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ORIGINAL RESEARCH

Favorable Outcomes of Maintenance Lenalidomide can be Reproduced in an Unselected Myeloma Patient Population at a Single Academic Center

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Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, with more than 33,000 individuals newly diagnosed in the United States in 2017.¹ Patients are stratified into standard and high risk prognostic categories according to cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) studies in accordance with the International Myeloma Working Group (IMWG). Cytogenetic risk category and depth of response to induction therapy have prognostic significance.^{2,3} Previously, the therapeutic options available for patients with MM resulted in a modest three year median overall survival (mOS) of 44.8 months.⁴ Incorporation of modern therapies, including proteasome inhibitors (PI) and imids, along with autologous hematopoietic stem cell transplantation (ASCT) in eligible patients has improved clinical outcomes.⁴⁻⁶ ASCT is not curative and the majority of patients will suffer a relapse.⁷⁻¹⁰ Administering post-transplantation maintenance therapy is an effective strategy to delay progressive disease^{2,11,12} and improve survival.⁶

Lenalidomide, an oral inhibitor of cereblon, exerts anti-myeloma effect through its immunomodulatory, anti-angiogenic, anti-inflammatory and anti-proliferative effects.^{13,14} The use of maintenance lenalidomide compared to observation resulted in improved progression free survival (PFS) in 3 randomized trials (CALGB100 104, IFM 2005-02 and GIMEMA),¹⁵⁻¹⁷ and the CALGB 100104 trial demonstrated improved overall survival (OS).¹⁶ A meta-analysis combining data from the 1,208 patients enrolled on these 3 studies demonstrated improved PFS (52.8 m vs. 23.5 months; HR 0.48; 95% CI, 0.41 to 0.55) and OS (not reached (NR) vs. 86.0 months; HR, 0.75; 95% CI, 0.63 to 0.90; $p=.001$) with the use of lenalidomide maintenance compared to the placebo or observation group respectively.⁶

The majority of published data describing clinical benefit of lenalidomide maintenance is in the context of clinical trials, but the applicability to real-world clinical settings is less clear. A retrospective study presented in abstract of 76 myeloma patients that underwent ASCT at the University of Virginia reported that maintenance therapy was the only variable associated with relapse by univariate analysis.¹⁸ Details were not provided about specific maintenance approaches employed. An observational study utilizing data from Connect MM, a largely community-based dataset, describe improved PFS and OS associated with lenalidomide maintenance compared to observation (PFS: 50.3 vs 30.8 months [hazard ratio (HR), 0.62;

95% confidence interval (CI), 0.46-0.82; $P, .001$, OS: NR in either group [HR, 0.54; 95% CI, 0.36-0.83; $P, .005$].¹⁹ Our study aims to describe clinical outcomes at a single academic institution of MM patients who have undergone ASCT with or without maintenance lenalidomide.

Methods

Patients and Study Design

We performed a single-center retrospective study of 221 patients that underwent ASCT for MM. Patients included received various induction strategies followed by an ASCT after high-dose melphalan conditioning at UCLA Ronald Regan Medical Center between 2005 and 2016. The primary outcome was PFS after stratifying for use of lenalidomide maintenance. Secondary outcomes included overall survival and cause of death. Lenalidomide maintenance was initiated 3 months post-transplantation. Use of lenalidomide maintenance was determined by treating physician based on cytogenetic risk category, anticipated tolerance and patient preference. Institutionally, patients received lenalidomide maintenance for a minimum of two years. This study was approved by the institutional IRB #16-001830.

Definitions

Patients were risk-stratified based on FISH analysis of specific translocations. High risk myeloma patients were defined in accordance with Revised International Staging System criteria and included those that had at least one of the following: $t(4;14)$, $t(14;16)$, and $del17$.²⁰ Patients with standard risk myeloma lacked high risk features. Response to therapy was defined according to International Myeloma Working Group guidelines.²¹

Statistical Analysis

Patient characteristics, myeloma-related variables and outcomes of interest were summarized using descriptive statistics and compared between treatment groups by Chi-square test. Outcomes of interest included treatment response, PFS, OS and cause of death. Treatment response was evaluated by comparing outcome no more than 30 days prior to ASCT compared to 12 months following ASCT. Chi-square tests were performed to assess treatment difference for treatment

response, as well as cause of death. OS was defined as death from any cause. Patients alive and without a PFS event were censored at last follow-up. PFS was defined as survival without myeloma progression or relapse, initiation of additional myeloma-directed therapy or death. Time to progression was defined as time from day 100 after ASCT to first documentation of progressive disease or initiation of additional myeloma-directed therapy. Kaplan-Meier estimates for OS and PFS were calculated and presented in figures. Median OS and PFS were reported, together with their corresponding 95% confidence interval. Comparison between treatment groups for OS and PFS were done by log-rank test. For all statistical investigations, tests for significance were two-tailed. A p-value of less than the 0.05 significance level was considered to be statistically significant. All statistical analyses were carried out using statistical software SAS version 9.4 (SAS Institute Inc. 2013).

