Patient-reported outcomes in systemic AL amyloidosis with Functional Assessment of Cancer Therapy-General (FACT-G) and Patient-Reported Outcomes Measurement Information System-Global Health (PROMIS-GH) in a real-world population

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Abstract

We performed an observational study on health-related quality of life (HRQoL) in patients with AL amyloidosis diagnosed between 2012 and 2017 at our institution. A total of 81 patients were included, with a median age of 64 years. The mean FACT-G (Functional assessment of Cancer Therapy-General) total score at baseline (2 months from diagnosis) was 74 (±15), compared to a normative score of 80 (±18) in the general U.S. population. Significant HRQoL deficit was noted only in the functional well-being (FWB) domain of FACT-G. Using PROMIS-GH (Patient-Reported Outcomes Measurement Information System-Global Health) at baseline (n=18), a greater deficit was noted in the global physical health (GPH) compared to global mental health (GMH) domain. FACT-FWB and PROMIS-GPH domain scores were able to significantly discriminate between revised Mayo stages. Development and validation of an amyloid-specific PRO instrument incorporating specific domains of interest is urgently needed to pursue patient-centered drug development.

Introduction

Management of patients with systemic light-chain (AL) amyloidosis remains a challenge for clinicians despite the availability of novel plasma cell directed therapies. Patients often present with amyloid-driven organ dysfunction, which leads to a high symptom burden and poor health-related quality of life (HRQoL)[1-3]. With early diagnosis and incorporation of proteasome inhibitors (PIs) along with autologous stem cell transplantation (ASCT), survival in AL amyloidosis has improved in recent years and early mortality has declined[4,5]. However, there is a paucity of literature on the impact of early recognition and modern

therapy on HRQoL in this patient population. An online cross-sectional survey of AL amyloidosis patients has revealed significant deficits in HRQoL compared to general US population[2]. Patients within a year of diagnosis and with cardiac involvement tend to have a worse HRQoL. Furthermore, higher patient-reported fatigue at diagnosis is an independent prognostic factor for early mortality[1].

Patient reported outcomes (PRO) is defined as patients' self-report of health status without interpretation by a clinician and is increasingly becoming an integral part of clinical care. There is high-level evidence suggesting that integration of PROs with routine clinical care leads to an improvement in QoL and survival in patients with cancer[6,7]. A large systematic review has shown that physician-reported information under-estimates the symptom burden and distress compared to patients' report[8]. In a disease entity like AL amyloidosis, which is characterized by a high symptom burden, monitoring PROs may be important to identify the trajectory of HRQoL and intervene appropriately for the specific needs of a given patient.

The primary aims of our study were to assess baseline HRQoL in patients with AL amyloidosis using FACT-G (Functional Assessment of Cancer Therapy-General) and PROMIS-GH (Patient Reported Outcomes Measurement Information System-Global Health), evaluate the degree of correlation between FACT-G and PROMIS-GH, and compare HRQoL at best hematologic response to front-line therapy.

Methods

Patients and HRQoL assessment

The study was approved by the Cleveland Clinic Institutional Review Board and was conducted in accordance with federal regulations and the principles of the Declaration of Helsinki. Cleveland Clinic, along with some other large health care organizations across the nation, have initiated systematic collection of PROs for improving patient satisfaction and quality of care[9]. The instruments used for measurement of patient-reported HRQoL at the Taussig Cancer Institute in Cleveland Clinic are FACT-G (version4.0) and PROMIS-GH. PRO data was obtained from the Knowledge Program (KP) database and clinical variables were abstracted by review of medical records. KP is an institutional initiative at Cleveland Clinic to capture PRO data on patients at various time-points of cancer therapy. It is incorporated in routine patient care. Clinicians can view patient score through electronic medical record and can counsel and intervene as needed. Completion of PRO instrument is voluntary. Measurement of HRQoL using FACT-G Version 4.0 was systematically implemented at the Taussig Cancer Institute at Cleveland Clinic on September 2012. The questionnaire is administered every 90 days. FACT-G is a 27-item compilation of general questions divided into four primary HRQoL domains: Physical Well-Being (PWB; 7 questions, scores 0-28), Social/Family Well-Being (SWB; 7 questions, scores 0-28), Emotional Well-Being (EWB; 6 questions, scores 0-24), and Functional Well-Being (FWB; 7 questions, scores 0-28)[9]. Each question is answered using a 5-point Likert scale ranging from 0 (Not at all) to 4 (Very much). The total FACT-G score is obtained by summing individual sub-scale scores (PWB + EWB + SWB + FWB). Higher scores indicate better health status. The FACT-G version 4.0 questionnaire is shown in Supplementary Appendix A. Measurement of HRQoL using PROMIS-GH was implemented on October 2015. The

