients; causes unrelated to POEMS syndrome in 16 (17%) patients; and unknown for the remaining 59 (64%) patients. The 5-year OS for the entire cohort was 78% and differed between those patients who had early R/P or death (42%) vs not (100%; $P < 0.0001$; Supplementary Figure 1a). Even if the 34 patients with early death due to unknown causes were excluded from the early R/P group, the OS difference persisted (68% vs 100%; $P < 0.0001$; Supplementary Figure 1b).

Patterns of relapse or progression for patients with a documented R/P

Of the 79 patients with a documented R/P, 10 (13%) had refractory disease to first-line treatment, and all went on to receive second-line treatment.

The patterns of R/P and respective management are shown in Table 3. Excluding the 10 patients who were refractory to first-line treatment, 42 of 79 patients (53%) had worsening of one or more symptoms upon R/P. The remaining 27 (27%) R/Ps were identified by a combination of worsening laboratory or radiographic evaluations in the absence of symptoms.

Eighteen (23%) patients presented with one or more symptoms that had not been identified upon initial diagnosis. Distribution of new symptoms across all patients were as follows: lung function abnormalities, 8 patients; endocrinopathies, 7; fluid overload, 5; thrombocytosis, 2; 1 with skin lesions, 1 with organomegaly, 1 with papilledema and 1 with fever.

Median times to VEGF, hematologic, radiographic and clinical R/P were 35 months (range, 4–327 months), 72 months (range, 4–327 months), 51 months (range, 4–327 months) and 48 months (range, 6–311 months), respectively ($P > 0.05$; Supplementary Figure 2). As routine VEGF and PET monitoring for patients with POEMS syndrome were more recently introduced,[14] we examined the influence of diagnosis period in the patterns of relapse. There was no difference in the frequency of clinical relapses for patients diagnosed after and before June 2003 (64% vs 69%; $P > 0.05$).

Second-line treatment

The most common second-line treatments included conventional chemotherapy in 22 (28%), radiation in 15 (19%) and ASCT in 12 (15%) patients. Of the 42 patients who presented with symptomatic worsening and of the 10 refractory patients, all but 1 received immediate treatment upon ascertainment of R/P (Supplementary Figure 3). Of the remaining 27 patients, 26 presented with asymptomatic R/P and in 1 patient the type of R/P and reason for initiating second-line treatment was unclear. Responses to second-line therapy are shown in Table 3. In all, 92% of patients responded to second-line therapy, and the 6 patients who were refractory to second-line treatment received third-line treatment (5 responded).

Eight (31%) patients were not treated immediately upon R/P but were observed for a median of 9 months (range, 6–124 months; Supplementary Figure 3). One patient had a symptomatic R/P and seven patients had an asymptomatic R/P. In the patient presenting with symptoms, the onset of symptoms predated radiographic R/P by 19 months but the patient had been lost to follow-up and for unclear reasons treatment with radiation was, inappropriately, delayed until he presented to the Mayo Clinic, at which point he was treated with radiation. Of the remaining seven patients, three were treated with radiation, two with chemotherapy and two remain on observation.

Subsequent relapses/progressions

Thirty patients went on to experience a second R/P (R/P-2). Of these, 2 (7%) were refractory to third-line treatment. The patterns of R/P-2 and responses to third-line therapy are shown in Supplementary Table 2. Nineteen (63%) patients had worsening of one or more symptoms upon R/P-2. Five (19%) patients presented with one or more symptoms that had not been identified or were not present upon initial first R/P.

Table 3. Types of first and second relapse or progression with respective responses

Type of R/P	*First relapse/progression*				
	N	*Second responses, % (% across rows)*			
	n = *79*[a]	*CR/VGPR*	*PR*	*NR*	*NE*
Hematologic	23[b]	39%	17%	26%	17%
PET	44[c]	16%	23%	7%	55%
VEGF	26[d]	16%	15%	8%	15%
Clinical R/P (n = *52*)	N[a]	*Response*	*MR-SD*	*CP*	*NE*
Neuropathy	38	42%	26%	11%	21%
Fluid overload	28	46%	14%	32%	7%
Erythrocytosis/thrombocytosis	12	67%	8%	8%	17%
Endocrinopathy	20	15%	40%	5%	40%
Skin changes	19	47%	11%	16%	26%
Lung function	16	38%	6%	13%	44
Organomegaly/lymphadenopathy	15	53%	20%	0%	27%
Papilledema	9	56%	0%	0%	44%
Other	6	67%	0%	17%	17%

Abbreviations: CP, clinical progression; CR, complete response; MR-SD, mixed response or stable disease; NE, not evaluated; NR, no response; PET, positron emission tomography; PR, partial response; R/P, relapse/progression; VEGF, vascular endothelial growth factor; VGPR, very good partial response. [a]Nine patients had refractory disease upon initial diagnosis and two were too sick to receive second-line therapy upon R/P and are not included in this table. [b]A serum/urine immunofixation was not evaluated/available in 21 patients. [c]PET scans upon R/P were not evaluated/available in 21 patients. [d]VEGF levels upon R/P were not evaluated/available in 39 patients.

Eight patients had a documented third R/P at a median of 22 months (range, 1–38 months) after the end of third-line treatment. Three were refractory to fourth-line treatment. One patient was refractory to treatment and died shortly after his third R/P. All the remaining patients responded to treatment: one patient received radiation only and the remaining patients received novel agents.

