Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2020 February ; 20(2): 98–104.e1. doi:10.1016/j.clml.2019.09.618.

Adherence to lenalidomide in older adults with newly-diagnosed multiple myeloma

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Abstract

Introduction—One of the most common orally administered anti-myeloma agent, lenalidomide, has significantly improved outcomes in multiple myeloma, including in older patients. However, despite its utilization and cost, the rates and factors related to adherence to lenalidomide in older adults with newly-diagnosed multiple myeloma remain unknown.

Patients and Methods—Data from adults with newly-diagnosed multiple myeloma over age 65 being treated with lenalidomide therapy between the years 2007-2014 in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked databases was collected. Adherence was measured as Medication Possession Ratio (MPR), which was defined as the ratio of the number of days the patient had pills in their possession to the number of days in the observation period in the first year following myeloma diagnosis. MPR of <90% was considered poor adherence.

Results—A total of 793 patients were included in the analysis. The mean MPR in our cohort was $89.5 \pm 9.3\%$. Overall 38% (n = 302) of the patients were considered to have poor adherence. Factors associated with poor adherence included: increasing age (adjusted Odds Ratio (aOR) 1.03 per year, 95% confidence interval [CI] 1.00-1.05, p=0.024), black race (aOR 1.72, 95% CI 1.08-2.73, p=0.022), and polypharmacy (aOR 1.04 per medication, 95% CI 1.01-1.08, p=0.008).

Conclusion—Over one-third of older adults with newly-diagnosed multiple myeloma were considered to have poor adherence to lenalidomide, using the medication possession ratio as a surrogate for adherence. This highlights the need to further understand factors and devise strategies to support adherence in this patient cohort.

Microabstract

Lenalidomide is a common oral anti-myeloma therapy. Using the (SEER)-Medicare databases, our study of 793 patients demonstrated that over one-third of older adults with newly-diagnosed myeloma have poor adherence to lenalidomide. Increasing age, black race and polypharmacy were

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Previous Presentation: Poster Abstract, American Society of Hematology 2017

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further associated with poor adherence. This study highlights the need to further understand factors and devise strategies to support adherence.

Keywords

Multiple myeloma; aged; adherence; geriatric assessment; polypharmacy

Introduction

Multiple myeloma, the second most common hematologic malignancy, is a disease of aging, with a median age at diagnosis of 69, and a median age at death of 75. By 2034, 3 out of 4 patients diagnosed with multiple myeloma will be over age 65¹, each facing challenges that accompany aging, including comorbidities, polypharmacy, functional limitations, depression and cognitive changes.

Newer myeloma treatments have significantly improved overall survival over the past 20 years²⁻⁴. Although there remain many effective parenteral chemotherapy regimens, orally administered myeloma therapies are increasingly being used due to their perceived convenience, especially in older adults with myeloma. Oral anti-myeloma agents include traditional chemotherapeutic agents such as melphalan and cyclophosphamide, immunomodulatory agents thalidomide, lenalidomide and pomalidomide, and most recently the oral proteasome inhibitor ixazomib, in addition to numerous agents currently in clinical testing.

Despite the frequency of use, and its significant cost, little is known about the rates and factors related to adherence to lenalidomide. While previous retrospective studies using administrative databases have aimed to identify factors related to non-adherence to lenalidomide including hospitalizations and socioeconomic status^{5, 6}, no published studies have focused specifically on adherence rates and associated factors in older adults with myeloma. Adherence may be more problematic in older adults with myeloma given that in addition to the unique toxicities of the disease and its associated therapy, additional age-related factors (i.e. polypharmacy, cognitive impairment, and comorbidities) are more prevalent⁷. Consistent with this, the International Society of Geriatric Oncology has emphasized the urgent need to understand adherence and the associated factors in order to design future interventional studies aimed at improving adherence and ultimately patient outcomes in this age cohort⁷.

