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Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged ≥65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial

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Abstract

In the MM-015 trial, melphalan–prednisone–lenalidomide followed by lenalidomide maintenance (MPR-R) significantly prolonged progression-free survival versus melphalan–prednisone (MP) in newly diagnosed patients with multiple myeloma aged ≥65 years. Health-related quality of life (HRQoL), a secondary endpoint of MM-015, was also improved with MPR-R. This sub-analysis evaluated the impact of individual predictive factors on HRQoL. Patients completed HRQoL questionnaires at baseline, every third cycle and at progressive disease (PD)/treatment discontinuation. In a mixed-effects model female gender, advanced age and PD negatively affected HRQoL while better treatment responses showed positive effects. Compared to PD, HRQoL during MPR-R treatment was statistically significantly better in two of six preselected domains both of which were also clinically meaningful. HRQoL scores at end of treatment were all either improved or not statistically significantly different versus baseline. In conclusion, continuous treatment with MPR-R, which delays PD, appears to be associated with clinically meaningful improvements in HRQoL.

Keywords: Health-related quality of life (HRQoL), lenalidomide, multiple myeloma, minimal important difference (MID), QLQ-C30, QLQ-MY20

Introduction

In the pivotal phase III MM-015 trial, the melphalan, prednisone and lenalidomide regimen, followed by lenalidomide maintenance therapy (MPR-R) significantly increased median progression-free survival (PFS; 31 months) compared with MPR followed by placebo maintenance (14 months; hazard ratio, 0.49; $p < 0.001$) or melphalan and prednisone (MP) followed by placebo maintenance (13 months; hazard ratio, 0.40; $p < 0.001$) in patients with newly diagnosed multiple myeloma (NDMM) aged ≥65 years [1]. The benefit was observed primarily in patients aged 65–75 years [1,2]. Health-related quality of life (HRQoL) was a predefined secondary endpoint of the MM-015 trial, and the analysis included determination of the minimal important difference (MID), which can identify clinically meaningful changes in HRQoL scores [3]. The results indicated that clinically meaningful improvements in HRQoL scores were more common in the MPR-R group than in the MPR and MP groups [4]. The present analysis expands on these findings. The objectives were to identify factors that predict differences in HRQoL score levels, and compare HRQoL status at baseline and during treatment with HRQoL status at time of treatment discontinuation due to progressive disease (PD) or discontinuation (DC) for other reasons. HRQoL determinants were derived for the overall patient group (aged ≥65 years) and the subset of patients aged 65–75 years.

Materials and methods

Study design

This multicenter phase III randomized study was designed to evaluate the efficacy and safety of MPR-R in transplant-ineligible patients with NDMM aged ≥65 years. Study details have been previously published [1]. Briefly, patients were randomized (1:1:1) to MPR-R (nine 4-week cycles

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of melphalan, prednisone and lenalidomide, followed by lenalidomide maintenance therapy); MPR (nine 4-week cycles of melphalan, prednisone and lenalidomide, followed by placebo maintenance therapy); or MP (nine 4-week cycles of melphalan, prednisone and placebo, followed by placebo maintenance therapy) [Figure 1(A)]. The primary objective was to compare PFS in the MPR-R and MP groups. Patients were stratified according to age (65–75 vs. >75 years) and International Staging System (ISS) stage (I/II vs. III). Treating physicians and patients were unaware of the treatment assignment. Patients received maintenance therapy until PD or DC. All patients were followed for ≥ 5 years from randomization or until death. The study was conducted in compliance with the Independent Review Board/Independent Ethics Committee procedures, the Declaration of Helsinki, the International Conference on Harmonization, Good Clinical Practices guidelines and local regulations governing the conduct of clinical studies (ClinicalTrials.gov identifier NCT00405756).

HRQoL assessment

For the HRQoL assessments the new consolidated standards of reporting trials (CONSORT) guidelines for patient reported outcomes (PROs) were used [5]. The HRQoL assessments were undertaken using two European Organisation for Research and Treatment of Cancer (EORTC) validated questionnaires: the generic 30-item EORTC QLQ-C30 [6], and the 20-item EORTC QLQ-MY20 [7] specifically designed for patients with multiple myeloma. The EORTC QLQ-C30 and QLQ-MY20 questionnaires were available in paper form