initial frequency of administration was every 30 days; however, it was changed to every 90 days in June 2017. PROMIS-GH is a questionnaire containing 10 global health items[10]. It generates raw scores for Global Physical Health (GPH) and Global Mental Health (GMH), which can be converted into T-scores ranging from 0 to 100. Higher T-scores indicate better GPH or GMH. The mean T-score for general US population is 50 with a standard deviation (S.D.) of 10. As per the instructions for scoring and interpretation of PROMIS-GH, a decrement of 0.5-1.0 standard deviation (S.D.) below the mean for reference population is consistent with a mild impairment, 1.0-2.0 S.D. below reference with moderate impairment and >2.0 S.D. below reference with severe impairment in the measured domain. The PROMIS-GH questionnaire is shown in Supplementary Appendix B. We have included all patients with systemic AL amyloidosis, diagnosed between September 2012 and December 2017, who had at least 1 PRO assessment in the KP database.

The time points of interest were baseline and time of best hematologic response (follow-up). Baseline PRO was obtained from an outpatient visit within 2 months of initiation of first-line therapy. If multiple visits fell within this range, baseline was selected as the closest visit before the start of treatment if available or the closest visit after the start of treatment otherwise. For hematologic responders, visit of best hematologic response was defined as the closest visit within 6 months after best hematologic response was achieved. Because there was no date for non-responders, the last PRO assessment provided by KP was used for the follow-up visit.

Statistical Analysis

Categorical variables are summarized as frequency counts and percentage; continuous variables are summarized as mean, S.D., median, and range. Pearson correlation was used to assess the association between FACT-G and PROMIS-GH among all visits where both instruments were captured. Results are summarized as the correlation coefficient (r) and P-value from the test that determines if the correlation differs significantly from 0 (0=no correlation). The correlations were interpreted with Cohen's criterion, so absolute value of correlation 0 to <0.3 is small, 0.3 to <0.5 is moderate, and 0.5-1 is large. PROs were compared between hematologic responders and non-responders with Wilcoxon rank sum test. This was done at baseline and at follow-up. PROs were compared by ordered levels of response with Jonckheere-Terpstra test to determine if PRO improves with better response. Association of baseline FACT-G scores with survival was assessed with Cox proportional hazards analysis; results are summarized as hazard ratio (HR) and 95% confidence interval (CI). Baseline FACT-G and PROMIS-GH scores were compared between patients with stages I-II and III-IV disease with Wilcoxon rank sum test. Baseline demographic and clinical characteristics were compared between patients who had PRO data at baseline and those who did not using Wilcoxon rank sum test or Chi-square test. Data were analyzed using SAS® software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Baseline Characteristics

A total of 96 patients with newly diagnosed AL amyloidosis were identified in the designated time-period who had at least 1 PRO assessment. Among these 96 patients, 14 had localized amyloidosis and 1 was treated outside of the Cleveland Clinic system. Hence 81 patients were included in our analysis. The baseline characteristics are depicted in Table I. The median age at diagnosis was 64 years (range, 38-91 years). Majority were Caucasians (89%) and males constituted 62% of the patient population. The median household income was $51,136, similar to that of general US population. The proportion of patients with revised Mayo stage I, II, III and IV disease were 41%, 19%, 19% and 21% respectively. Cardiac involvement at diagnosis was present in 49%, renal involvement in 63%, and ≥2 organ systems were involved in around 60% of patients. The most common front-line induction therapy was cyclophosphamide-bortezomib-dexamethasone (CyBorD; n=70; 86%) followed by bortezomib-dexamethasone (VD; n=5; 6%). High-dose melphalan conditioning followed by ASCT was performed in 31 (38%) patients as part of frontline therapy. However, none of our patients underwent ASCT alone without induction therapy with proteasome inhibitors (PIs) or immunomodulatory drugs (IMiDs)[11]. Response was evaluable in 73 of 81 patients. Among evaluable patients, the rate of overall hematologic response (partial response [PR] or better) was 81%, with a complete response (CR) rate of 42%. At a median follow-up of 35 months, 3-year survival of the entire cohort was 69%.