In this study, we aimed to estimate the rate of adherence of the most common orally administered anti-myeloma therapy, lenalidomide, using prescription refill data in a cohort of older adults with newly-diagnosed multiple myeloma in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked administrative database. We also aimed to investigate factors associated with poor adherence in order to identify older adults at highest risk for poor adherence.

Materials and Methods

Data Source

The data source for this study was the SEER-Medicare linked database which provides cancer registry data from 18 geographic areas covering approximately 28% of the US population and is linked to billing claims for Medicare beneficiaries⁸. This linked database contains information regarding patient demographics, tumour characteristics and survival for those with a cancer diagnosis who reside in the coverage area. This linked data source broadly represents the health care experience of older patients in the United States diagnosed with cancer and who are insured through traditional fee-for-service Medicare plans. This study was performed under a protocol approved by the Washington University School of Medicine Human Subject Committee.

Participants

Using the SEER-Medicare linked database, we identified older adults (age >65) with newly-diagnosed multiple myeloma (International Classification of Disease for Oncology [third edition] code 9732) diagnosed between the years 2007–2013 and who had received two or more prescriptions for lenalidomide within one year following multiple myeloma diagnosis. To limit the population to patients with newly diagnosed myeloma, only those with a lenalidomide prescription occurring within 60 days following diagnosis were included. Participant selection is detailed in Figure 1. Demographic and clinical characteristics collected included: age, gender, marital status, indicators of performance status⁹, Charlson Co-morbidity Index^{10, 11}, history of cognitive impairment (supplementary table S1), history of depression (supplementary table S1), polypharmacy (number of unique prescriptions within 90 days following diagnosis), Medicaid enrollment and low-income subsidy at time of myeloma diagnosis. We also collected the date of diagnosis, available disease characteristics, details of the lenalidomide prescriptions dispensed and overall survival.

Medication Possession Ratio

Currently, there is no single method considered as the “gold-standard” for measuring adherence both retrospectively or prospectively¹². Medication possession ratio (MPR), the number of days a patient has medication in their possession, is a surrogate for adherence that can be estimated using administrative data¹³. In this study, adherence was estimated from the database using the MPR, which was defined as ratio of the number of days the patient had pills in their possession to the number of days in the observation period (first prescription date through the last prescription in the first year following myeloma diagnosis). We limited the observation period to the first year following diagnosis to limit the number of individuals excluded due to shorter follow-up. We calculated a modified MPR as $[\text{Number of days supply}/(\text{last claim date} + \text{days supply} - \text{index date}) \times 100]$.

Because most lenalidomide-containing regimens incorporate a 7-day break, but not all claims reflect this (e.g. 21 pills were dispensed for a 21-day supply, but with a 7 day delay in the next dispensation), a “grace period” of 7 days was calculated in these instances in order to avoid underestimation of adherence. Discontinuation of lenalidomide treatment was assumed if there was a 70-day gap between dispensations, corresponding to a 6-week delay

following next anticipated dispensation. Poor adherence to lenalidomide was defined as MPR of < 90% consistent with other published studies including those in chronic myeloid leukemia where an adherence rate of less than 90% was associated with poor disease response^{14,15, 16}. We also calculated the MPR by the median number of prescriptions filled over time.

Statistical Analysis—Patient baseline demographic factors were described using measures of central tendency and proportions. To investigate factors associated with poor adherence (MPR < 90%), bivariate analyses and multivariable logistic regression was conducted. The association of poor adherence with overall survival was analyzed using Kaplan-Meier curves and log-rank test. P-values less than 0.05 were considered significant. All analyses were performed using SAS Enterprise Guide 5.1.

Results

A total of 793 older adults with multiple myeloma that met the inclusion criteria were included in the analysis dataset. The baseline characteristics of the patients are described in Table I. The median age was 73 (range 65–95), with 43% of the patients age 75 or older. Most patients had one or more comorbidities; 15.3% had indicators of poor performance status. There were high rates of polypharmacy, with the median number of medications, not including lenalidomide, being 10 (range 0–31) in our cohort. Many patients were affected by myeloma-related co-morbidities including anemia and renal impairment which were present in 60.3% and 39.1% of the patients, respectively. In our cohort, the median overall survival was approximately 4 years, consistent with published literature¹⁷. In terms of treatment, most patients received their first prescription for lenalidomide about 5 weeks following diagnosis (median 38 days) and filled a median of 8 prescriptions over one year. More than one-third of the patients remained on lenalidomide one year following diagnosis.