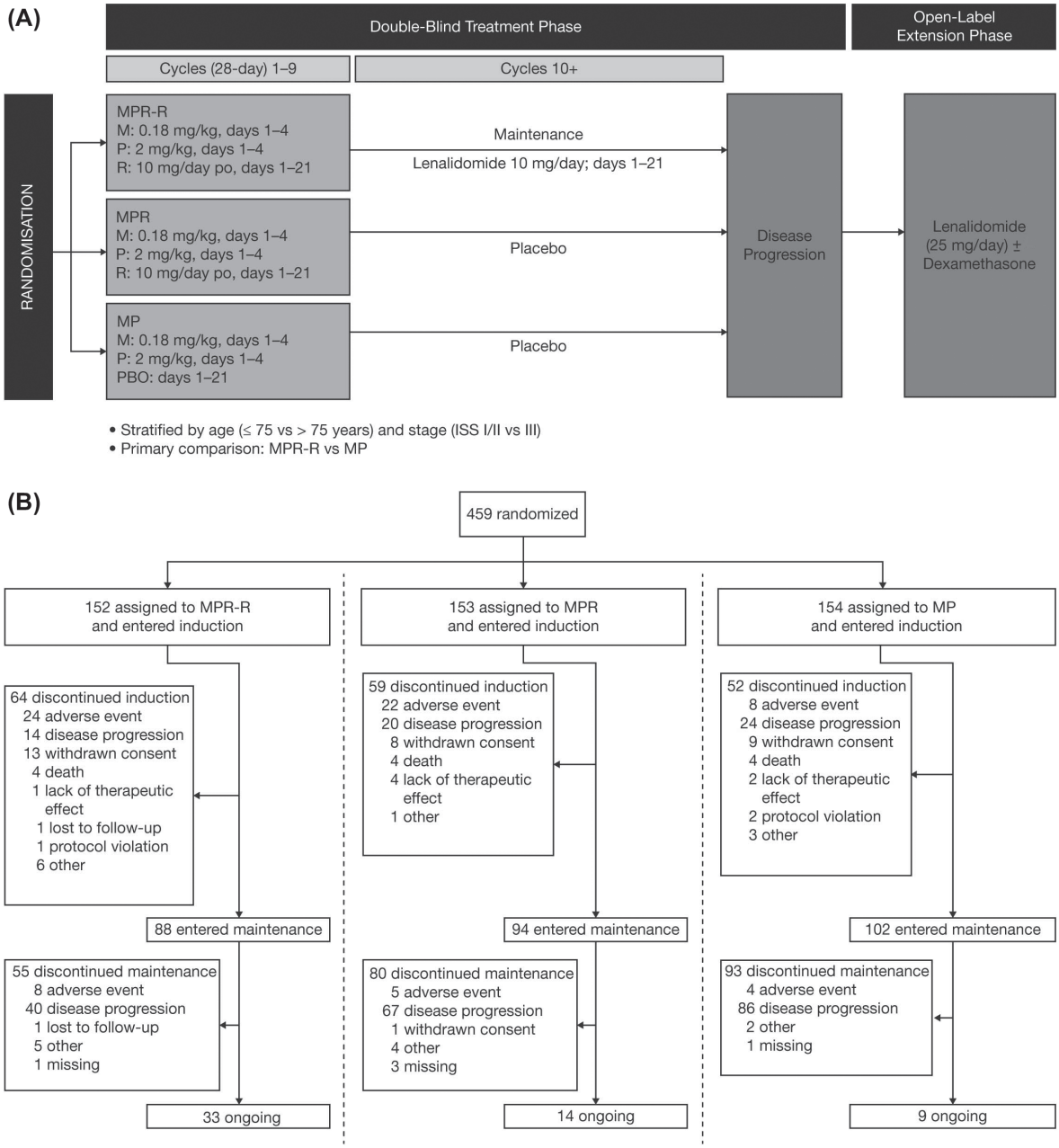


Figure 1. (A) Design overview of trial MM-015. (B) Flow of participants in trial MM-015. ISS, International Staging System; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR, melphalan, prednisone and lenalidomide followed by maintenance therapy with placebo; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; PBO, placebo; po, by mouth.

in the primary languages spoken at MM-015 study sites. The 30 items are scored in five functional domains (Physical Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning and Role Functioning) where a higher score indicates better function. Eight domains assess symptoms (Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation and Diarrhea) and one assesses Financial Difficulties, where a lower score indicates fewer symptoms or financial difficulties. The EORTC QLQ-C30 also contains an item on overall Global Health Status/QoL (subsequently referred to as Global QoL), where a higher score indicates better overall QoL. The QLQ-MY20 is a 20-item questionnaire that includes two functional domains (Future Perspective and Body Image) and two symptom domains (Disease Symptoms and Side Effects of Treatment), each scored similarly to the QLQ-C30. Each instrument takes approximately 10–15 min to complete [6,7].

The HRQoL questionnaires were completed at baseline, after every third treatment cycle (i.e. at the start of cycles 4, 7, 10, 13 and 16, etc.) and at PD or DC. Follow-up included HRQoL assessment every 6 months (168 days) during the open-label extension phase. Results are presented for six prespecified HRQoL domains, selected for up-front analysis based on their perceived clinical relevance: Global QoL, Physical Functioning, Fatigue and Pain from the EORTC QLQ-C30; and Disease Symptoms and Side Effects of Treatment from the EORTC QLQ-MY20 [4]. Scores were calculated if $\geq 50\%$ of boxes for the items in that particular domain were filled according to standard handling of missing or incomplete data [8].

Compliance of the HRQoL was assessed and previously described for patients enrolled in this study [4]. A patient was considered compliant when at least 50% of the questionnaire items were completed. The overall compliance during treatment until cycle 16 was high: $> 76\%$ for each instrument and at least 65% at PD or DC, and were consistent across treatment arms. The patient and disease characteristics of patients who dropped out or were not compliant were similar between treatment arms [4].

Identification of MID

Clinically meaningful changes in HRQoL were defined as MIDs and were assessed by calculating the standard error of measurement (SEM), an error estimate for a single use of the questionnaire at baseline [9,10]. The SEM is directly related to the variability of the data through its standard deviation, and the reliability of the scale, as indicated by Cronbach's alpha (i.e. SEM = standard deviation $\times$ $\sqrt{1 - \text{Cronbach's alpha}}$). The SEM is considered a good estimate of the MID, being the smallest amount of change from baseline that indicates a clinically meaningful change in HRQoL [11]. MIDs for the six prespecified HRQoL domains have been identified [4]. Positive values indicate improvements for Global QoL and Physical Functioning. Negative values indicate improvements for Pain, Fatigue, Disease Symptoms and Side Effects of Treatment. MIDs were identified as $+7$ points for Global QoL, $+9$ for Physical Functioning, -10 for Fatigue, -12 for Pain, -10 for Disease Symptoms and -6 for Side Effects of Treatment [4].