HRQoL at baseline

Data on HRQoL at baseline was available for 45 out of 81 patients. Patients with baseline PRO data had a significantly higher median income compared to those without baseline PRO data (median, $54,272 vs. 46,321, P=0.032; Supplementary Appendix C). There was no significant difference in Mayo 2012 stage, age at diagnosis, race, and number of organs involved between patients with or without baseline PRO data. The mean FACT-G total score at baseline was 74 (S.D. 15). In comparison, the mean FACT-G total score for general US population is 80 (S.D. 18) and that of US cancer patients is 79 (S.D. 17)[12]. Maximal HRQoL deficit in AL amyloidosis patients was seen in the FWB domain of FACT-G, with the mean score being >0.5 S.D. below that of U.S. general and cancer populations. Baseline FACT-G scores at each domain are summarized in Table II along with reference values for US general and cancer population.

Subsequently, we compared the baseline HRQoL score in patients with Mayo 2012 stage I/II to those with stage III/IV disease. There was no statistically significant difference in the FACT-G total score among patients with stage I/II and stage III/IV disease. However, patients with stage III/IV disease had a significantly lower FWB score compared to stage I/II (mean score, 11 vs 16; P=0.02). The baseline HRQoL scores stratified by stage at diagnosis is summarized in Table III.

Data on HRQoL using PROMIS-GH was available in 18 patients at baseline (Table II). There was a greater deficit in GPH compared to GMH score, with the GPH mean T-score being 37.7 (S.D. 7.8) and GMH mean T-score of 44.4 (S.D. 6.7). We also compared baseline

PROMIS-GH scores in patients with Mayo 2012 stage I/II and III/IV disease (Table III). Patients with stage I/II disease had a PROMIS-GPH score of 42.0 (S.D. 8.1), compared with that of 33.3 (S.D. 4.7) in those with stage III/IV disease (P=0.016). This indicates mild impairment in physical health (0.5-1.0 S.D. below general U.S. population) in patients with stage I/II and moderate impairment (1.0-2.0 S.D. below general U.S. population) in those with stage III/IV disease. No statistically significant difference in mental health was observed in patients with stage I/II (47.1±7.3) versus III/IV disease (41.6±5.1) (P=0.10).

Correlation between FACT-G and PROMIS-GH

A total of 72 patients in our database had 128 outpatient visits where FACT-G and PROMIS-GH were captured concurrently (range, 1-4 visits per patient). Using Cohen's criterion, GPH domain of PROMIS-GH had a large and statistically significant correlation with FACT-G total score (r=0.66), PWB score (r=0.77) and FWB score (r=0.66). PROMIS GMH domain also had a strong and statistically significant correlation with FACT-G total (r=0.73), PWB (r=0.60), EWB (r=0.64) and FWB (r=0.73) scores. There was no significant correlation seen between any of the PROMIS-GH domains and FACT-G SWB scores. The correlation coefficients between FACT-G and PROMIS-GH domains are shown in Supplementary Appendix D and the scatter-plots are shown in Supplementary Appendix E.

Hematologic Response and HRQoL

A total of 50 out of 81 patients had data on HRQoL assessment at best hematologic response using FACT-G. Patients achieving hematologic complete response (CR) had a significantly superior HRQoL at all FACT-G domains compared to other response categories (Table IV). Notably, patients achieving a CR had FACT-G scores (total and domain scores) comparable to that of general U.S. population.

Discussion

In summary, patients with systemic AL amyloidosis have an inferior HRQoL at diagnosis compared to general and cancer patient population in the US. The HRQoL deficit in these patients is greatest in the FWB domain of FACT-G and GPH domain of PROMIS-GH. Both domains (FWB: FACT-G and GPH: PROMIS-GH) were able to significantly discriminate between revised Mayo stage I/II and III/IV patients, which is widely used for quantifying the burden of disease and risk of mortality in AL amyloidosis. We found a strong and significant correlation between most FACT-G and PROMIS-GH domains except for SWB and EWB domains of FACT-G. Patients achieving a hematologic CR to first-line therapy had superior HRQoL compared to other response categories consistent across all FACT-G domains, with HRQoL scores of CR patients being comparable to that of general U.S. population.