The results of the MPR analysis are shown in Table II. The mean MPR in our cohort was $89.5 \pm 9.3\%$. Overall, 38% ($n = 302$) of the patients were considered to have poor adherence (defined as MPR < 90%). Only 7% of the patients ($n = 57$) had an MPR of 100%, suggesting perfect adherence. Generally, the mean MPR tended to improve over the span of the year, as the median number of prescription refills increased ranging from 78.7% for those with two prescriptions and 89.9% for those with five or more prescriptions filled ($p < 0.001$). While there was a trend for inferior overall survival among those with poor adherence (HR 1.10; 95% CI 0.88–1.38), it was not statistically significant.

On multivariate analysis, factors significantly associated with poor adherence (defined by MPR < 90%) are shown in Table III. Factors included age (adjusted Odds Ratio [aOR] 1.03 per year, 95% confidence interval [CI] 1.00–1.05, $p = 0.024$), black race (aOR 1.72, 95% CI 1.08–2.73, $p = 0.022$), and polypharmacy (aOR 1.04 per unique prescription, 95% CI 1.01–1.08, $p = 0.008$). Factors that were not significantly associated with poor adherence included gender, other race, performance status indicator, overall Charlson Co-morbidity Index, history of depression, history of cognitive impairment, low-income subsidies or Medicaid enrollment. Additionally, while each increase in Charlson comorbidity index score was associated with poor adherence (aOR 1.09; 95% CI 1.00–1.20), this relationship was not

statistically significant in the multivariate model, likely due to covariance between it and other measures including age, poor performance status, and polypharmacy.

DISCUSSION

In our cohort of 793 older adults with newly-diagnosed multiple myeloma, we found a mean medication possession ratio of 89.5%, suggesting that adherence was suboptimal, with 38% of the patients considered to have poor adherence. Only 7% of the patients had a medication possession ratio of 100%, without any delayed refills. Factors found to be significantly associated with lower medication possession ratio were increasing age, black race, and polypharmacy.

While most adherence studies have focused on older adults with chronic conditions, they may not always be applicable to older adults with cancer, who are also influenced by disease and treatment-related factors, health related quality-of-life impairment and overall decreased tolerance to medical interventions⁷. A systematic literature review in patients of all ages and in those over age 65 showed that adherence in oncology varies from 46 to 100% depending on the patient sample, medication type, follow-up period, assessment measure, and calculation of adherence^{18, 19}. In myeloma specifically, there is a paucity of data with regards to adherence in older patients and our study is the first to report both the rates and the associated factors linked to adherence in this age cohort.

In our study, the mean MPR was 89.5%, with 38% of patients considered to have poor adherence using an MPR cut off of 90%. This is consistent with a large retrospective study of over 6700 patients of all ages with myeloma enrolled in a dispensing program at a specialty pharmacy which also showed an average MPR of 85% for lenalidomide²⁰. A similar study using another database with over 7600 patients demonstrated that approximately 25% were considered to have poor adherence; however, a lower MPR cut off of 80% was used to define nonadherence, and the participants were likely younger given that this analysis was performed among individuals with commercial insurance.⁶ Lastly, a recent single center prospective study of 63 patients conducted in France showed that adherence rates greatly differed depending upon the measurement method¹⁵. Self-reported questionnaire non-adherence rates were 24%; however, if an MPR cut off of 90% alone was used, only a small fraction of patients (6%) were considered to be non-adherent. Due to the prospective nature of this study, the authors were able to ascertain the exact reasons for discontinuation and subsequently account for it in the MPR calculation, potentially leading to a lower non-adherence rate. These studies highlight the variability in understanding adherence rates among different subgroup of patients using different adherence measurement and study designs.