Statistical methods

Analyses were conducted on the intent-to-treat (ITT) population using data collected until the time of un-blinding of the first study site (May 2010), which occurred after the first planned interim analysis [1]. Measurements included baseline and five subsequent time points (cycles 4, 7, 10, 13 and 16). Patients with valid data at each assessment were included in the analysis. Analyses were conducted on data up to the cycle at which each study arm had ≥ 30 participants (cycle 16). All analyses were performed using SAS® version 9.22 (SAS Institute Inc., Cary, NC).

A mixed-effects model was developed for predicting HRQoL scores (EORTC QLQ-C30: Global QoL, Physical Functioning, Fatigue and Pain; and EORTC QLQ-MY20: Disease Symptoms and Side Effects of Treatment) at cycles 4, 7, 10, 13 and 16, where the patient was the random effect. The following variables were included: cycle number (4, 7, 10, 13,and 16 [reference cell]), treatment arm (MPR-R, MPR and MP [reference cell]), age at baseline (years), gender (female, male [reference cell]), baseline HRQoL score, clinical response (very good partial response or better [$\geq$VGPR], partial response [PR] and stable disease [SD] [reference cell]), PD (1 = yes, 0 = no), DC (1 = yes, 0 = no), neutropenia grade 3–4 (1 = yes, 0 = no) and anemia grade 3–4 (1 = yes, 0 = no). Clinical response, PD, DC, neutropenia grade 3–4 and anemia grade 3–4 variables were defined at each cycle for each patient. The modeling cohort was limited to patients in the ITT population who met the following conditions: randomized to MPR-R, MPR or MP, had HRQoL data available at baseline and had at least one post-baseline cycle.

Regression β-coefficients, *p*-values (based on a *t*-test statistic that examines whether or not the β-coefficient is statistically different from zero) and 95% confidence intervals were calculated from these models. The β-coefficients for continuous variables represented the effect on HRQoL score for each unit change (i.e. each additional year for age, and each additional score point for baseline HRQoL). Based on an alpha level of 0.05, these results determined statistically significant β-coefficients for each of the variables (i.e. determinants of HRQoL). For each of the six preselected HRQoL scores, clinically meaningful effects of each variable were assessed by examining whether the β-coefficient exceeded the MID [4].

A separate analysis was conducted based on the subset of patients who had PD or DC prior to cycle 16, which included the following comparisons: (i) HRQoL at end of treatment versus baseline; and (ii) HRQoL during treatment versus end of treatment. For the end of treatment versus baseline comparison, patients were included if they belonged to the ITT population, were randomized to MPR-R, MPR or MP treatment, had PD or DC prior to cycle 16, and had non-missing scores at baseline and end of treatment. Statistical significance was assessed for the difference between mean baseline score and mean PD/DC score within treatment group from a paired *t*-test statistic.

For the during-treatment versus end of treatment comparison, patients were included if they belonged to the ITT population, were randomized to MPR-R, MPR or

MP treatment, had PD or DC prior to cycle 16, and had non-missing scores for end of treatment and at least one treatment cycle excluding baseline. A mixed model was developed where the patient was specified as the random effect and cycle as a fixed effect. From this model, mean HRQoL was calculated across all during-treatment HRQoL scores and at PD or DC for each treatment group. Statistical significance for the difference between mean HRQoL scores at end of treatment and during treatment within treatment group was assessed with a *t*-test statistic produced from the model.

To minimize the effects of multiple testing associated with baseline, during treatment and end of treatment analyses in patients who had PD or DC, statistical significance was assessed after a Bonferroni adjustment was applied to *p*-values. That is, the statistical significance level was established at 0.017 by dividing 0.05 by the number of treatment groups ($n = 3$). Therefore, p-values ≤ 0.017 were considered statistically significant.

Role of the funding source

The trial was designed by the academic authors in collaboration with Celgene. Employees of the company assisted with the study design, data collection, data analysis and writing of the manuscript in collaboration with the senior academic authors. The first draft of the manuscript was developed by the authors. All authors had full access to all the data on study un-blinding and had final responsibility for the decision to submit the manuscript for publication. Assistance in manuscript preparation was provided by ICON Clinical Research, Oxford Outcomes and Excerpta Medica, which was funded by Celgene. All authors were fully responsible for all content and editorial decisions for this manuscript and vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol.

Results

A total of 459 patients were enrolled at 82 treatment centers in Europe, Australia and Israel between February 2007 and September 2008 [Figure 1(B)] [1]. Among patients assigned to MPR-R ($n = 152$), MPR ($n = 153$) or MP ($n = 154$), similar proportions of patients were female (53%, 48% and 51%, respectively), had ISS stage III disease (48%, 48% and 51%, respectively) and were aged > 75 years (24%, 24% and 25%, respectively).

Determinants of HRQoL: patients aged ≥ 65 years

Predictive factors for HRQoL, based on data from 404 patients in the ITT population treated with MPR-R, MPR or MP, are presented in Table I. Choice of treatment (MPR-R vs. MP and MPR vs. MP) had no statistical or clinical significant effect on the six HRQoL domains, indicating that the addition of lenalidomide to MP with lenalidomide maintenance therapy did not adversely affect HRQoL. Achieving ≥VGPR (vs. SD) was associated with statistically significant improvement for all six domain scores and the MID was exceeded in the Global QoL score. With the exception of a slight improvement in Side Effect of Treatment, achieving PR (vs. SD) had no effect on HRQoL scores. Having PD was associated with a statistically significant and clinically meaningful deterioration in Global QoL and a statistically significant (but not clinically meaningful) worsening of Physical Functioning, Fatigue, Pain and Disease Symptoms. Deterioration in Global QoL and Physical Functioning due to DC was statistically significant but not clinically meaningful. Anemia grade 3–4 had a statistically significant and clinically meaningful negative impact on Global QoL, Physical Functioning, Fatigue and Side Effects of Treatment. Disease Symptoms was also negatively affected, but the MID was not reached. Neutropenia grade 3–4 had no effect on HRQoL scores.

