Real-World Outcomes With Generic Pomalidomide in Relapsed Refractory Multiple Myeloma—Experience From a Tertiary Care Cancer Center

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PURPOSE The prognosis of relapsed and refractory multiple myeloma (RRMM) that is refractory to bortezomib and lenalidomide is very poor wherein the median survival is between 3 and 9 months. We did this retrospective analysis to study the pattern of utilization, tolerance, and outcomes with pomalidomide in these patients having RRMM.

MATERIALS AND METHODS Retrospective analysis of all the patients who were treated with generic pomalidomide at Tata Memorial Centre, Mumbai, during the period of May 2017 to March 2019 was done. Patients with secretory disease and who had completed at least one cycle of pomalidomide were analyzed for response rates, toxicity, and survival outcomes.

RESULTS A total of 81 patients received pomalidomide-based therapy during this study period, out of which 75 were included in the survival analysis. Forty-eight patients (59.3%) were refractory to both lenalidomide and bortezomib. Overall response rate was 58.7%. Five patients (6.7%) achieved complete response, very good partial response was seen in 13 patients (17.3%), and partial response was seen in 26 patients (34.7%). After a median follow-up of 11 months (range 2-27 months), median progression-free survival was 9.1 months (95% CI, 5.4 to 12.9 months). Median progression-free survival for patients who were refractory to both lenalidomide and bortezomib versus nonrefractory was 5.5 and 12.6 months, respectively, which was significant statistically ($P = .04$, hazard ratio, 0.35, 95% CI, 0.28 to 0.97). The median overall survival was not reached. Important toxicities included anemia (28%), neutropenia (16%), pneumonia (16%), and venous thrombosis (5%).

CONCLUSION Generic pomalidomide-based therapy is an effective option and is well tolerated in patients with RRMM. Higher response rates and longer survival seen in our study are possibly because of heterogeneity of the study population.

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INTRODUCTION

Patients with multiple myeloma present and respond to therapy in a heterogeneous pattern and invariably relapse. Disease becomes less responsive to therapy and remission duration shortens with subsequent lines of treatment. Relapsed and refractory multiple myeloma (RRMM) is defined as progression of disease in patients who achieve minor response or better, while on therapy or within 60 days of their last treatment. Pomalidomide is a third-generation immunomodulatory agent wherein exerting its action by binding to cereblon E3 ubiquitin ligase and inhibiting downstream signaling through IRAF and other pathways leading to death of plasma cells. Pomalidomide is in combination with low-dose dexamethasone is an effective therapy for patients with relapsed and refractory MM who have received prior therapy with both lenalidomide and bortezomib. The pivotal MM-003 and MM-0010 trials showed a significant improvement in overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) with pomalidomide in RRMM in comparison to high-dose dexamethasone. The MM-003 study, which compared pomalidomide and low dose dexamethasone with high dose dexamethasone in patients who progressed on two prior
lines including bortezomib and lenalidomide, reported an ORR of 32% versus 11%, with a median PFS of 4 months versus 1.9 months and median OS of 13.1 versus 8.1 months, respectively.\(^1\) Pomalidomide does not require dose modification in presence of renal failure and has been reported to have particularly benefited in patients with p53 deletions and/or t(4:14).\(^6\) Generic pomalidomide has recently become available in India and is inexpensive compared with innovator molecule. Oral administration makes it an attractive candidate to use in relapse setting and thus, pomalidomide-based regimens are commonly used for RRMM in our setup.

Patients in developing countries tend to present late with higher proportion of patients having renal dysfunction and other CRAB (hypercalcemia, anemia, renal insufficiency and bone lesions) features at baseline.\(^7\) They often receive less intense therapy and majority of them do not undergo autologous stem cell transplant (ASCT). This combined with often suboptimal induction leads to inferior responses and shorter PFS and OS in our patients. Given the difference in the prior lines of therapy, outcomes of RRMM in our setup may be different including responses to a particular drug. Given the less intense prior treatment, our patients with RRMM may derive greater benefits than reported in literature.\(^7\) Similarly, given the widespread use of pomalidomide-based regimen in RRMM, it is equally important to understand its tolerance in our patient population. Hence, we planned this retrospective analysis to characterize our patient population receiving pomalidomide and to evaluate the tolerance and outcomes with generic molecule.