With regards to variables associated with adherence in our cohort of older adults with myeloma, increasing age was found to be associated with adherence. This is in contrast to the study done by Leng *et al.* where gender and age had no effect on lenalidomide adherence⁶. This discrepancy may be partially explained by the difference in the population cohorts as the study by Leng *et al.* included all patients with myeloma over age 18, whereas our study only focused on individuals over the age of 65. Increasing age may be associated with the

additive effect of accumulated age-associated vulnerabilities in older patients potentially leading to poor adherence. Although the link between age and adherence is variable in the literature, many previous studies have shown results similar to our study, with increasing age, particularly over age 75, associated with decreasing adherence rates^{19, 21–23}.

Consistent with our results, the influence of race and polypharmacy have also been documented as variables associated with poor adherence. In non-oncology studies of adherence, there is literature to support an association between non-adherence and race²⁴, although variability exists, which is reflective of the heterogeneity in both methodology and in the measurement of adherence between studies²⁵. In myeloma, specifically, racial disparity has been known to affect the utilization of therapeutic modalities, with African-Americans noted to have significantly lower rates of lenalidomide usage²⁶. Although the exact reasons for the disparity of therapeutic modalities among different group remains to be determined, some studies suggest that racial differences in multiple myeloma outcomes may be mitigated by access to better therapeutic agents including clinical trials²⁷. Our study highlights another potential area of improvement in the care of patients in specific racial subgroups by understanding the rates, factors and strategies for optimal adherence.

Polypharmacy is another variable which has been linked to adherence in older patients²⁸ and those with co-morbidities take an average of 6 medications per day and that number is felt to be higher in cancer patients^{29, 30}. Consistent with other studies^{31, 32}, the mean number of medications in our study was high, with the median being approximately 10 medications. Increasing number of concomitant medications has been associated with poorer adherence in a number of chronic conditions^{33, 34, 35, 36}; however, in other populations, including those with stroke³⁷ or mild cognitive impairment³⁸, polypharmacy has not always been a significant factor in adherence. There may also be a differential effect of polypharmacy on adherence based on the types and number of concomitant medications^{39, 40}. These studies underscore the fact that determinants of adherence may differ across conditions and at different time points.

Utilizing the World Health Organization framework for medication adherence⁴¹, multiple other factors related to adherence in older adults undergoing cancer treatment have been described which include patient-related factors (marital status⁴², co-morbidities, cognition²², depression^{43, 44} therapy-related factors (regimen duration/complexity^{23, 43, 45}, side effects^{46, 47}), disease-related symptoms⁴⁸, health system related factors (clinic wait times⁴⁹) and socioeconomic factors (costs/subsidies^{5, 21}). Interestingly, in our study we did not find an association between a history of cognitive impairment or depression, two geriatric domains commonly associated with poor adherence²². This likely reflects the under-recognition of these syndromes in routine oncology practice and subsequent undercoding into an administrative database. Additionally, a relationship between co-morbidities and adherence was also not found in our model reflecting the interdependence between variables. Given the paucity of the data and the heterogenous ways in which studies are conducted and adherence is defined, many of these factors are not consistently found throughout each study, emphasizing the need to conduct well-designed studies in different population groups in order to understand the unique factors linked to adherence in each subgroup of cancer patients.

In our cohort, we found that the medication possession ratio varied based on how many prescription refills were obtained during the study period, with the lowest medication possession ratio when only two prescriptions were obtained and the rates of improving adherence with five or more prescriptions. Although, we are unable to ascertain the exact reasons for lower MPR for patients with fewer prescriptions, hematological and non-hematological toxicity has been shown to be a major determinant of early discontinuation of lenalidomide, whereas disease progression is associated with drug discontinuation in the long-term⁵⁰. This finding of dynamic adherence in our study highlights the different patterns of adherence that can exist among and within the same patients at different time points in the disease trajectory⁵¹.