Table I. Overview of determinants of HRQoL following baseline assessment in patients treated with MPR-R, MPR or MP* (statistical significance: $p < 0.05$).

	Global QoL ($n = 394$), MID + 7	Physical Functioning ($n = 404$), MID + 9	Fatigue ($n = 398$), MID − 10	Pain ($n = 399$), MID − 12	Disease Symptoms ($n = 393$), MID − 10	Side Effects of Treatment ($n = 391$), MID − 6
Cycle 4 vs. cycle 16	− 5.24 ($p < 0.001$)	− 3.74 ($p = 0.001$)	+ 4.54 ($p < 0.001$)	NS	NS	+ 2.38 ($p = 0.004$)
Cycle 7 vs. cycle 16	− 3.35 ($p = 0.015$)	NS	NS	NS	NS	+ 2.32 ($p = 0.005$)
Cycle 10 vs. cycle 16	NS	NS	+ 3.19 ($p = 0.018$)	NS	NS	+ 1.70 ($p = 0.038$)
Cycle 13 vs. cycle 16	NS	NS	NS	NS	NS	NS
MPR-R vs. MP	NS	NS	NS	NS	NS	NS
MPR vs. MP	NS	NS	NS	NS	NS	NS
Female vs. male	− 4.03 ($p = 0.006$)	− 3.61 ($p = 0.022$)	NS	+ 4.60 ($p = 0.037$)	+ 3.62 ($p = 0.017$)	+ 3.62 ($p < 0.001$)
Age, years	− 0.42 ($p = 0.006$)	− 0.67 ($p < 0.001$)	+ 0.39 ($p = 0.032$)	NS	NS	+ 0.27 ($p = 0.010$)
Baseline HRQoL score	+ 0.34 ($p < 0.001$)	+ 0.47 ($p < 0.001$)	+ 0.38 ($p < 0.001$)	+ 0.32 ($p < 0.001$)	+ 0.45 ($p < 0.001$)	+ 0.50 ($p < 0.001$)
PR vs. SD	NS	NS	NS	NS	NS	− 1.42 ($p = 0.038$)
VGPR or better vs. SD	***+ 9.80*** ($p = 0.007$)	+ 8.47 ($p = 0.008$)	− 8.58 ($p = 0.021$)	− 11.01 ($p = 0.020$)	− 6.97 ($p = 0.028$)	− 5.28 ($p = 0.018$)
Progressive disease	***− 8.38*** ($p < 0.001$)	− 7.45 ($p < 0.001$)	+ 7.22 ($p < 0.001$)	+ 8.33 ($p < 0.020$)	+ 3.97 ($p = 0.007$)	NS
Discontinued	− 5.41 ($p = 0.015$)	− 3.82 ($p = 0.046$)	NS	NS	NS	NS
Neutropenia grade 3–4	NS	NS	NS	NS	NS	NS
Anemia grade 3–4	***− 11.23*** ($p = 0.004$)	***− 19.02*** ($p < 0.001$)	***+ 20.27*** ($p < 0.001$)	NS	+ 7.72 ($p = 0.020$)	***+ 7.58*** ($p = 0.001$)

HRQoL, health-related quality of life; MID, minimal important difference; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR, melphalan, prednisone and lenalidomide followed by placebo maintenance therapy; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; NS, not significant; PR, partial response; SD, stable disease; VGPR, very good PR.

*Data show HRQoL score point changes (i.e. improvement or deterioration): increases in HRQoL score indicate improvements for Global QoL and Physical Functioning; decreases in HRQoL score indicate improvements for Fatigue, Pain, Disease Symptoms and Side Effects of Treatment. ***Italicized bold text*** means MID has been reached.

Treatment cycle, gender, age and baseline HRQoL scores had the following effects. Cycle 4 was associated with a significant but not clinically meaningful difference in Global QoL, Physical Functioning, Fatigue and Side Effects of Treatment score compared with cycle 16. Similarly, cycle 7 and cycle 10 were associated with a statistically significant but not clinically meaningful difference in Global QoL (cycle 7 only), Fatigue (cycle 10 only) and Side Effects of Treatment compared to cycle 16; none of these differences reached the MID. Cycle 13 did not differ from cycle 16 on any of the six HRQoL domains. Female gender was associated with significantly worsened scores for five out of six HRQoL domains (Global QoL, Physical Functioning, Pain, Disease Symptoms and Side Effects of Treatment) but had no clinically meaningful impact on these HRQoL scores. Increasing age was associated with significant deterioration in four out of six HRQoL domains (Global QoL, Physical Functioning, Fatigue and Side Effects of Treatment) also with no clinically meaningful impact. Better baseline HRQoL scores were associated with better HRQoL in all six domain scores ($p < 0.001$).

Determinants of HRQoL: patients aged 65–75 years

The second set of mixed-effects models for the subset of patients aged 65–75 years ($n = 316$) indicated a similar pattern with regard to factors that influence HRQoL (Table II). Developing PD was associated with a statistically significant worsening in all six HRQoL domain scores; the worsening of Global QoL (by 8.62 points [MID + 7]) was also clinically meaningful (i.e. exceeded the MID). Achieving ≥VGPR (vs. SD) was also associated with a statistically significant improvement in all six HRQoL domain scores. Improvements in three of these HRQoL domain scores were also clinically meaningful: Global QoL (+ 12.19 [MID + 7]), Fatigue (− 11.29 [MID − 10]) and Pain (− 14.23 [MID − 12]). Having DC was associated with a statistically significant worsening in three out of six HRQoL domain scores (Global QoL, Physical Functioning and Fatigue), but the MID was not reached for any of these scores. For this subset of patients, the MPR treatment group improved compared to the MP treatment group in Disease Symptoms (− 4.91; $p = 0.017$). Because this subset of patients was aged 65–75, age was only statistically significant with respect to the Physical Functioning domain score, where deterioration in HRQoL occurred with each increasing year of age.