Results

A total of 221 patients who achieved at least a partial response (PR) to frontline therapy at UCLA Ronald Reagan Medical center between May 2005 and December 2016 were included in the study. One hundred and thirty two patients received lenalidomide maintenance and 89 patients received no maintenance therapy. Median follow up post-ASCT was 39.0 months (range 1.0-143.0 months) and 30.5 months (range 1.0-117.0 months) for the lenalidomide and observation group respectively. The cohorts were well balanced with respect to age, gender and monoclonal protein sub-type (Table 1). IgG was the most commonly expressed monoclonal protein for both cohorts (lenalidomide: $n=75$, 56%, observation: $n=48$, 53.9%), followed by IgA, kappa light chains and lambda light chains. The majority of patients were younger than 65 years old (lenalidomide: $n=104$, 78.8%, observation: $n=72$, 80.9%). Prior to ASCT, the majority of patients in both groups received induction therapy containing a PI combined with an imid (lenalidomide: $n=88$, 67.2%, observation: $n=42$, 47.2%). Thirty-five (26.5%) and 18 (20.2%) patients in the lenalidomide and observation group respectively did not receive an imid as part of their induction treatment. There was missing data for cytogenetic risk categorization for 39 of the 132 (43.8%) patients in the lenalidomide group and 39 of the 89 (29.6%) patients in the observation group. For patients with available cytogenetic risk category data, a significant difference between the 2 cohorts was not observed.

The 2 groups were well balanced with respect to disease status at the time of ASCT (Table 2). Evaluation of depth of response 12 months after ASCT was available for 115 of 132 (87.1%) patients in the lenalidomide group and 61 of 89 (68.5%) patients in the observation group. Disease response improved 12 months post ASCT in 34 (25.9%) and 13 (14.6%) patients in the lenalidomide and observation group respectively. Fifty-four (41.2%) compared to 35 (39.3%) patients achieved stable disease and 26 (19.9%) compared to 13 (14.6%) patients experienced disease progression in the lenalidomide and observation groups respectively. The distribution of clinical

outcomes differed between the 2 groups; however this difference was largely driven by missing data (Table 3).

The three year mPFS was not reached for either cohort ($p=0.18$) (Figure 1a). Median PFS for all follow up was 46 months (range 39-59 months) and 41 months (range 32-57 months) for the lenalidomide vs observation group respectively ($p=0.63$) (Figure 1b). The 3 year mOS was not reached for either cohort ($p=0.67$) (Figure 2a). Median OS for all follow up was 99 months (range 82 months-NR) and 95 months (range 66 months-NR) for the lenalidomide and observation groups respectively ($p=0.72$) (Figure 2b).

A smaller proportion of patients died in the lenalidomide group (19.6%) compared to the observation group (32.6%) ($p=0.03$). The most common cause of death was relapsed disease in both cohorts (lenalidomide: $n=19$ (73.1%), observation: $n=24$ (82.8%)), followed by infection, unknown cause and hemorrhage. One patient in the lenalidomide group died of a second primary malignancy (SPM) compared to no patients in the observation group (Table 4).

Discussion

We conducted a single center retrospective study of 221 MM patients who received maintenance lenalidomide or underwent observation following an ASCT. To our knowledge, this is the largest retrospective study evaluating the feasibility and efficacy of maintenance lenalidomide at a single center academic institution. Median progression free and OS did not differ between the 2 groups. The observed rates of PFS and OS in our lenalidomide maintenance group are similar to those published in 3 prospective randomized trials providing support that these outcomes are achievable outside the context of a clinical trial. Comparison with our observation group was impeded by a small number of patients and missing data.

Lenalidomide has the benefit of once daily oral administration with a favorable toxicity profile, making its incorporation into standard of care clinical practice feasible. Due to geographic challenges, many patients transition to co-management by the transplantation center and referring oncologist 3 months post-transplantation. While the data did not allow for a comparison of outcomes between patients treated strictly at the transplantation center compared to those that were co-managed in the community, the comparable outcomes of this study to those of previously published prospective studies utilizing selected patients suggest this approach does not compromise patient outcomes. The outcomes of our lenalidomide maintenance cohort are similar to those described in the Connect MM data analysis,¹⁹ providing additional support that maintenance lenalidomide contributes to favorable MM patient outcomes in the real-world.

Our observation group had favorable outcomes compared to those in prior published studies. The discrepancy in PFS between our analysis and previously published prospective trials is likely explained by the inherent bias in retrospective

studies. Treatment allocation was not random; but rather at the discretion of the treating physician. Higher functioning, lower risk patients may have been chosen for observation. Missing patient data is an additional source of bias. Health status may have impacted a patient’s ability to follow up.