Measuring PROs ensures incorporation of patients' voice at the heart of health-care delivery and also improves patient and physician satisfaction[13]. However, measuring what matters for a specific disease entity is critical to ensure that we are capturing reliable and actionable information. To standardize the reporting of PROs in randomized clinical trials (RCTs), the CONSORT (Consolidated Standards of Reporting Trials) statement had published a PRO extension in 2013[14]. One of the components of CONSORT PRO extension is to

categorically mention a PRO hypothesis in the protocol and identify relevant domains to be measured. It is important for investigators to be aware of the HRQoL trajectory and PRO domains which are most sensitive to change in a specific disease to be able to rationally design a comparative effectiveness trial with a PRO endpoint. A large study from the Boston University group using SF-36 showed that patients with AL amyloidosis have the largest pre-treatment deficit in physical health status, as measured by the Physical Component Summary (PCS) score. The poor physical health status was more pronounced in transplant-ineligible patients and was prognostic for early mortality[15]. Another study from the Mayo Clinic used Hematology Patient-Reported Symptom Screen (HPRSS) which asks 3 questions on fatigue, pain and QoL[1]. Patients with a higher baseline fatigue had a higher likelihood of dying within a year of diagnosis on multivariable analysis. Furthermore, baseline fatigue and HRQoL of amyloid patients was worse than those with advanced cancers. The association between hematologic response and HRQoL in AL amyloidosis has also been shown in prior studies. A study from the UK National Amyloidosis Center demonstrated that patients who achieve a deeper response to therapy (CR or VGPR [very good partial response]) had a superior global health status and QoL at 12 months, compared to those achieving PR or less[16]. Similarly, in the context of high-dose melphalan and ASCT, achievement of CR leads to a superior physical functioning with normalization (compared to demographically-matched population norms) at 2 years after ASCT[17]. Apart from prompt administration of plasma-cell directed therapies and best supportive care, additional interventions which have been shown to improve HRQoL in these patients is nutritional counselling. In an Italian randomized trial, patients who were assigned to rigorous nutritional counselling, including personalized dietary prescription along with regular dietary advice by a registered dietician, had a superior mental QoL at 12 months, compared to those assigned to usual care[18].

Across several HRQoL domains measured by FACT-G, the largest deficit in our study relative to both US general and cancer populations was seen in the FWB domain. The FWB domain contains questions on ability to work, enjoy life, sleep, acceptance of illness and overall QoL. In a study establishing the normative scores for FACT-G in US cancer population, a cut-off score of 0.5 S.D. below the mean was established to be significant at a group level for identifying patients with low HRQoL[12]. The mean FWB score for amyloid patients at diagnosis was below 0.5 S.D. of the mean of US cancer patient population. In patients with Mayo stage III/IV disease, the mean baseline FACT-G FWB score was 11, which is 1 S.D. below the mean score of U.S. cancer patients. Although we did not have enough patients with paired assessment at baseline and follow-up, the mean follow-up FWB score of patients achieving a CR was 18 ($\pm$7), which is comparable to that of general and cancer patient population in the U.S. However, with the exception of the FACT-G FWB scale, there were no significant associations between the other FACT-G scores and the revised Mayo stages. These results do not support good discriminant validity of FACT-G in terms of disease severity, however, formal psychometric validation was not done in our analysis. The FWB scale of FACT-G does not include items specific to the impact of therapy, which potentially makes it a better measure to assess pre-treatment HRQoL in this population.

