



Impact of Prolonged Lenalidomide Maintenance (≥ 3 years) and Outcomes in Patients with Multiple Myeloma Post Autologous Stem Cell Transplant

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BACKGROUND

- Lenalidomide is the preferred maintenance strategy following autologous stem cell transplantation (ASCT), especially in non-high-risk patients with MM, with multiple randomized studies consistently demonstrating an improvement in progression free survival (PFS) with lenalidomide maintenance.
- The optimal duration of maintenance therapy is unclear and current prevalent practice is to continue lenalidomide maintenance till progression or intolerable side effects.
- Here we present the outcomes of patients treated with lenalidomide maintenance and study impact of depth of response and duration of maintenance therapy

METHODS

- Consecutive patients with MM diagnosed between 1/1/2005 and 12/31/2016 and treated with lenalidomide (with or without dexamethasone) as maintenance therapy post upfront ASCT (within 1year) were included in this retrospective study.
- The timing of starting maintenance therapy following ASCT and starting dose of lenalidomide was based on routine prevalent practices.
- The mSMART 3.0 criteria were used for risk stratification based on cytogenetics features on interphase FISH.
- Response to therapy was determined using the 2016 IMWG criteria. For deepening of response with maintenance, the best recorded response post initiation of maintenance therapy was used for comparison with the pre-maintenance therapy response.
- The Kaplan Meier method was used to estimate the time-to-event points. All statistical analyses were performed using SPSS (version 19; SPSS Inc., Chicago, IL, USA).

RESULTS

- A total of 213 patients were included. The baseline characteristics and details of therapies prior to maintenance therapy are depicted in Table 1.
- The median follow-up was 5.4 (95% 93 CI: 4.9, 5.9) years from diagnosis and 4.6 (95% CI: 4.2, 5) years from the start of maintenance.
- The median time to ASCT from diagnosis was 6.2 months (range 2.8 to 12). The median duration of maintenance therapy was 1.8 years (95% CI: 1.6-2 years).
- Out of 213 patients 190 (89%) received lenalidomide alone whereas 23 patients (11%) received lenalidomide with dexamethasone as maintenance. Details of maintenance regimen are depicted in Table 2.
- One-hundred-twenty-eight (60%) patients achieved a very good partial response or better ($\geq$ VGPR) prior to the initiation of lenalidomide maintenance; with 72 (34%) patients achieving complete response (CR) (Figure 1a); 152 (73%) patients achieved or maintained $\geq$ VGPR as best response while on lenalidomide maintenance (Figure 1a).
- Patients who achieved or maintained a best response of $\geq$ VGPR within 2 years of maintenance were noted to have a significantly better OS (5-year OS: 82% compared with patients with $\leq$ PR (5-year OS 67%; $p=0.003$)) and PFS [median PFS 4.4 yrs (95% CI: 3.9-4.9) for $\geq$ VGPR vs 3.7 years (95% CI: 2.2-4.3) for $\leq$ PR; $p=0.003$].
- Adjusting for age, ISS stage 3, cytogenetic risk group, and patients who received Rd maintenance, a best response of $\geq$ VGPR within 2 years of maintenance was associated with an improved OS [HR 0.32 (95% CI: 0.18-0.58)] and PFS [HR 0.56 (95% CI: 0.38-0.83; $p=0.004$].
- At time of data cutoff, 60 (28%) patients had died and the median OS was not reached. The 5-year OS was 77% from diagnosis and 71% from the start of maintenance
- We performed landmark analysis at 3-years post initiation of maintenance. Sixty-five (31%) patients who stopped lenalidomide maintenance within 3 years due to progression on maintenance were excluded from the analysis to control for guaranteed-time bias.
- The 5-year OS from start of maintenance was 100% in the ≥ 3 year cohort (n=48) versus 78% the < 3 year group (n=100; $p=0.011$) (Figure 2a).
- Median PFS from start of maintenance was 6.2 (95% CI: 5.2, 7.2) years in patients who received lenalidomide for > 3 years versus 3.6 (95% CI: 3.2, 4) years in those who received < 3 years of maintenance (Figure 2b).

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS AT DIAGNOSIS.