Several limitations of our study must be acknowledged. Using a retrospective administrative database for calculation of the medication possession ratio may not accurately reflect adherence, as the reason for there being days where the patient was not in possession of medication are unknown. We may underestimate adherence if lenalidomide was held at the instructions of the clinical team due to toxicity or the refill delayed due to close monitoring of laboratory parameters prior to dispensing, which may be particularly important when the medication is first initiated. We may also overestimate adherence if the patient is in possession of the medication but does not actually take it. Other retrospective methods for measuring adherence, such as questionnaires, are also at risk for recall bias and may not accurately reflect adherence, with poor concordance found between medication possession ratio and specific adherence questionnaires¹⁵. While our study did capture many demographic and baseline factors, we did not have access to any myeloma-specific factors such as the stage or cytogenetics, therapy-related toxicities or patient-reported outcomes, which may also influence adherence. Some of the factors included may underestimate true prevalence in the population. For example, bone disease was present in 35% of the study population as claims for fractures are the only indicator available. Additionally, although the effect of poor adherence on inferior disease-related outcomes has been shown in other hematological malignancies including chronic myeloid leukemia^{14, 23}, the effect of adherence rates on response rates and progression-free survival could not be determined from our study as these outcomes are not available in this administrative data set. We did not find a statistically significant relationship between the medication possession ratio and overall survival; however, this does not necessarily preclude a relationship between poorer adherence and disease-related outcomes, as a relationship may have been obscured by other reasons for holding the medication and possession does not ensure adherence.

In conclusion, our study is the first to focus on the impact of aging-associated factors on medication possession ratio as a surrogate for adherence rates in older patients with multiple myeloma taking the most commonly-utilized anti-myeloma therapy lenalidomide. Currently, there is no routine monitoring of adherence in older adults taking oral anti-myeloma therapy and no systematic means to screen for individuals at greater risk for non-adherence. Our study highlights the suboptimal adherence in older patients with myeloma and specific modifiable risk factors, such as polypharmacy, which may place patients at higher risk for non-adherence. Additionally, our study emphasizes the need for both better clinical monitoring of adherence and for future prospective studies in accurately understanding the

rates and predictors of adherence while simultaneously developing strategies for improving adherence for patients that are at high risk of non-adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources/Disclaimer: This research was made possible by Grant Number K12CA167540 through the National Cancer Institute (NCI) at the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. The Center for Administrative Data Research is supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR002345 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) and Grant Number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ).

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, National Cancer Institute; the Office of Research, Development and Information, Centers for Medicare & Medicaid Services; Information Management Services Inc; and the SEER program tumor registries in the creation of the SEER-Medicare database.

References

1. Rosenberg PS, Barker KA, Anderson WF. Future distribution of multiple myeloma in the United States by sex, age, and race/ethnicity. *Blood*. 2015;125:410–412. [PubMed: 25573972]
2. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood advances*. 2017;1:282–287. [PubMed: 29296944]
3. Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. *Leukemia*. 2017;31:1915–1921. [PubMed: 28008176]
4. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28:1122–1128. [PubMed: 24157580]
5. Olszewski AJ, Dusetzina SB, Eaton CB, Davidoff AJ, Trivedi AN. Subsidies for Oral Chemotherapy and Use of Immunomodulatory Drugs Among Medicare Beneficiaries With Myeloma. *J Clin Oncol*. 2017;35:3306–3314. [PubMed: 28541791]
6. Leng S, Lentzsch S, Chen Y, et al. Factors associated with non-adherence to lenalidomide in patients with multiple myeloma. 2018;36:e20031–e20031.
7. Mislang AR, Wildes TM, Kanavaras R, et al. Adherence to oral cancer therapy in older adults: The International Society of Geriatric Oncology (SIOG) taskforce recommendations. *Cancer treatment reviews*. 2017;57:58–66. [PubMed: 28550714]
8. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40:IV–3–18.
9. Griffiths RI, Gleeson ML, Mikhael J, Danese MD. Impact on Medical Cost, Cumulative Survival, and Cost-Effectiveness of Adding Rituximab to First-Line Chemotherapy for Follicular Lymphoma in Elderly Patients: An Observational Cohort Study Based on SEER-Medicare. *J Cancer Epidemiol*. 2012;2012:978391. [PubMed: 22969803]
10. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *Journal of clinical epidemiology*. 2000;53:1258–1267. [PubMed: 11146273]
11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology*. 1992;45:613–619. [PubMed: 1607900]

