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Adherence to and effectiveness of lenalidomide after 1 year of treatment in a real world setting

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Abstract

Background: In combination with dexamethasone, lenalidomide is prescribed in the oral treatment of Multiple Myeloma for patients who have received at least one previous therapy.
Objective: The objective of this study is to evaluate medication adherence to lenalidomide of Multiple Myeloma patients, as well as Progression Free Survival and Overall Survival one year from the beginning of the treatment.
Setting: The study was carried out in Pescara Hospital, in Italy. All Multiple Myeloma patients who began lenalidomide therapy between January 1, 2012 and June 30, 2016 were included in our study.
Methods: Adherence to treatment was calculated by using the ratio between the Received Daily Dose and the Prescribed Daily Dose. Effectiveness in real world has been evaluated as Progression Free Survival and Overall Survival one year from the beginning of the treatment.
Main outcomes measure: We assessed medication adherence and effectiveness of lenalidomide in the treatment of Multiple Myeloma.
Results: Adherence to the overall mean treatment was 0.73 ± 0.15, relative to 81 patients evaluated in our study. 32% of patients achieved an adherence equal to or greater than 80%. Real-life effectiveness in terms of Progression Free Survival and Overall Survival showed values of 53.75% and 88%, respectively, one year from the beginning of treatment.
Conclusion: The analysis of adherence in Multiple Myeloma patients treated with lenalidomide one year from the beginning of therapy reveal a concerning lack of adherence. Moreover, the lack of correlation of the levels of adherence with patient-related variables shows that, in the case of Multiple Myeloma, adherence is not related to personal, social and environmental characteristics that may determine each patient's correct treatment implementation, but is directly influenced by disease evolution.

Keywords

Medication adherence, multiple myeloma, lenalidomide, real-life analysis, effectiveness

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Introduction

Multiple Myeloma (MM) is the most common plasma cell dyscrasia, with about 86,000 new cases diagnosed per year in the world[1] and an annual incidence in Italy of 8 cases per 100,000 inhabitants.[2] Doxorubicin, bortezomib, thalidomide, lenalidomide, pomalidomide,carfilzomib, ixazomib, panobinostat, daratumumab and elotuzumab are the latest treatments available for MM therapy, together with stem cell transplantation.[3–5] In particular, in combination with dexamethasone,

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oral lenalidomide therapy is prescribed to MM patients who have received at least one previous therapy.[6] The efficacy of lenalidomide has been evaluated in several phase III studies, in patients with newly diagnosed and relapsed MM, with increased Progression Free Survival (PFS), 11.3 months vs. 4.7 months,[7] Overall Survival (OS), 29.6 months vs. 20.2 months,[8] and clinical response compared to placebo.[9,10] Adherence to medications is defined as "the process by which patients take their medications as prescribed".[11]

The role of medication adherence to home oral therapies is widely studied and recognized; indeed, good patient adherence to a medical prescription increases the percentage of therapeutic success, leading to a reduction of health costs, morbidity and mortality.[12,13] The crucial role of treatment adherence has also been investigated in oral oncological therapies by demonstrating that the greater treatment adherence is, the greater the chance that the patient reacts well to the treatment.[14–17] Unlike intravenous therapy, whose administration is under the control of doctors and nurses, oral therapy involves patients' commitment for the entire duration of treatment to complying with the instructions provided by physicians.[18–20] Regarding oral cancer therapy, it has been estimated that about 39% of patients take the wrong dose, 10% forget one or more doses, 13.6% take the wrong drug and 11% does not comply with the duration of therapy.[21,22] These data underscore how medication adherence is a matter of great importance for public health.[23,24] It is generally accepted that the threshold-value of medication adherence that distinguishes an adherent from a non-adherent patient is 80%; as a result, a loss of 20% of adherence is tolerable in order to obtain a clinical response.[25] Lenalidomide is administered according to a particular regimen; namely, it is taken once a day for a period of 21 days, followed by 7-day suspension, for a cycle of 28 days.[26]

Aim of the study

The objective of this study is to evaluate medication adherence to lenalidomide of MM patients in the relapsed setting after at least one previous therapy, as well as Progression Free Survival (PFS) and Overall Survival (OS) one year from the beginning of the treatment.

Ethics approval

The study entitled MedAMyelo was authorized by the Internal Committee of Department of Hematology - Pescara General Hospital. According to Italian regulatory provisions in force, the Informed Consent form was not required, since the information we evaluated in this study does not interfere in any way with clinical practice and does not influence doctor and patient, but relied on data collected during standard daily practice.