PARAMETERS	ALL PATIENTS (N=213)
Demographics	N (%)
Median age at time of maintenance (range)	60 (35–76) years
Gender: Female	84 (39%)
Disease characteristics	
ISS stage	
I	65 (31)
II	72 (34)
III	55 (26)
Not available	21(10)
Cytogenetic risk	
Standard risk	139 (65)
High risk	63 (30)
• t(4;14)	7 (3)
• t(14;16)	14 (6)
• t(14;20)	5 (2)
• del(17p)	17 (7)
• gain(1q)	29 (12)
Not available	11(5)
Therapy prior to ASCT	
Patients who received IMiDs	149 (70)
Patients who received thalidomide	9 (4)
Patients who received lenalidomide	140 (66)
Lines of therapies before maintenance	
1	170 (80)
2	34 (16)
≥ 3	10 (5)
No. of lines of IMiD-based therapies before	
0	64 (30)
1	140 (66)
2	8 (4)
≥ 3	1(1)

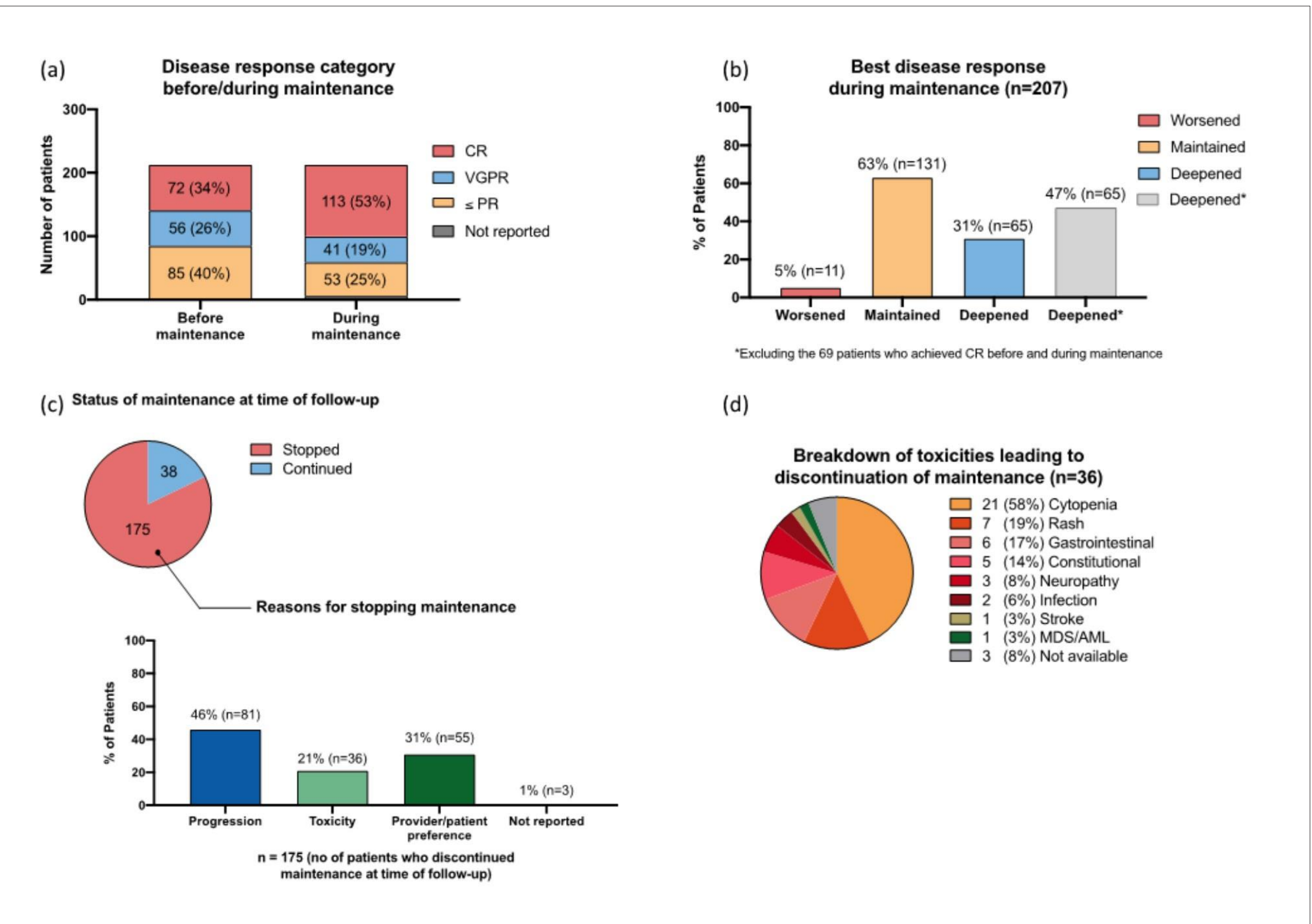


FIGURE 1
a) Response before and during maintenance therapy (b) Best Response during maintenance therapy (c) Reason for discontinuation of maintenance therapy (d) Toxicity leading to discontinuation of maintenance therapy.