Although the number of patients with baseline PROMIS-GH assessment was low, the maximal deficit was noted in physical health. The GPH domain of PROMIS-GH contains questions on physical health, physical activities of daily living, fatigue and pain. Fatigue is an important symptom in AL amyloidosis[3]. The PROMIS-GMH score at baseline was higher compared to GPH score in our cohort, which is similar to a prior study reporting PROs with PROMIS-GH in a phase 2 interventional trial in AL amyloidosis[19]. Since patients with AL amyloidosis often have a significant delay between onset of symptoms and diagnosis/referral to a tertiary care center, there might be a sense of relief and hope after receiving a definitive diagnosis and treatment plan, which can potentially account for better mental health compared to physical health in these patients. Although our numbers were low, PROMIS-GMH score was not able to significantly discriminate between Mayo stages I/II and III/IV patients. A study on patient-reported distress in AL amyloidosis has shown that amyloid stage and type of organ involvement is not predictive of distress[20]. Furthermore, a large study from the Boston University has shown that poor physical health but _not_ mental health at baseline was associated with higher mortality[15]. The advantage of using PROMIS-GH is that it is freely accessible, easily interpretable and incorporates the option of computerized adaptive testing, which can generate dynamic questionnaires accommodating a broad range of patient functioning. In hematopoietic stem cell transplant patient population, PROMIS-GH had a strong correlation with SF-36 in both physical and mental health domains[21] and CIBMTR recommends PROMIS as a core questionnaire in future studies to allow for easy comparison across trials. Since SF-36 is the only validated PRO instrument in AL amyloidosis population to the best of our knowledge[22,23], development of validated PROMIS questionnaires incorporating different item banks would be valuable for patient-centered drug development and supportive care in this population.

Our study has limitations. Firstly, being a retrospective study, there can be a potential bias due to missing data. Ideally, for longitudinal analysis, we would have used repeated measures analysis of variance (RMANOVA) to analyze PRO data, considering the follow-up value as a function of the baseline value and the response group. However, RMANOVA only uses records with complete data at all time-points of interest, and hence this was not possible due to missing follow-up or baseline data in many patients. We could not use multiple imputation to fill in missing data since it was not clear that assumptions needed to do imputation were valid. Moving forward, we are enforcing real-time monitoring for data compliance and taking steps for caregiver and patient engagement since systematic PRO assessments have been shown to improve quality of life and survival[6,24]. Since PROMIS-GH was introduced at our institution relatively recently, the number of patients who used this instrument was low, however, results were similar to a prior prospective study. In conclusion, our study adds to the literature on HRQoL in this patient population using FACT-G and PROMIS-GH instruments. Future studies should focus on development of an amyloid specific PRO instrument based on existing literature and qualitative studies.

Supplementary Material

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Table I:

Baseline clinical and demographic characteristics

Variable	
Median age at diagnosis, years (range)	64 (38-91)
Males (%)	61.7
Caucasian race (%) [n=80]	88.8
Marital status (%) [n=80]	
Married	78.8
Divorced	12.5
Single	8.8
Median income, range ($/year)	51,136 (27,646-113,122)
Number of organs involved (%)	
1	39.5
2	38.3
>2	22.2
Cardiac Involvement (%)	49.4
Kidney Involvement (%)	63.0
Mayo 2012 Stage [n=80]	
I	41.2
II	18.8
III	18.8
IV	21.2
Median NT-pro-BNP, pg/mL (range) [n=80]	1,369 (24-70,000)
Median serum albumin, g/dL (range) [n=80]	3.2 (1.6-4.7)
First-line regimen (%)	
CyBorD	48.1
Vd	2.5
CyBorD followed by ASCT	35.8
Vd followed by ASCT	2.5
Other	11.1
Best hematologic response to first-line therapy (%)	
CR	42.0
VGPR	25.9
PR	9.9
NR	12.3
Unknown/Not evaluable	9.9
Cardiac response (%)	
Yes	24.7
No	19.8
Not applicable (heart not involved)	50.6
Unknown	4.9
Renal response (%)	

Variable	
Yes	37.0
No	18.5
Not applicable (kidney not involved)	37.0
Unknown	7.4

Abbreviations: NT-pro-BNP: N-terminal pro-brain natriuretic peptide; CyBorD: Cyclophosphamide-Bortezomib-Dexamethasone; Vd: Bortezomib-Dexamethasone; ASCT: Autologous Stem Cell Transplantation; CR: Complete response; VGPR: Very Good Partial Response; PR: Partial Response; NR: No response.

Table II.