HRQoL scores at PD or DC versus baseline

No statistically significant differences in mean HRQoL scores between baseline and end of treatment were observed in the PD group, DC group or combined PD/DC group for MPR-R, MPR or MP. However, with respect to patients receiving MPR-R who developed PD, clinically meaningful improvements were observed in two HRQoL domains: Global QoL and Pain (+ 10.7 [MID + 7] and − 15.7 [MID − 12], respectively). Furthermore, for patients receiving MPR-R who had DC, clinically meaningful improvement was seen in Disease Symptoms (− 10.9 [MID − 10]). Finally, in the combined PD/DC group of patients receiving MPR-R, improvements in Global QoL and Pain scores were also clinically meaningful (+ 9.1 [MID + 7] and − 12.2 [MID − 12], respectively) (results not shown).

HRQoL scores at PD or DC versus during treatment

Differences in mean HRQoL scores, between during treatment and end of treatment due to PD or DC, are presented in Figure 2. In patients receiving MP, HRQoL was significantly better during treatment versus the time of PD/DC for Global QoL ($p < 0.001$; $n = 59$) and Physical Functioning ($p = 0.001$; $n = 58$); the difference was also clinically meaningful for

Table II. Overview of determinants of HRQoL following baseline assessment in patients aged 65–75 years treated with MPR-R, MPR or MP* (statistical significance: $p < 0.05$).

	Global QoL ($n = 308$), MID + 7	Physical Functioning ($n = 316$), MID + 9	Fatigue ($n = 311$), MID − 10	Pain ($n = 312$), MID − 12	Disease Symptoms ($n = 307$), MID − 10	Side Effects of Treatment ($n = 306$), MID − 6
Cycle 4 vs. cycle 16	− 5.28 ($p < 0.001$)	− 4.85 ($p < 0.001$)	+ 5.21 ($p < 0.001$)	NS	NS	+ 2.42 ($p = 0.005$)
Cycle 7 vs. cycle 16	− 3.20 ($p = 0.031$)	− 2.38 ($p = 0.047$)	+ 3.52 ($p = 0.013$)	NS	NS	+ 2.38 ($p = 0.005$)
Cycle 10 vs. cycle 16	NS	NS	+ 3.18 ($p = 0.024$)	NS	NS	NS
Cycle 13 vs. cycle 16	NS	NS	NS	NS	NS	NS
MPR-R vs. MP	NS	NS	NS	NS	NS	NS
MPR vs. MP	NS	NS	NS	NS	− 4.91 ($p = 0.017$)	NS
Female vs. male	− 5.46 ($p < 0.001$)	− 4.84 ($p = 0.006$)	+ 5.43 ($p = 0.007$)	+ 5.84 ($p = 0.014$)	+ 5.02 ($p = 0.003$)	+ 4.28 ($p < 0.001$)
Age, years	NS	− 0.80 ($p = 0.004$)	NS	NS	NS	NS
Baseline HRQoL score	+ 0.34 ($p < 0.001$)	+ 0.45 ($p < 0.001$)	+ 0.37 ($p < 0.001$)	+ 0.33 ($p < 0.001$)	+ 0.44 ($p < 0.001$)	+ 0.50 ($p < 0.001$)
PR vs. SD	NS	NS	NS	NS	NS	− 1.50 ($p = 0.040$)
VGPR or better vs. SD	***+ 12.19*** ($p = 0.003$)	+ 7.92 ($p = 0.029$)	***− 11.29*** ($p = 0.008$)	***− 14.23*** ($p = 0.009$)	− 9.63 ($p = 0.008$)	− 6.49 ($p = 0.009$)
Progressive disease	***− 8.62*** ($p < 0.001$)	− 7.91 ($p < 0.001$)	+ 7.63 ($p < 0.001$)	+ 8.45 ($p < 0.001$)	+ 4.46 ($p = 0.004$)	+ 2.41 ($p = 0.025$)
Discontinued	− 6.45 ($p = 0.012$)	− 6.02 ($p = 0.007$)	+ 5.34 ($p = 0.038$)	NS	NS	NS
Neutropenia grade 3–4	NS	NS	NS	NS	NS	NS
Anemia grade 3–4	NS	***− 14.79*** ($p < 0.001$)	***+ 19.21*** ($p < 0.001$)	NS	NS	NS

HRQoL, health-related quality of life; MID, minimal important difference; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR, melphalan, prednisone and lenalidomide followed by placebo maintenance therapy; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; NS, not significant; PR, partial response; SD, stable disease; VGPR, very good PR.

*Data show HRQoL score point changes (i.e. improvement or deterioration): increases in HRQoL score indicate improvements for Global QoL and Physical Functioning; decreases in HRQoL score indicate improvements for Fatigue, Pain, Disease Symptoms and Side Effects of Treatment. ***Italicized bold text*** means that MID has been reached.