Although other published reports indicate an increased incidence of SPM approaching 7-8% in patients receiving maintenance lenalidomide,^{8,16,22} our analysis showed a low incidence of death from secondary malignancies in the lenalidomide group. Numerous factors contribute to the development of SPM: genetic predisposition, prior treatment and host characteristics. These factors should be considered when discussing the risk benefit balance of maintenance lenalidomide with patients.

Limitations of this study include data analyzed from a single center, the inherent bias in a retrospective analysis, treatment assignment by investigator discretion and the relatively small sample size. As with any observational study, missing data may further compound bias. Differences may exist between the 2

groups not captured by our comparison of patient and disease characteristics. Although this is one of the largest single center analyses of post-transplantation lenalidomide maintenance published to date, the number of patients and events are too small to perform adequately powered comparative analyses of relevant subgroups. With longer follow up, a difference may have been observed.

Despite these limitations, this study demonstrates the feasibility and safety of administering maintenance lenalidomide at a single center institution, with and without support from community practices. We further contribute to the growing body of evidence supporting that favorable clinical outcomes of maintenance lenalidomide in unselected transplant-eligible patient with MM are feasible and reproducible outside the context of a prospective clinical trial with no new safety signals.

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Figures

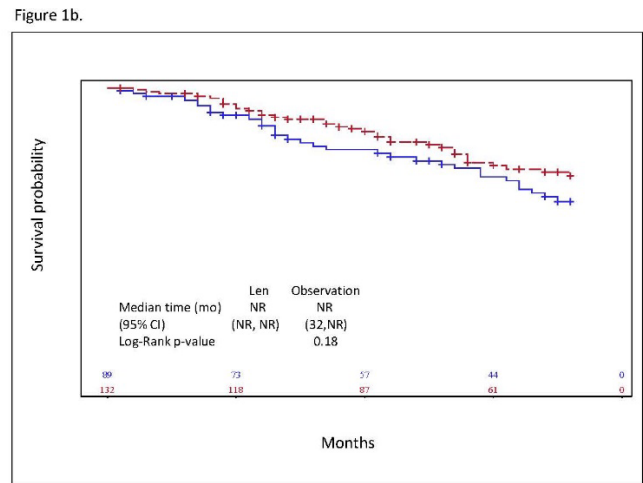
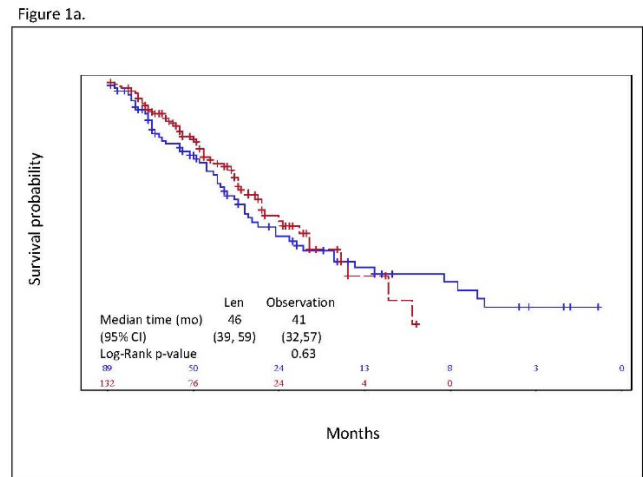


Figure 1. Kaplan-Meier estimates of PFS. The top panel shows the probability of PFS for all follow up (A) and at 3 years (B). Tick marks indicate censored data. NR (not reached).

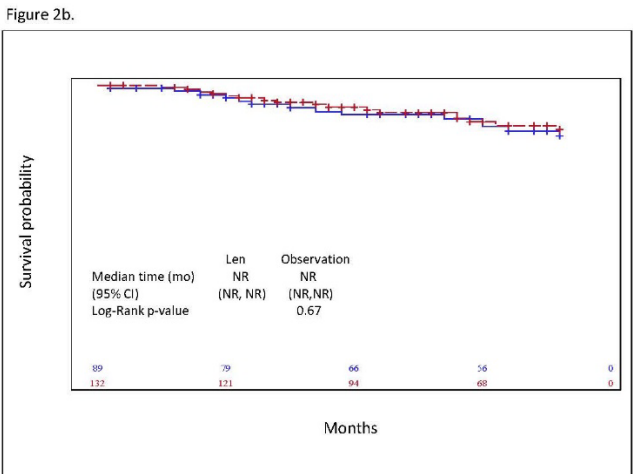
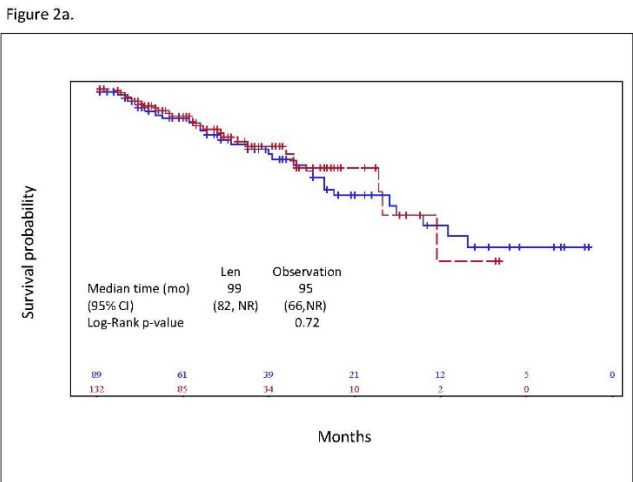