**MATERIALS AND METHODS**

**Study Method**

Patients receiving pomalidomide for RRMM between May 2017 and March 2019 were included in this analysis. All the patients received the same generic brand of pomalidomide. A total of 81 patients were identified. Patients who have had secretory disease and completed at least one cycle of pomalidomide with follow-up response evaluation were included in the analysis. The baseline characteristics and the prior treatment details of these patients were noted from the electronic medical records. All adverse effects were recorded using CTCAE version 4 grading system. Refractory myeloma has been defined as progression on therapy or within 60 days of stopping bortezomib and/or lenalidomide. Fluorescence in-situ hybridization (FISH) analysis of cytogenetics was available in select patients. High-risk FISH is defined as del(17/17p), t(4,14), t(14,16), t(14,20), gain(1q), or non-hyperdiploid karyotype as per International Myeloma Working Group (IMWG) risk stratification in MM.\(^8\) The study was approved by the institutional ethics committee.

**Response Assessment**

Response rates including complete response (CR), stringent complete response, very good partial response (VGPR), partial response (PR), minor response, stable disease, and progressive disease were defined as per IMWG 2016 criteria.\(^9\) PFS and OS were calculated from the first day of pomalidomide administration. PFS was defined as the time from the initiation of pomalidomide therapy till disease progression or death. The OS was defined as a period from pomalidomide therapy initiation until all-cause death occurrence.

**Statistical Analysis**

Statistical analysis was done using the SPSS software (Version 21, IBM Corp., Armonk, NY). Survival analysis was done using the Kaplan-Meier method to estimate the survival, and comparison between the groups was done using the log-rank test. Proportions were compared using chi-square or Fisher exact test.

**RESULTS**

**Demographic Profile**

Overall, 81 patients received pomalidomide during the study period as mentioned. Median age of study population was...
61.5 years (range 34-78 years); 30 patients (37%) were older than 65 years of age, including 5 patients older than 75 years of age. Fifty-three (65%) were male and 21 patients (25.9%) had an Eastern Cooperative Oncology Group performance status of three or more at the time of treatment. Renal failure (glomerular filtration rate < 40 mL/min by Cockcroft-Gault formula) was seen in 20 (24.7%) patients at the start of pomalidomide-based therapy and 10 patients received dialysis at some point after the start of pomalidomide-based therapy. FISH results were available for 57 patients. High-risk cytogenetics as per IMWG criteria was seen in 27 (33%) with 17p deletion seen in six patients (7.4%). The median time from diagnosis to initiation of pomalidomide therapy was 56 months (range 9-160 months). Median number of previous lines was three (range 1-6), with 63% patients having received three or more prior lines of therapies. Seventy-eight patients (96.3%) received prior bortezomib, 67 patients (82.7%) received lenalidomide, and 32 patients had received thalidomide. Overall, 80.2% and 76.5% were refractory to bortezomib and lenalidomide, respectively, whereas 48 (59.3%) of patients were double-refractory, ie, to both bortezomib and lenalidomide. Eleven patients (13.6%) had undergone prior ASCT. Majority of patients (n = 49) received pomalidomide in combination with low-dose dexamethasone. Few patients received triplet therapy.

### TABLE 1. Demographic Characteristics

| Characteristic                          | Number of Patients (N = 81) |
|----------------------------------------|----------------------------|
| Median age, years                      | 61.5 (range 34-78)         |
| < 65                                   | 51 (63%)                   |
| > 65                                   | 30 (37%)                   |
| Sex                                    |                            |
| Male                                   | 53 (65%)                   |
| Female                                 | 28 (35%)                   |
| ECOG performance status               |                            |
| 0-2                                    | 60 (74.1%)                 |
| 3-4                                    | 21 (25.9%)                 |
| International staging system          |                            |
| N = 81                                 |                            |
| 1                                      | 11 (13.6%)                 |
| 2                                      | 29 (35.8%)                 |
| 3                                      | 41 (50.6%)                 |
| FISH available                         |                            |
| N = 57 (70%)                           |                            |
| High-risk cytogeneticsa                | 27 (33%)                   |
| 17p deletion                           | 6 (7.4%)                   |
| Median time from diagnosis to start of pomalidomide | 56 months (range 9-160)   |
| Median no. of prior antinyeloma therapies | 3 (range 1-6)          |
| Prior lenalidomide                    | 67 (82.7%)                 |
| Lenalidomide refractory               | 62 (76.5%)                 |
| Prior bortezomib                      | 78 (96.3%)                 |
| Bortezomib refractory                 | 65 (80.2%)                 |
| Lenalidomide and bortezomib refractory| 48 (59.3%)                 |
| Prior autologous HSCT                 | 11 (13.6%)                 |
| Combination therapy                   |                            |
| Pomalidomide plus dexamethasone        | 49 (60.5%)                 |
| Pomalidomide plus dexamethasone plus bortezomib | 22 (27.2%)             |
| Pomalidomide plus dexamethasone plus carfilzomib | 8 (9.9%)               |
| Pomalidomide plus dexamethasone plus daratumumab | 1 (1.2%)                |
| Pomalidomide plus dexamethasone plus cyclophosphamide | 1 (1.2%)                |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in-situ hybridization; HSCT, hematopoietic stem-cell transplantation.