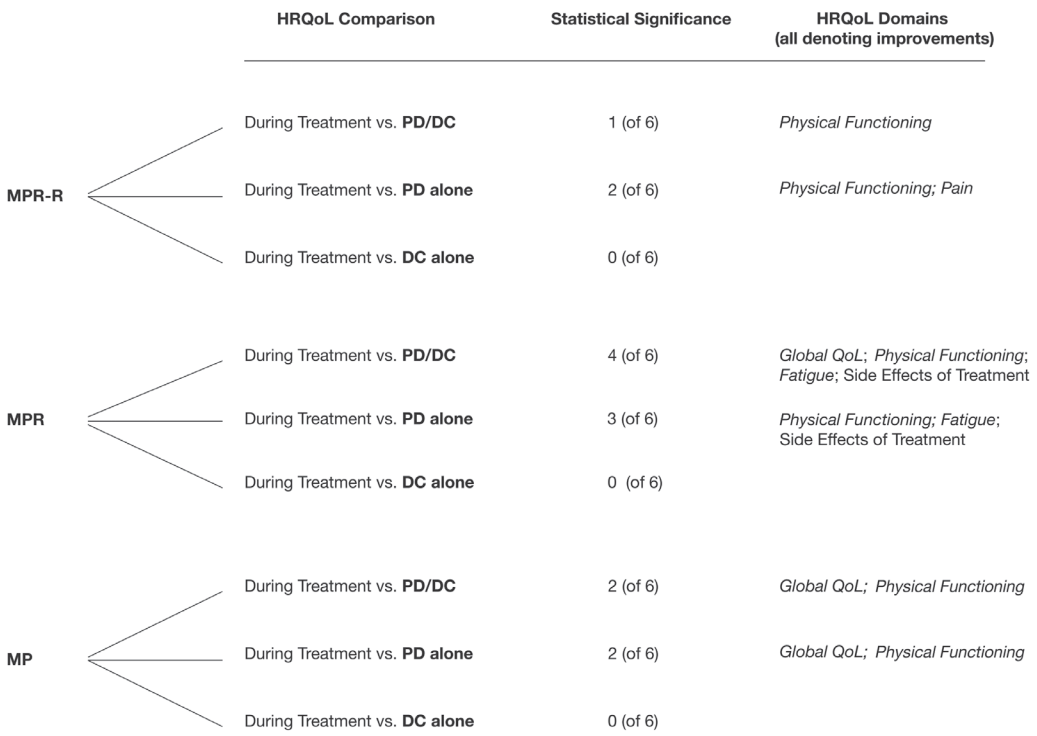


Figure 2. Analysis outline of HRQoL assessment: comparison of during treatment versus end of treatment (PD or DC). Statistical significance was determined after applying a Bonferroni adjustment for multiple treatments. *Italicized text* means that the MID was achieved. DC, discontinuation (for any reason other than progressive disease); HRQoL, health-related quality of life; MID, minimal important difference; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; PD, progressive disease.

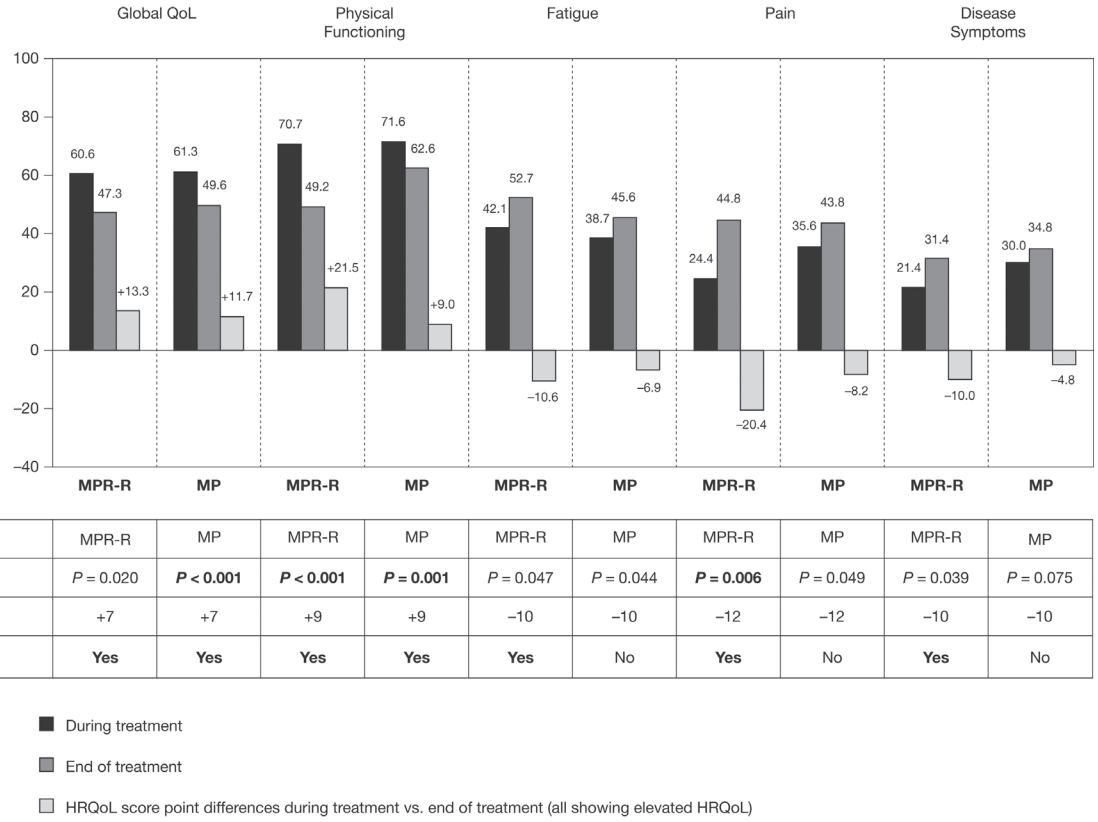
Global QoL (+ 10.7 [MID + 7]). For patients receiving MPR, HRQoL was significantly better during treatment versus at the time of PD/DC for four of the six domain scores: Global QoL ($p = 0.006$; $n = 57$), Physical Functioning ($p = 0.004$; $n = 61$), Fatigue ($p < 0.001$; $n = 59$) and Side Effects of Treatment ($p = 0.017$; $n = 60$). The MID was achieved for Global QoL (+ 9.4 [MID + 7]) and Fatigue (− 11.0 [MID − 10]). In patients receiving MPR-R, HRQoL was significantly better during treatment versus the time of PD/DC for Physical Functioning ($p = 0.003$; $n = 49$), which was also clinically meaningful (+ 10.6 [MID + 9]). No statistically significant differences during treatment versus end of treatment were observed in DC patients for any of the treatment groups.