Figure 2. Kaplan-Meier estimates of OS. The top panel shows the probability of OS for all follow up (A) and at 3 years (B). Tick marks indicate censored data. NR (not reached).

Tables

Table 1. Patient characteristics

	No maintenance (n=89)	Lenalidomide (n= 132)	p-Value
Gender (N, %)			0.08
M	40 (44.9%)	75 (56.8%)	
F	49 (55.1%)	57 (43.2%)	
Age (N, %)			0.70
< 65 y	72 (80.9%)	104 (78.8%)	
≥ 65 y	17 (19.1%)	28 (21.2%)	
Monoclonal protein (N, %)			0.96
IgG	48 (53.9%)	74 (56.0%)	
IgA	19 (21.4%)	29 (22.0%)	
IgD	0 (0.0%)	1 (0.8%)	
kappa light chain	11 (12.4%)	13 (9.9%)	
lambda light chain	8 (8.9%)	11 (8.3%)	
NK	3 (3.4%)	4 (3.0%)	
Cytogenetic risk category (N, %)			0.03
High risk	8 (9.0%)	26 (19.7%)	
Standard risk	42 (47.2%)	67 (50.7%)	
NK	39 (43.8%)	39 (29.6%)	
Induction regimen (N, %)			<0.001
Imid-containing	29 (32.6%)	9 (6.1%)	
PI-containing	14 (15.7%)	33 (25.2%)	
Both	42 (47.2%)	88 (67.2%)	
Other	4 (4.5%)	2 (1.5%)	
Median follow up (months) (min, max)	39.0 (1.0, 143.0)	30.5 (1.0, 117.0)	0.04

Table 2. Response to Induction therapy

	No maintenance (n=89)	Lenalidomide (n= 132)	p-Value
Response to induction therapy at time of transplantation			0.02
CR	23 (25.8%)	41 (31.1%)	
VGPR	39 (43.8%)	60 (45.5%)	
PR	19 (21.3%)	30 (22.7%)	
Missing data	8 (8.9%)	1 (0.8%)	

Table 3. Patient outcomes from time of ASCT to 12 months post-ASCT

	No maintenance (n=89)	Lenalidomide (n= 132)	p- value
Deepening of response			<0.01
VGPR→CR	9 (10.0%)	23 (17.5%)	
PR→CR	2 (2.3%)	5 (3.8%)	
PR→VGPR	2 (2.3%)	6 (4.6%)	
	N=13 (14.6%)	N=34 (25.9%)	
Stable disease			
CR→CR	11 (12.4%)	20 (15.3%)	
VGPR→VGPR	16 (18.0%)	23 (17.5%)	
PR→PR	8 (8.9%)	11 (8.4%)	
	N=35 (39.3%)	N=54 (41.2%)	
Progressive disease			
CR→VGPR	2 (2.3%)	9 (6.9%)	
CR→PR	1 (1.1%)	4 (3.1%)	
CR→PD	0 (0.0%)	1 (0.8%)	
VGPR→PR	0 (0.0%)	5 (3.8%)	
PR→PD	5 (5.6%)	2 (1.5%)	
VGPR→PD	5 (5.6%)	5 (3.8%)	
	N=13 (14.6%)	N=26 (19.9%)	
Missing data	N=28 (31.5%)	N=17 (13.0%)	

CR complete remission, VGPR very good partial response, PR partial response, PD progressive disease

Table 4. Deaths

	No maintenance (n=89)	Lenalidomide (n= 132)	p-Value
Deceased	29 (32.6%)	26 (19.6%)	0.03
Relapsed disease	24 (82.8%)	19 (73.1%)	0.81
Infection	2 (7.0%)	3 (11.5%)	
Hemorrhage	1 (3.4%)	1 (3.9%)	
Unknown	1 (3.4%)	2 (7.7%)	
Transplant-related	1 (3.4%)	0 (0.0%)	
Secondary malignancy	0 (0.0%)	1 (3.8%)	

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