12. Huang WC, Chen CY, Lin SJ, Chang CS. Medication adherence to oral anticancer drugs: systematic review. *Expert Rev Anticancer Ther.* 2016;16:423–432. [PubMed: 26935964]
13. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf.* 2006;15:565–574; discussion 575–567. [PubMed: 16514590]
14. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol.* 2010;28:2381–2388. [PubMed: 20385986]
15. Cransac A, Aho S, Chretien M-L, Giroud M, Caillot D, Boulin M. Adherence to immunomodulatory drugs in patients with multiple myeloma. *PLOS ONE.* 2019;14:e0214446. [PubMed: 30917164]
16. Daouphars M, Ouvry M, Lenain P, et al. Preliminary validation of self-assessment tool to measure imatinib adherence in patients with chronic myeloid leukemia. *Pharmacotherapy.* 2013;33:152–156. [PubMed: 23359430]
17. Blimark CH, Turesson I, Genell A, et al. Outcome and survival of myeloma patients diagnosed 2008–2015. Real-world data on 4904 patients from the Swedish Myeloma Registry. *Haematologica.* 2018;103:506–513. [PubMed: 29217784]
18. Greer JA, Amoyal N, Nisotel L, et al. A Systematic Review of Adherence to Oral Antineoplastic Therapies. *Oncologist.* 2016;21:354–376. [PubMed: 26921292]
19. Puts MT, Tu HA, Tourangeau A, et al. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. *Ann Oncol.* 2014;25:564–577. [PubMed: 24285020]
20. Lee C, Grigorian M, Nolan R, Binder G, Rice G. A retrospective study of direct cost to patients associated with the use of oral oncology medications for the treatment of multiple myeloma. *J Med Econ.* 2016;19:397–402. [PubMed: 26652728]
21. Winn AN, Keating NL, Dusetzina SB. Factors Associated With Tyrosine Kinase Inhibitor Initiation and Adherence Among Medicare Beneficiaries With Chronic Myeloid Leukemia. *J Clin Oncol.* 2016;34:4323–4328. [PubMed: 27998234]
22. Klepin HD, Geiger AM, Bandos H, et al. Cognitive factors associated with adherence to oral antiestrogen therapy: results from the cognition in the study of tamoxifen and raloxifene (Co-STAR) study. *Cancer Prev Res (Phila).* 2014;7:161–168. [PubMed: 24253314]
23. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood.* 2009;113:5401–5411. [PubMed: 19349618]
24. Xie Z, St Clair P, Goldman DP, Joyce G. Racial and ethnic disparities in medication adherence among privately insured patients in the United States. *PLoS One.* 2019;14:e0212117. [PubMed: 30763400]
25. Gerber BS, Cho YI, Arozullah AM, Lee SY. Racial differences in medication adherence: A cross-sectional study of Medicare enrollees. *Am J Geriatr Pharmacother.* 2010;8:136–145. [PubMed: 20439063]
26. Ailawadhi S, Frank RD, Advani P, et al. Racial disparity in utilization of therapeutic modalities among multiple myeloma patients: a SEER-medicare analysis. *Cancer Med.* 2017;6:2876–2885. [PubMed: 29105343]
27. Ailawadhi S, Jacobus S, Sexton R, et al. Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials. *Blood Cancer J.* 2018;8:67. [PubMed: 29980678]
28. Banning M Older people and adherence with medication: a review of the literature. *Int J Nurs Stud.* 2008;45:1550–1561. [PubMed: 18395727]
29. Reason B, Turner M, Moses McKeag A, Tipper B, Webster G. The impact of polypharmacy on the health of Canadian seniors. *Family Practice.* 2012;29:427–432. [PubMed: 22223743]
30. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. *J Geriatr Oncol.* 2016;7:346–353. [PubMed: 27498305]
31. Nightingale G, Hajjar E, Guo K, et al. A pharmacist-led medication assessment used to determine a more precise estimation of the prevalence of complementary and alternative medication (CAM)

use among ambulatory senior adults with cancer. *J Geriatr Oncol.* 2015;6:411–417. [PubMed: 26277113]