aHigh-risk FISH is defined as del(17/17p), t(4,14), t(14,16), t(14,20), gain(1q), or non-hyperdiploid karyotype as per International Myeloma Working Group risk stratification in MM.8
therapy—with the third drug being bortezomib in 22 patients, carfilzomib in eight patients, daratumumab in one patient, and cyclophosphamide in one patient. Median number of pomalidomide cycles administered was six, with range from one cycle to 28 cycles. Starting dose of pomalidomide was 2 mg in 39 patients (52%), 3 mg in 22 patients (29.3%), and 4 mg in 14 patients (18.7%) (Table 1).

**Disease Response**

Response rates are summarized in Table 2. Follow-up data were available for 75 patients and were analyzed. Among the six excluded patients, four patients died within one month of starting pomalidomide and follow-up details were not available for two patients.

The ORR was 58.7% with CR in 6.7%, VGPR in 17.3%, and PR in 34.7% of the patients. Among patients who received the doublet of pomalidomide and dexamethasone (n = 46), the ORR was 65.2%. The median time to best response was 3 months. There was no significant difference in the response rates according to ISS staging or high-risk cytogenetics.

**Survival Outcomes**

The median follow-up duration was 11 months. The median PFS of the whole group of patients who were included for analysis was 9.1 months (95% CI, 5.4 to 12.9) as given in Figure 1. The median OS was not reached.

Median PFS for patient with double-refractory (refractory to both bortezomib and lenalidomide) myeloma was 5.5 months versus 12.6 months in others (P = .039, hazard ratio [HR] 0.53, 95% CI 0.29 to 0.97, Fig 2). There was significant difference in 18-month survival for double-refractory myeloma versus nonrefractory, which was 55% and 80%, respectively (P = .025, HR 0.31, 95 CI 0.11 to 0.90).

The median PFS for patients who were lenalidomide refractory was 7.3 months, for high-risk cytogenetics 6.1 months, and among patients with age < 65 years and > 65 years—9 months and 6 months, respectively. The median PFS in patients treated with doublet (Pom dexa) was 10.3 months and in those treated with triplet combination was 5.3 months. However, since the cohort is small, accurate comparisons could not be made among the subgroups.

The median PFS was not reached in patients who achieved CR and VGPR, whereas it was 14 months (95% CI, 7.9 to 20 mg, P = .001) in patients with PR. The median PFS was 6.0 months in patients receiving 2 mg/3mg of pomalidomide and 24.8 months in those who received 4 mg daily-dose pomalidomide (P = .001, HR, 0.19, 95% CI, 0.07 to 0.50).

**Toxicity and Tolerability**

Toxicities seen with pomalidomide have been summarized in Table 3. Grade 3 or more hematologic toxicity was seen in around 30% of the patients, the most common being anemia in 23 patients. Thirteen patients (16%) had grade 3 or more neutropenia, and 15 (18.5%) had grade 3 or more thrombocytopenia. Among nonhematologic toxicities, fatigue of any grade (most common) was seen in 22 patients (27.2%), followed by pneumonia in 13 patients (16%). Peripheral neuropathy (any grade) was seen in nine patients (11%). Significant venous thromboembolism occurred in four patients—one of whom had coexisting diabetes, hypertension, and chronic kidney disease. Pomalidomide therapy was discontinued in six patients. The causes for discontinuation include pulmonary embolism (n = 4), grade 3 anemia (n = 1), and worsening peripheral neuropathy (n = 1). Dose reduction was done in three patients because of myelosuppression. Notably, no patient died because of toxicity. But, three patients died within one month of starting pomalidomide because of disease progression.

**DISCUSSION**

RRMM represents an unmet medical need and this is particularly challenging in our setup because of cost constraints. Here, we report outcomes in a large cohort of patients treated with pomalidomide-based regimen and demonstrate the utility and safety in our setting.