Figure 3 depicts differences in HRQoL during treatment versus the end of treatment (PD) for MPR-R and MP groups (MPR not shown). In the MPR-R group, statistically significant and clinically meaningful differences in HRQoL scores were observed for two out of six domains (Physical Functioning and Pain; Figure 2). Two HRQoL domains showed statistically significant differences and were clinically meaningful during MP treatment versus PD (Global QoL and Physical Functioning; Figure 2). For patients receiving MPR, three HRQoL domain scores had statistically significant differences during treatment compared to PD, with two of these differences achieving the MID (Physical Functioning and Fatigue; Figure 2). All three treatment groups deteriorated in Physical Functioning at the time of PD.

Figure 4 summarizes the mean scores for each of the six HRQoL domains at baseline, during treatment (based on best score) and at the time of PD for each treatment group. HRQoL scores often significantly improved under treatment versus baseline. The development of PD, while not statistically significantly different compared with baseline HRQoL scores, was often associated with significant worsening in HRQoL scores across treatment arms as compared to best HRQoL scores during treatment.

Discussion

This analysis of HRQoL data from trial MM-015 was undertaken to identify predictors of HRQoL and compare HRQoL scores at baseline or during therapy with those at the time of PD or DC. The results suggest that female gender, advanced age and development of PD negatively affect HRQoL, whereas better HRQoL scores at baseline and better response to treatment (≥ VGPR) were associated with improvements in HRQoL. Better response (≥ VGPR) was more frequently observed with MPR-R than with MP (33% vs. 12%), whereas PD was observed less often with MPR-R than with MP (PFS hazard ratio 0.40; $p < 0.001$) [1]. DC, which was more commonly observed in the MPR-R group than in the MP group (43% vs. 23%) [1], had a statistically significant but no clinically meaningful effect on HRQoL. Neutropenia grade 3–4 was found to not exert any significant influence on HRQoL. Anemia grade 3–4, which occurred at a similar incidence in the MPR-R and MP groups (24% vs. 14%, respectively; $p = 0.091$), negatively affected some HRQoL domains. Findings in the subset of patients aged 65–75 years were generally consistent with the overall findings in patients aged > 65 years. Taken together, these data show that the addition of lenalidomide to MP with subsequent lenalidomide maintenance therapy had no adverse effect on HRQoL, and that



Treatment	MPR-R	MP	MPR-R	MP	MPR-R	MP	MPR-R	MP	MPR-R	MP
p-value	$P = 0.020$	**$P < 0.001$**	**$P < 0.001$**	**$P = 0.001$**	$P = 0.047$	$P = 0.044$	**$P = 0.006$**	$P = 0.049$	$P = 0.039$	$P = 0.075$
MID score	+7	+7	+9	+9	–10	–10	–12	–12	–10	–10
MID score reached?	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	No	**Yes**	No	**Yes**	No

During treatment

End of treatment

HRQoL score point differences during treatment vs. end of treatment (all showing elevated HRQoL)

Figure 3. Mean HRQoL scores during treatment versus end of treatment (PD) by treatment group. Mean differences in scores were added to the *x*-axis. Bold table entries were statistically significant after applying a Bonferonni adjustment for multiple treatments and/or were clinically meaningful. HRQoL, health-related quality of life; MID, minimal important difference; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; PD, progressive disease.

MPR-R may positively affect HRQoL through achievement of better response and delay in PD.

Patients experienced on average better HRQoL during treatment than at the time of PD, and the difference in HRQoL was particularly pronounced in the MPR-R treatment group. However, in no instances were mean HRQoL scores at the time of PD significantly worse than scores at baseline. These findings confirm the negative impact of PD on HRQoL and underscore the importance of delaying PD in patients with NDMM.

Positive effects of MPR-R on HRQoL found in this analysis contrast with recently published data from the VISTA trial, which indicate that use of melphalan, prednisone and bortezomib was associated with a temporary worsening in HRQoL, especially between cycles 3 and 6 [13]. However, it is not possible to directly compare results from MM-015 and VISTA due to differences in study design (MM-015 is double-blind and VISTA is open-label), treatment regimens, study populations and follow-up duration. The findings highlight the potential effects of treatment on HRQoL and suggest that further studies are needed to directly compare the impact of bortezomib- and lenalidomide-based regimens on HRQoL.

One limitation of this analysis is that it is based on interim data; therefore, an updated analysis using final MM-015 data is recommended. A second limitation could be the preselection of six HRQoL domains. This focus was considered justifiable, however, as longitudinal results of these six HRQoL domains have been found to be mostly comparable to the remaining group of HRQoL domains [4]. This study has shown a clear negative association between HRQoL and PD, whereby PD was defined as a laboratory progression in accordance with the European Group for Blood and Marrow Transplantation criteria [1]. In clinical practice it is conceivable that patients would be treated until symptom relapse according to CRAB criteria ([elevated] calcium, renal failure, anemia, bone lesions); these associations were not tested here due to heightened levels of complexity. However, this reinforces the importance of the findings in this publication and indicates that there may be an even stronger negative correlation between HRQoL and symptom progression.