Methods

The retrospective study was carried out in the Pharmacy and Hematology Units of the Pescara Hospital, in Italy. All MM patients who began lenalidomide therapy between January 1, 2012 and June 30, 2016 were included in our study. The accepted practice in MM treatment is to enter patients' data in a hospital's database (Pharmadd.it), including: age, sex, disease, disease stage at time zero (T0) according to the Durie-Salmon classification and the International Staging System (ISS) score,[27] treatment line, dose prescribed by the doctor, dose dispensed at the time of refill, and clinical response according to the IMWG (International Myeloma Working Group) classification,[28] which provides for the classification of the clinical response in Partial Response (PR), Very Good Partial Response (VGPR), Complete Response (CR), Stability Disease (SD), Progressive Disease (PD). The date of death, if applicable, is also added in order to estimate the Overall Survival. We assessed medication adherence and effectiveness on the basis of recorded data. Medication adherence was calculated for each patient using the ratio between the Received Daily Dose (RDD) and the Prescribed Daily Dose (PDD), by reviewing drug dose information, (PDD) we were able to adequately evaluate all drug dose change and patient behavior in accordance with physicians' prescriptions. PDD values are not surrogates but represent all dosage changes performed by clinicians for any reason. Precisely for this reason, the RDD/PDD ratio is a reliable method for calculating adherence. The daily dose (RDD) is calculated as the dose received at the time of refill divided by the interval of days that elapse until the next refill. The RDD is calculated on every individual range, that is, every time the patient collect the drug and until the suspension of the treatment. The calculation is performed starting from the second dispensation onwards and then renewed at each dispensation following the second one. Practically, by dividing the total dose dispensed to the patient by the days of coverage between two successive date ranges. The PDD is the interpretation of prescription and is calculated by taking into account every individual range. In the particular case of lenalidomide, the withdrawal period of 7 days after 21 days of treatment is considered in the calculation by distributing the total dose of a drug pack across 28 days. For example, for a pack of 25 mg, the calculations hall be performed by multiplying 21 capsules by 25 mg across 28 days of treatment. By dividing the total dose contained in a

pack, 525 mg, across 28 days, you will get the proper dosage prescribed by a clinician. A similar calculation was also performed for 15, 10 and 5-mg dosages.

As a result, matching between RDD and PDD indicates optimal adherence between what was prescribed by the doctor and what was taken by the patient; the lower the ratio, the least faithfully a patient followed his/her doctor's instructions.[29] Adherence values between 0 and 1 were stratified according to gender, age, treatment line and disease staging. OS and PFS were estimated one year after the start of treatment; effectiveness was assessed according to the IMWG scale. For the construction of the PFS curve, we considered patient who experience disease progression (PD). All recorded data were processed anonymously.

Statistical analyses

Adherence was assessed using the RDD/PDD ratio directly calculated by the software, named pharmadd. it, as a weighted RDD average on day intervals by single patient. The relationship between OS and PFS with potentially predictive variables (adherence to therapy after 1 year from start, sex, age, ISS and Durie-Salmon) was investigated by applying two Multivariate Cox regression analysis models. We assessed the relationship between the IMGW response criteria and adherence to 1-year therapy by relying on the Spearman's rank correlation coefficient. All statistical analysis was performed by SPSS 18.0. The threshold for statistical significance was set at 0.05.

Results

We considered 81 patients; the sample characteristics are shown in Table 1; The average patient adherence was 0.73 ± 0.15, with values ranging from a minimum of 0.3 to a maximum of 1; 26 patients (32%) achieved treatment adherence rates equal to or greater than 0.8. 4 patients had adherence <= of 0.5, 11 patients between 0.51 and 0.6, 22 patients between 0.61 and 0.7, 18 patients between 0.71 and 0.8, 15 patients between 0.8 and 0.9 and 11 patients greater than 0.9, 5 of these patients were completely adherent to treatment. The stratified adherence rates for gender, age, treatment line and baseline staging variables did not show significant differences. (Table 2). No difference in adherence media rates between different subgroups of the sample yielded a statistically significant difference; the main difference is found in patients with different treatment line. Indeed, second-line patients showed a rate of adherence equal to 0.76, and fifth- and seventh-line patient scoring 0.72, 0.65 and 0.63, respectively ($p = 0.06$). One year after the start of therapy, 8 of 81 patients (10%) died. According to IMWG criteria, 38 patients (47% of the sample) experienced disease progression (PD), 6 patients (7%) had stable disease (SD), 17 patients (21%) had partial response (PR), 8 patients (10%) had a VGPR, and 12 patients (15%) had a complete response (CR), as shown in Table 3. Real world effectiveness in terms of PFS and OS were 53.75% and 89.3%, respectively, one year

Table 1. Baseline characteristics.

Baseline characteristics	N = 81
Age (years) (mean ± SD)	70.8 ± 8.5
Age > 65	64 (79%)
Sex, male	36 (44%)
Treatment line	
II	37 (46%)
III	25 (31%)
IV	13 (16%)
V	5 (6%)
VII	1 (1%)
International staging system score (ISS)	
1	38 (47%)
2	27 (33%)
3	16 (20%)
Durie Salmon stage	
I	10 (12%)
II	15 (19%)
III	56 (69%)

Table 2. Adherence to Lenalidomide.