Generic pomalidomide has been available in India since mid-2017. This is a huge benefit for developing countries such as India, where affordability of the innovator brand (which costs around $900 for 21 capsules of 4 mg when compared with around $170 for generic) is low. With a huge cost difference and likely prolonged use of pomalidomide with more effective regimens such as Daratumumab-pom-

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**TABLE 2. Response Rates**

| Best Response | Response Rate—Entire Cohort (n = 75) | Response Rate—Doublet Cohort (n = 46) |
|---------------|-------------------------------------|--------------------------------------|
| Complete response | 5 (6.7%) | 3 (6.5%) |
| VGPR | 13 (17.3%) | 9 (19.6%) |
| PR | 26 (34.7%) | 18 (39.1%) |
| Minimal response | 4 (5.3%) | 3 (6.5%) |
| Stable disease | 4 (5.3%) | 1 (2.2 %) |
| Progressive disease | 23 (30.7%) | 12 (26.1%) |

Abbreviations: PR, partial response; VGPR, very good partial response.
The financial implications of use of generic molecule are likely to be important for Western patient populations or healthcare system as well.

ORR in our study was 65.2% among patients who received the doublet (pom dexa), which is higher than that observed in pivotal pomalidomide trials (31% in MM-003 and 32.6% in MM-010 trial) and other real-world studies from Australia, United Kingdom, and Poland. Median PFS in our study is 10.3 months (doublet cohort) in contrast with 4.0 and 4.6 months seen in MM-003 and MM-010 trials, respectively. Similarly, median OS is not reached in our study, whereas it was 13.1 months in the MM-003 trial and 11.9 months (doublet cohort) in the MM-010 trial.5 Real-world experience of pomalidomide from Australia showed a median PFS of 3.4 months and a median OS of 7.5 months, which was similar to the MM-003 and MM-010 trials.11 Similarly, a multicenter analysis from United Kingdom, which retrospectively studied about 70 patients, reported a PFS of 5.2 months and an OS of 13.7 months.12 The Polish myeloma group, which retrospectively analyzed 50 patients on pomalidomide, revealed a PFS and OS of 10 months and 14 months, respectively, which closely resembles our study results.13

The higher response rates and survival seen in our study when compared with the pivotal trials of pomalidomide therapy can be explained by the background difference in the study population and the treatment administered. The MM-003 study included patients only who failed treatment with both bortezomib and lenalidomide, have received prior alkylator therapy, and Eastern Cooperative Oncology Group performance status 0, 1, or 2; patients with creatinine clearance \( \leq 45 \text{ mL/min} \) were excluded from the MM-003 study.14
TABLE 3. Toxicity

| Toxicity                        | Number of patients (N = 81) |
|---------------------------------|-----------------------------|
| Anemia grade 3 or 4             | 23 (28.3%)                  |
| Fatigue, any grade              | 22 (27.2%)                  |
| Thrombocytopenia, grade 3 or 4  | 15 (18.5%)                  |
| Neutropenia, grade 3 or 4       | 13 (16%)                    |
| Pneumonia                       | 13 (16%)                    |
| Peripheral neuropathy, any grade| 9 (11.1%)                   |
| Venous thromboembolism          | 4 (4.9%)                    |
| Febrile neutropenia G3 or G4    | 3 (3.9%)                    |
| Diarrhea G3 or G4               | 3 (3.7%)                    |
| Renal failure                   | 3 (3.7%)                    |
| Atrial fibrillation             | 2 (2.6%)                    |

trial. However, in our study, around 13 patients (17.3%) never received lenalidomide because of renal failure (glomerular filtration rate < 30 mL/min), who would have been excluded in the MM 003 study, and median lines of prior therapy were three in the current study compared with five in MM-003. This could account for a higher response rates with pomalidomide in our study. Also, studies have shown that there is no significant difference in response rates in patients with or without poor renal function. Smaller number of double-refractory patients (60%) and lower number of prior ASCT (13.6% v 71% in MM-003) study are other possible explanations for the higher rates and PFS. Other differences with the MM-003 study include a lesser percentage of patients older than 65 years of age (37% v 45%). Pomalidomide was relatively well tolerated in our study population. Grade 3 or 4 hematologic or nonhematologic toxicities were seen in about 30% of cases as opposed to 60% in the MM-003 trial. This may be because of differences in patient selection. However, it may be more likely because of the use of 2 mg dose in more than half of our patients. The dosage of 4 mg has been criticized because of higher toxicity and reports of similar efficacy between 2 and 4 mg doses.14 In a study by Sehgal et al,15 which compared 2 mg versus 4 mg of pomalidomide, comparable response rates were observed between both the cohorts with higher toxicity (venous thromboembolism or myelosuppression) reported using 4 mg dosage in that cohort study.

The limitations of our study include its retrospective design and heterogeneous nature of treatment regimens, besides variation in the pomalidomide dose used. This is common in real-world studies and would predict outcomes in settings like ours than the registered studies on pomalidomide with strict eligibility criteria.

In conclusion, generic pomalidomide-based therapy is an effective option and is well tolerated in patients with RRMM. Higher response rates and longer survival seen in our study are possibly because of heterogeneity of the study population.

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