Lastly, although the inclusion of neutropenia and anemia in our mixed-effects model provides interesting observations, a more detailed analysis of the relationship between adverse events and HRQoL may provide further insights into this area of research.

Conclusion

Based on the MM-015 NDMM population, several factors were identified that predicted HRQoL, including achievement of VGPR (which was associated with improved HRQoL) and PD (which negatively affected HRQoL). The MPR-R regimen, which has been shown to prolong PFS compared with MP, was associated with several statistically significant and clinically meaningful improvements of HRQoL. This suggests that MPR-R is an important

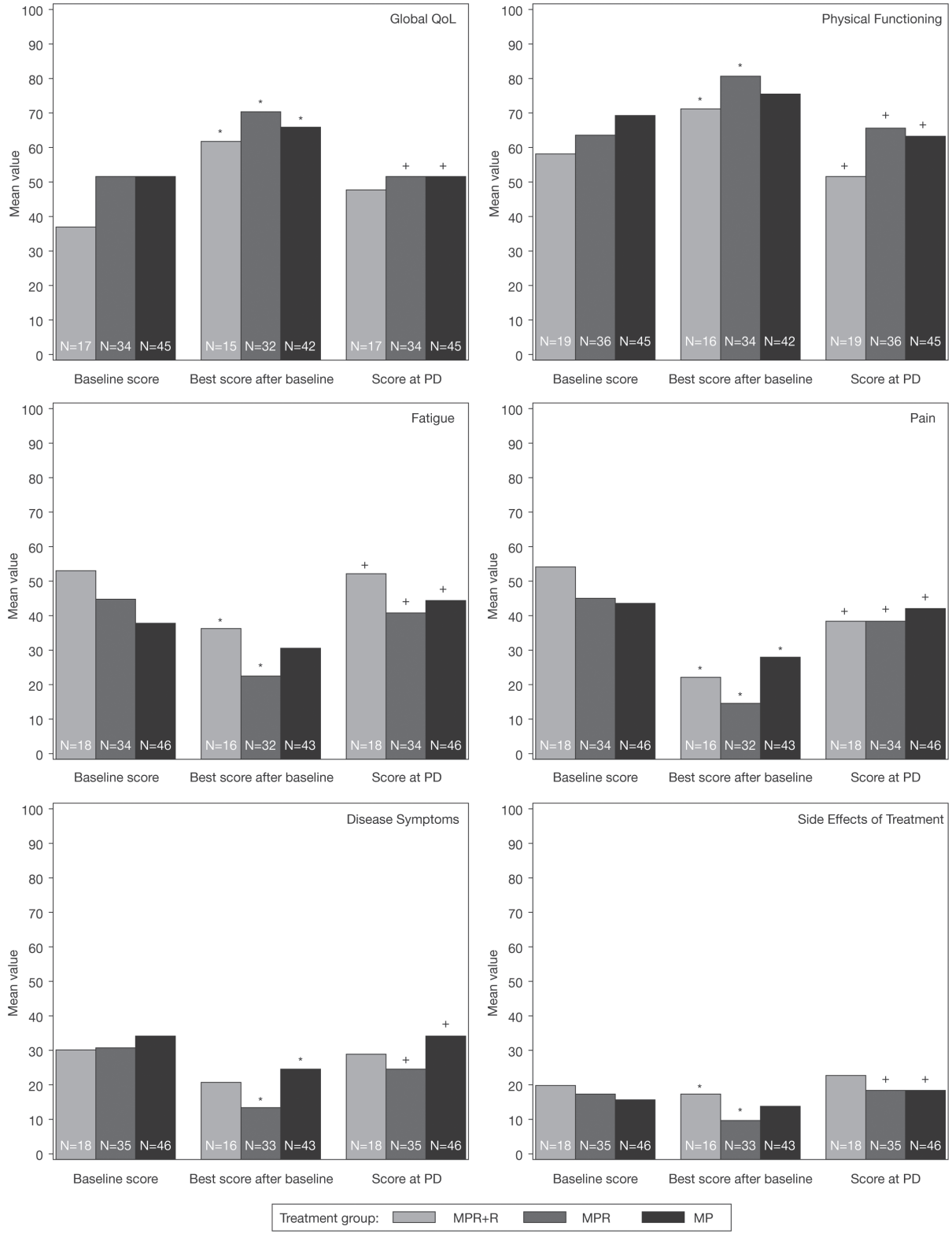


Figure 4. Mean HRQoL scores for baseline, best during treatment and at PD according to treatment group. Increases in HRQoL score indicate improvements/better HRQoL for Global QoL and Physical Functioning; decreases in HRQoL score indicate improvements/better HRQoL for Fatigue, Pain, Disease Symptoms and Side Effects of Treatment. Symbols indicate statistical significance based on Bonferroni-adjusted *p*-values for comparisons of multiple treatments of best score versus baseline score (*) and best score versus PD score (+) within treatment group. HRQoL, health-related quality of life; MP, melphalan, prednisone and placebo followed by maintenance therapy with placebo; MPR, melphalan, prednisone and lenalidomide followed by maintenance therapy with placebo; MPR-R, melphalan, prednisone and lenalidomide followed by maintenance therapy with lenalidomide; PD, progressive disease.

treatment option for transplant-ineligible patients with NDMM. HRQoL may be especially relevant in circumstances where a survival advantage is difficult to demonstrate, such as in frontline treatment for multiple myeloma, where there is an increasing use of novel agents as salvage therapy. The marked deterioration in HRQoL observed at PD in this analysis emphasizes the clinical importance of delaying PD, even in situations where an overall survival advantage has not yet been demonstrated due to a limited number of events.

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