DISCUSSION

Patients with POEMS have excellent long-term OS, and therefore OS is not an adequate end point to capture the morbidity of this rare disease.[10] In this large study of patients with POEMS syndrome, we have focused on R/P as this end point has not been well studied to date. We demonstrated that ~4% of patients with POEMS had primary refractory disease, 20% had a documented R/P within 5 years of diagnosis and an additional 10% after 5 years. Not surprisingly, patients who had early R/P or refractory disease had inferior OS as compared with those who did not, but even these patients did reasonably well. The majority of patients with R/P could be salvaged with second-line therapy, consistent with prior results.[7] Even the 11% of patients who go on to experience a second R/P can do well, with 92% of them responding to second-line therapy.

We identified low serum albumin level at diagnosis and failure to achieve a hematologic CR after first-line therapy as independent predictors of progression or death. Albumin is a negative acute-phase reactant and has been shown to be prognostic in many diseases including multiple myeloma, lymphoma and Castleman's disease.[13–15] Depth of hematologic response was also important, with patients achieving a CR doing significantly better than those who did not, an observation that is novel and consistent with prior reports.[4,5] When performing a landmark analysis at 12 months, only depth of hematologic response and not albumin was a significant predictor of progression. This suggests that albumin is predictive of early progression and patients with a low albumin at diagnosis should be treated early and aggressively.

Although patients receiving radiotherapy or ASCT appeared to have longer PFS, the type of first-line treatment was not associated with PFS in multivariate analyses. Selection bias needs to be considered when interpreting these results, as patients who are candidates for ASCT might be healthier and being a candidate for radiation might be a surrogate for low disease burden. Nonetheless, this suggests that deep hematologic responses, preferably a CR, are more important than the type of treatment that helps to achieve them.

It is interesting to note that in our study two-thirds of patients with R/P presented with worsening of their clinical symptoms and one-third were identified before symptom development with routine hematologic, VEGF and PET surveillance. This is in contrast to prior results in patients undergoing ASCT[4] and is likely explained by the fact that ASCT patients probably had more standardized follow-up that included 'routine' PET scans and VEGF levels. The proportion of clinical R/Ps was similar for subsequent R/Ps and was not different for patients diagnosed more recently. It is possible that routine and uniform use of VEGF and PET surveillance could have identified more R/Ps in the preclinical/asymptomatic stage.[16–18] Our retrospective data do not support that earlier detection of relapse improves second PFS or OS, and we have no information of its impact on quality of life and patient morbidity.

Although follow-up tends to be focused on the features/organ systems that were affected at baseline, new organ involvement was frequently identified in patients upon R/P. It is unclear whether these symptoms were present but not identified upon initial diagnosis or whether they truly represent new manifestations of the syndrome over time. Irrespective of the reason, patients should be comprehensively reevaluated for new organ involvement upon R/P, and especially lung function abnormalities and endocrinopathies, which were commonly identified in this series, can be challenging to diagnose but can potentially affect patient outcomes significantly if missed.

Treating physicians made the decision to observe approximately one-third of patients who had an asymptomatic R/P for a median of 9 months before initiating treatment, although eventually all but one patient required treatment. Parsing out which asymptomatic patients are candidates for close observation rather than immediate therapy can be challenging and should be considered on a case-by-case basis. At the current time, we do not recommend initiating treatment in asymptomatic patients based only on VEGF elevation alone as a number of conditions can cause transient VEGF elevations.[11,19] Observation of patients who have achieved a hematologic CR and present with an isolated hematologic relapse is also reasonable as demonstrated by the single patient relapsing in that manner in this study. However, most asymptomatic PET R/Ps should be treated early, especially if there is bony destruction, as more often than not further radiographic or clinical progression is noted. We found that in these cases patients can be considered for radiation if they tend to have 1–2 dominant lesions on PET imaging that are amenable to radiation therapy. If more extensive disease is present, then systemic therapy should be considered.

CONCLUSIONS

This study has a number of limitations inherent to a retrospective series from a referral institution, spanning more than 40 years of data. Clinical follow-up was not complete for up to 15% of patients. Furthermore, there was a lack of standardized follow-up and as a result data on radiographic, hematologic and VEGF progression were not available for many patients. Finally, validated response criteria are not available in this disease.

Despite these limitations, this study reaches important conclusions about the natural history of the disease. It is the largest study to date to systematically report on the outcomes of patients with POEMS who experience R/P. Our results suggest that a third of patients with POEMS can have R/P, some of them late after first-line treatment. Although a late R/P is less common and does not seem to affect long-term survival, it can still remain a challenge to diagnose and treat. Therefore, patients with POEMS should undergo life-long follow-up as R/P appears to be salvageable with second-line treatment. The results of this study suggest that closer follow-up is indicated during the first 5 years from diagnosis, that is, every 3–6 months, followed by every 6–12 months thereafter. Closer follow-up is also indicated in patients who have not achieved a hematologic CR to first-line treatment. Routine PET and VEGF surveillance identifies subclinical disease activity and should be strongly considered in the long-term follow-up of these patients. Treatment should be initiated in all patients with a clinical R/P and most patients with radiographic R/P, but observation is reasonable in patients with an isolated hematologic R/P. These results can help set expectations between physicians and patients, as OS underestimates the morbidity related to R/P in these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design and data analysis and interpretation: Taxiarchis V Kourelis and Angela Dispenzieri; provision of study materials of patients, collection and assembly of data, writing of manuscript and final approval of manuscript: all authors.

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