32. Hanigan MH, Dela Cruz BL, Thompson DM, Farmer KC, Medina PJ. Use of prescription and nonprescription medications and supplements by cancer patients during chemotherapy: questionnaire validation. *J Oncol Pharm Pract.* 2008;14:123–130. [PubMed: 18719067]
33. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabet Med.* 2002;19:279–284. [PubMed: 11942998]
34. Vetrano DL, Bianchini E, Onder G, et al. Poor adherence to chronic obstructive pulmonary disease medications in primary care: Role of age, disease burden and polypharmacy. *Geriatr Gerontol Int.* 2017;17:2500–2506. [PubMed: 28656664]
35. Calabria S, Cinconze E, Rossini M, et al. Adherence to alendronic or risedronic acid treatment, combined or not to calcium and vitamin D, and related determinants in Italian patients with osteoporosis. *Patient Prefer Adherence.* 2016;10:523–530. [PubMed: 27143860]
36. Calderon-Larranaga A, Diaz E, Poblador-Plou B, Gimeno-Feliu LA, Abad-Diez JM, Prados-Torres A. Non-adherence to antihypertensive medication: The role of mental and physical comorbidity. *Int J Cardiol.* 2016;207:310–316. [PubMed: 26814635]
37. Polymeris AA, Traenka C, Hert L, et al. Frequency and Determinants of Adherence to Oral Anticoagulants in Stroke Patients with Atrial Fibrillation in Clinical Practice. *Eur Neurol.* 2016;76:187–193. [PubMed: 27705975]
38. Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community? *Eur J Clin Pharmacol.* 2001;57:589–594. [PubMed: 11758637]
39. Calip GS, Xing S, Jun DH, Lee WJ, Hoskins KF, Ko NY. Polypharmacy and Adherence to Adjuvant Endocrine Therapy for Breast Cancer. *J Oncol Pract.* 2017;13:e451–e462. [PubMed: 28287854]
40. Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat.* 2006;99:215–220. [PubMed: 16541307]
41. Adherence to Long-Term Therapies: Evidence for Action (Chronic disease and health promotion) World Health Organization. Accessed April 8, 2019 https://www.who.int/chp/knowledge/publications/adherence_report/en/.
42. Barcenas CH, Zhang N, Zhao H, et al. Anthracycline regimen adherence in older patients with early breast cancer. *Oncologist.* 2012;17:303–311. [PubMed: 22371383]
43. Bender CM, Gentry AL, Brufsky AM, et al. Influence of patient and treatment factors on adherence to adjuvant endocrine therapy in breast cancer. *Oncol Nurs Forum.* 2014;41:274–285. [PubMed: 24769592]
44. Berry DL, Blonquist TM, Hong F, Halpenny B, Partridge AH. Self-reported adherence to oral cancer therapy: relationships with symptom distress, depression, and personal characteristics. *Patient Prefer Adherence.* 2015;9:1587–1592. [PubMed: 26604712]
45. Timmers L, Boons CC, Kropff F, et al. Adherence and patients' experiences with the use of oral anticancer agents. *Acta Oncol.* 2014;53:259–267. [PubMed: 24266637]
46. Guth U, Myrick ME, Schotzau A, Kilic N, Schmid SM. Drug switch because of treatment-related adverse side effects in endocrine adjuvant breast cancer therapy: how often and how often does it work? *Breast Cancer Res Treat.* 2011;129:799–807. [PubMed: 21750963]
47. Winterhalter R, Hoesli P, Delmore G, et al. Self-reported compliance with capecitabine: findings from a prospective cohort analysis. *Oncology.* 2011;80:29–33. [PubMed: 21606661]
48. Jacobs JM, Ream ME, Pensak N, et al. Patient Experiences With Oral Chemotherapy: Adherence, Symptoms, and Quality of Life. *J Natl Compr Canc Netw.* 2019;17:221–228. [PubMed: 30865917]
49. Shaheen JA, Amin M, Harty JJ. Patient compliance in treatment of prostate cancer with luteinizing hormone-releasing hormone (LHRH) agonist. *Urology.* 1993;42:533–535. [PubMed: 8236595]
50. Pistone A, Maerevoet M, Wittnebel S, et al. Early Discontinuation of Lenalidomide in Patients with Relapsing or Refractory Multiple Myeloma: Predictive Factors for Stopping in the Real Life. *Blood.* 2016;128:4504–4504.

51. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51:789–796. [PubMed: 23685406]

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Figure 1:
Selection of the Study Cohort

Table I:

Baseline characteristics of 793 older adults with newly diagnosed multiple myeloma receiving lenalidomide prescriptions within 1 year of diagnosis

Demographics	(N=793)
Age, years (median, range)	73 (65–95)
75	340 (43%)
Gender	
Female	384 (48.4%)
Male	409 (51.6%)
Ethnicity	
Caucasian	643 (81.1%)
Black	102 (12.9%)
Other	48 (6.1%)
Marital Status	
Married	472 (64.2%)
Divorced/Widowed/Other	263 (35.8%)
Unknown	58 (7.3%)
Medicaid enrollment	188 (23.7%)
Low income subsidy	77 (9.7%)
Comorbidity/Performance Status Indicators	
Charlson Comorbidity Index	
0	324 (40.9%)
1–2	183 (23.1%)
>2	286 (36.1%)
Poor Performance Status Indicator	121 (15.3%)
Cognitive impairment	35 (4.4%)
Depression	161 (20.3%)
Polypharmacy (median, range for number of medications)	10 (0–31)
Disease characteristics	
Myeloma-related Renal Impairment	310 (39.1%)
Myeloma-related Anemia	478 (60.3%)
Myeloma-related Bone disease	281 (35.4%)
Treatment characteristics	

Demographics	(N=793)
Time from diagnosis to first lenalidomide prescription (days, median, range)	38 (−22 – 60) *
Number of lenalidomide prescriptions (median, range)	8 (2–16)
Lenalidomide usage at 1-year mark	302 (38%)
Overall Survival (months, median, 95% confidence intervals)	47.1 (45.0–53.0)

* Date of lenalidomide prescription may precede date of myeloma diagnosis due to database nuances

Table II:

Medication Possession Ratio results for the cohort by number of prescriptions filled

Cohort	Mean MPR (Range)
Entire Cohort (N=793)	89.5 (43–100)
Prescriptions	
2	78.7 (61–97)
3	88.1 (43–100)
4	91.5 (58–100)
5	89.9 (52–100)

MPR, medication possession ratio

Table III:

Multivariate logistic regression variables for predicting poor adherence (MPR<90%)

Demographics	aOR^a	95% Confidence Interval	P-value^b
Age (per year)	1.03	1.00–1.05	0.024
Gender			
Female	0.86	0.63–1.16	0.321
Race			
Black	1.72	1.08–2.73	0.022
Other	0.99	0.52–1.86	0.984
Medicaid Enrollment	1.28	0.88–1.86	0.191
Low Income Subsidy	1.42	0.87–2.31	0.154
Co-morbidities/Functional Status			
Charlson Co-morbidity Index (per increase)	0.99	0.87–1.10	0.791
Poor performance status indicator	0.97	0.63–1.48	0.876
Cognitive Impairment	1.19	0.58–2.41	0.632
Depression	1.07	0.73–1.55	0.742
Polypharmacy (per medication)	1.04	1.01–1.08	0.008

^aAdjusted odds ratio reflects adjustment for all covariates listed in the table^bLikelihood ratio test

MPR, medication possession ratio; aOR, adjusted odds ratio