Baseline Health-Related Quality of Life in patients with systemic AL amyloidosis compared to US general and cancer patient populations

HRQoL Domains	AL Amyloidosis, mean (S.D.)	AL Amyloidosis, median (range)	US Cancer Population, mean (S.D.) [Ref-12]	US General Population, mean (S.D.) [Ref-12]
FACT-G Total (n=43)	74 (15)	76 (38-101)	79 (17)	80 (18)
PWB (n=44)	19 (6)	21 (3-28)	21 (6)	23 (5)
SWB (n=44)	23 (4)	24 (9-28)	22 (5)	19 (7)
EWB (n=43)	17 (5)	19 (5-24)	18 (5)	20 (5)
FWB (n=43)	14 (6)	14 (3-28)	18 (7)	19 (7)
PROMIS-GPH (n=18)	37.7 (7.8)	37.4 (32.4-42.3)	--	50 (10)
PROMIS-GMH (n=18)	44.4 (6.7)	43.5 (38.8-50.8)	--	50 (10)

Abbreviations: HRQoL: Health-Related Quality of life; AL: AL: Light chain; FACT-G: Functional Assessment of Cancer Therapy-General; PWB: Physical Well Being; EWB: Emotional Well Being; SWB: Social Well Being; FWB: Functional Well Being. PROMIS-GPH: Patient Reported Outcomes Measurement Information System-Global Physical Health. PROMIS-GMH: Patient Reported Outcomes Measurement Information System-Global Mental Health. S.D.: Standard Deviation

Table III:

Baseline patient-reported outcome stratified by clinical stage (Mayo 2012 stage) at diagnosis.

Baseline PRO Mayo 2012 Stage	Number of patients (n)	Mean score (S.D.)	*P*-value
FACT-G Total Score			
I-II	25	76 (17)	0.36
III-IV	18	71 (13)	
FACT-G PWB score			
I-II	26	19 (7)	0.66
III-IV	18	20 (5)	
FACT-G SWB score			
I-II	26	23 (4)	0.43
III-IV	18	22 (4)	
FACT-G EWB score			
I-II	25	17 (4)	0.68
III-IV	18	17 (5)	
FACT-G FWB score			
I-II	25	16 (6)	0.020
III-IV	18	11 (6)	
PROMIS GPH T-score			
I-II	9	42.0 (8.1)	0.016
III-IV	9	33.3 (4.7)	
PROMIS GMH T-score			
I-II	9	47.1 (7.3)	0.10
III-IV	9	41.6 (5.1)	

Abbreviations: PRO: Patient-reported outcome; SD: Standard deviation; FACT-G: Functional Assessment of Cancer Therapy-General; PWB: Physical Well Being; SWB: Social Well Being; EWB: Emotional Well Being; FWB: Functional Well Being; GPH: Global Physical Health; GMH: Global Mental Health; PROMIS: Patient-Reported Outcome Measurement Information System

Table IV:

Health related quality of life stratified by best hematologic response to first-line therapy

PROs at best hematologic response	Response category	Number of patients (n)	Mean score (S.D.)	Median score (range)	*P*-value
FACT-G Total score	NR	4	62 (26)	65 (30-89)	
	PR+VGPR	16	65 (13)	68 (40-83)	<0.001
	CR	22	83 (20)	89 (18-108)	
FACT-G PWB score	NR	5	18 (8)	23 (8-25)	
	PR+VGPR	19	19 (6)	17 (6-28)	0.031
	CR	26	22 (6)	24 (2-28)	
FACT-G SWB score	NR	5	22 (6)	23 (13-28)	
	PR+VGPR	18	20 (6)	22 (0-27)	0.029
	CR	25	24 (5)	26 (7-28)	
FACT-G EWB score	NR	4	16 (4)	17 (9-19)	
	PR+VGPR	17	15 (5)	17 (5-20)	0.005
	CR	22	19 (5)	21 (3-24)	
FACT-G FWB score	NR	4	9 (8)	10 (0-18)	
	PR+VGPR	16	12 (6)	12 (3-26)	0.002
	CR	22	18 (7)	21 (2-28)	

Abbreviations: PRO: Patient-reported outcome; SD: Standard deviation; FACT-G: Functional Assessment of Cancer Therapy-General; PWB: Physical Well Being; SWB: Social Well Being; EWB: Emotional Well Being; FWB: Functional Well Being; GPH: Global Physical Health; GMH: Global Mental Health; PROMIS: Patient-Reported Outcome Measurement Information System. NR: No Response; PR: Partial Response; VGPR: Very Good Partial Response; CR: Complete Response.