- Major changes:
- Added a conclusion section
- Please re-arrange the tables and figures as suggested.

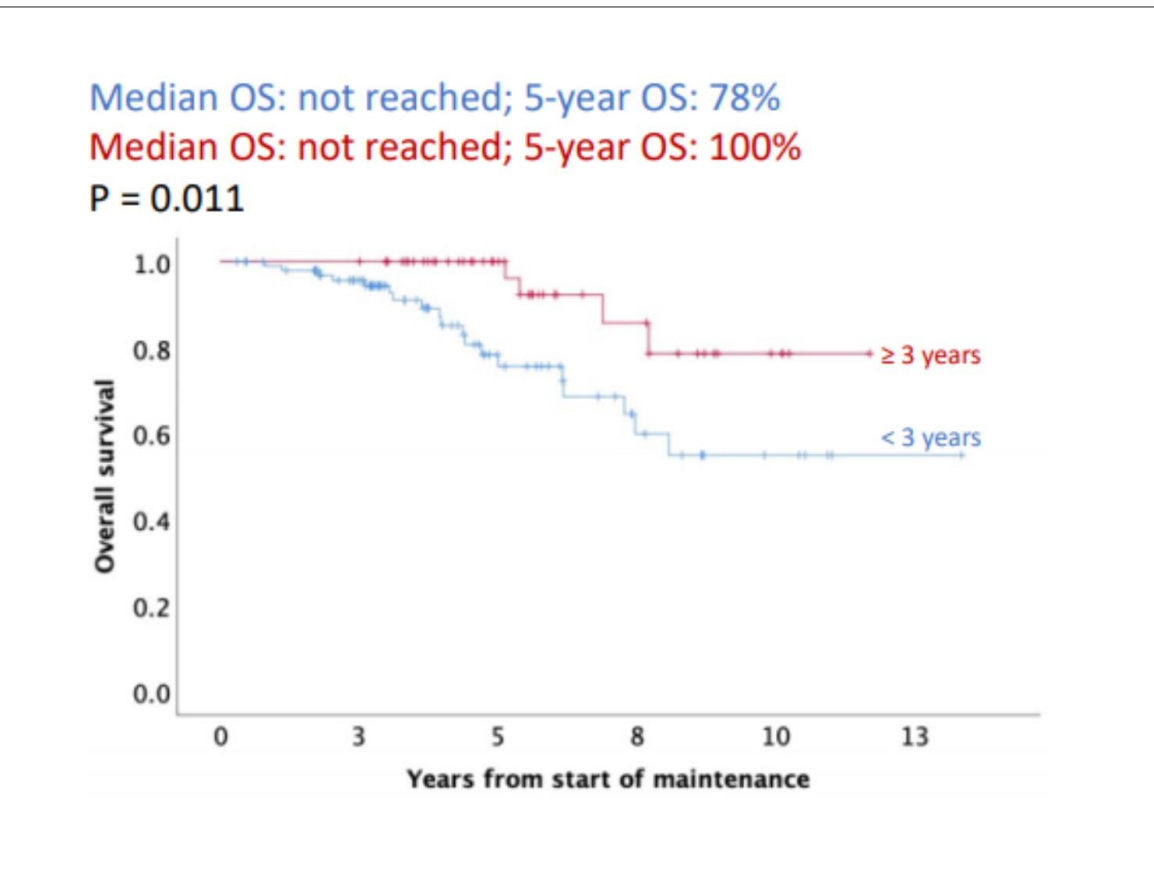


FIGURE 2A
The 5-year OS from start of maintenance was significantly better (100%) in the ≥ 3 year cohort versus < 3 year group (78%; $p=0.011$).

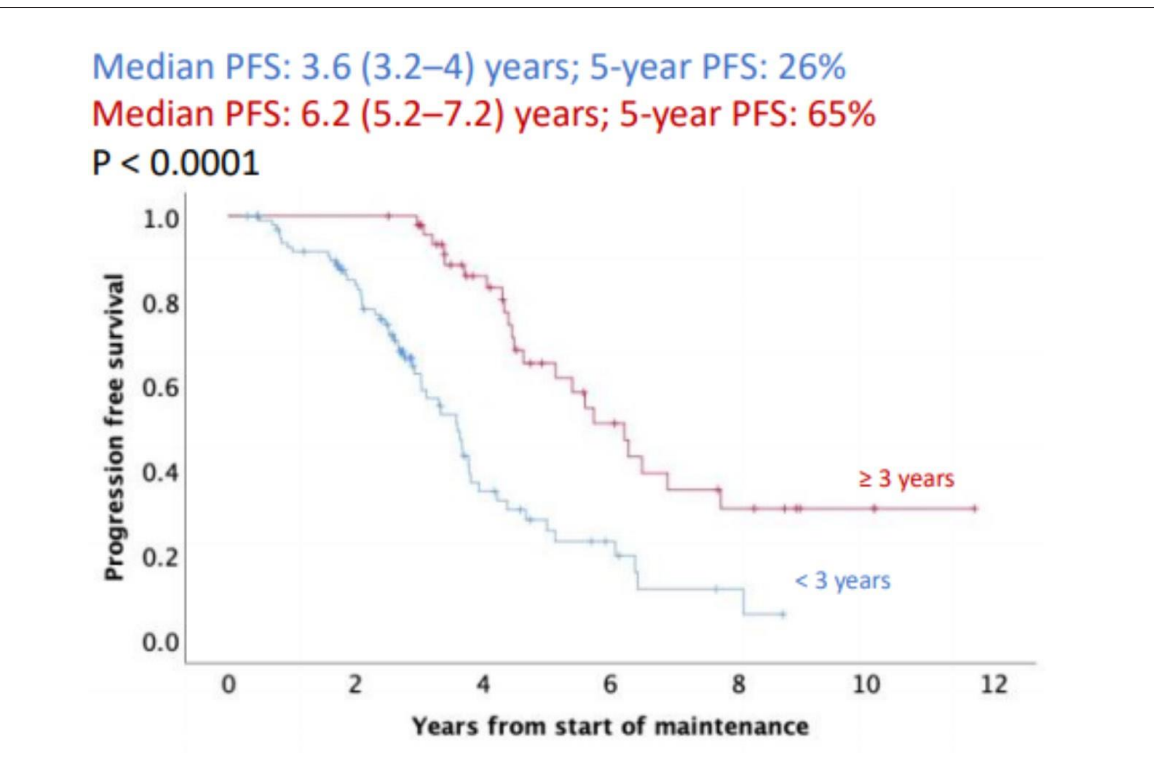


FIGURE 2B
Median PFS from start of maintenance was significantly better in patients receiving maintenance ≥ 3 years [median 6.2 (95% CI: 5.2, 7.2) years compared to those who received < 3 years of maintenance [median 3.6 (95% CI: 3.2, 4) years; $p<0.0001$].

TABLE 2: DETAILS OF MAINTENANCE REGIMEN

PARAMETERS	N (%)
Median time to start of maintenance from diagnosis (months)	9.9 (IQR: 8.6–11.6)
Median time to start of maintenance from ASCT (months)	3.4 (IQR: 3.1-3.9)
Maintenance regimen	
Lenalidomide alone	190 (89)
Lenalidomide + dexamethasone	23 (11)
Lenalidomide starting dose	
5 mg/d	6 (3)
10 mg/d	96 (45)
15 mg/d	91(43)
20 mg/d	(0.5)
25 mg/d	1(7)
Not available	5 (2)
Dose reductions	90 (44)
Duration of maintenance	
Duration < 3 years	165 (77)
Duration ≥ 3 years	48 (23)
Patients who discontinued maintenance	175 (82)
Progression	81(38)
Toxicity	39 (18)
Provider/patient preference	55 (26)

CONCLUSION

- Maintenance therapy with lenalidomide is well tolerated and a longer duration (≥ 3 years) is associated with improvement in OS, after adjusting for cytogenetic risk group and ISS stage.
- Deepening of response on maintenance therapy ($\geq$ VGPR) within 2 years of starting maintenance was associated with improved PFS and OS