Subgroup	
-Total (SD)	0.73 (0.15)
-Adherence Higher than 80%, %	32%
Adherence ≤ 0.5 n. pt, (%)	4 (5)
Adherence between 0.51 and 0.6 n. pt (%)	11 (14)
Adherence between 0.61 and 0.7 n. pt (%)	22 (28)
Adherence between 0.71 and 0.8 n. pt (%)	18 (22)
Adherence between 0.81 and 0.9 n. pt (%)	15 (19)
Adherence ≥ 0.91 n. pt (%)	11 (13)
- Men	0.74
- Women	0.73
- > 65 years	0.74
- < 65 years	0.69
- ISS I	0.73
- ISS II	0.71
- ISS III	0.73
- Durie-Salmon IA	0.72
- Durie-Salmon IIA	0.8
- Durie-Salmon IIIA	0.71
- II line	0.76
- III line	0.72
-IV line	0.72
-V line	0.65
- VI line	0.63

Table 3. Clinical outcomes at 1 year.

Clinical outcomes	
Response to therapy	% patients
Disease progression	47
Stable disease	7
artial response	21
Very good partial response	10
Complete response	15
Progression-free survival	
Mean n. of days (SD)	253 (98)
Equal to 365 days, %	53.7
Overall survival	
Mean n. of days (SD)	352 (41)
Equal to 365 days, %	89.3

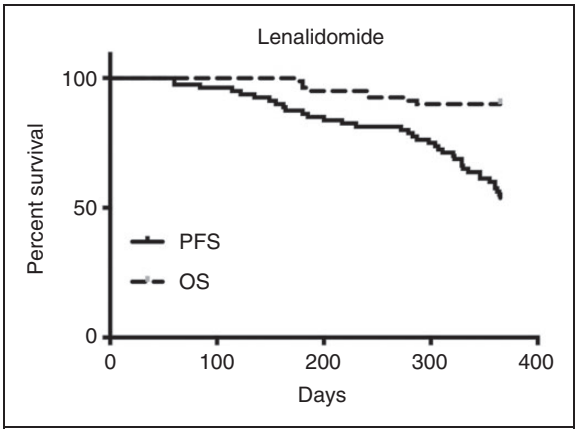

Figure 1. PFS and OS for Lenalidomide in the treatment of MM.

from the beginning of treatment. (Figure 1) The correlation between clinical outcome according to IMWG criteria and adherence did not reach statistical significance (Spearman's rho = −0.06, p = 0.961). The Cox regression model for PFS was not statistically significant (p = 0.205), whereas the Cox regression for OS yielded a significant result (p = 0.041) only in relation to treatment adherence, and not in relation to other variables (Table 4). We analyzed the dosage variations as indicated by the clinician, providing the number and % of patients whose dosages did not change since the original prescription, and those whose dosages were modified during treatment, with 68% of patients (n = 55) being prescribed 25 mg; 11% (n = 9) 15 mg; 20% (n = 16) 10 mg; and, 1% (n = 1) 5 mg. 16% of patients changed their dose. This analysis was performed to distinguish patients who did not changed the drug dose compared to those who changed the prescription during the first year of treatment with lenalidomide.

Table 4. Overall Survival correlations.

Results of Cox regression model for OS	p-value
Gender	0.504
Durie-Salmon	0.559
ISS	0.419
1-year adherence to therapy	0.041
Age	0.772

Discussion

Adherence data is a quantitative measure in that it describes how the patient interprets therapy in terms of intake compared to what is prescribed. The choice to use the relationship between RDD/PDD as a calculation method for adherence is justified by the opportunity to have these two indexes available to calculate adherence for each single interval and measure the patient on the actual days of treatment. All the methods of analysis have limitations, but in the case of retrospective observational studies, patients' questionnaires cannot be applied and present other limitations.[30] Indeed, today the trend is the sum of two methods in order to provide a comparison, minimize the limitations of each method and offer data that are as straightforward as possible.[31] The influence of adverse reactions on adherence is a key aspect, and must be necessarily considered in calculating adherence. A non-adherent patient is the patient who developed an adverse reaction which prevented him from taking the drug. A patient who has not taken the drug because he has had an adverse reaction cannot be considered an adherent patient. Conversely, low levels of adherence can be explained by the onset of adverse reactions. In this sense, the study of adherence offers an opportunity to investigate the causes and highlight the role of adverse reactions in terms of effectiveness and safety of treatment. In this sense, the adherence index becomes a proxy to assess drug safety.[32] These types of studies are quite common in the oncology field, especially because the use of oral therapy has substantially increased.[33,34] Home therapy has the advantage of being more accepted and preferred than intravenous treatment, though exposes patients to management issues that could engender loss of adherence to treatment.[35] In the field of Oncology, data on treatment adherence varies widely, as they range from a minimum of 23% to a maximum of 100%.[36] This variability may be explained by the type of disease and its treatment, as well as the choice of analysis method and the type and number of sample analyzed. Although there is considerable interest in the study of adherence in the field of oncology, there are no specific studies on lenalidomide and MM. A single study reports adherence data calculated in accordance

with the Medication Possession Ratio (MPR) method, with a datum of 0.85.[37] This value is higher than we recorded in this study, where treatment adherence is 0.73 and only 32% of patients showed values equal to or greater than 0.8. Assuming that patients with an adherence level above 0.8 are considered adherent,[38] it follows that only 1/3 of the analyzed sample is adherent to lenalidomide treatment. Furthermore, the fact that there are no differences between sample subgroups means that adherence rates do not depend on variables related to patient characteristics, but are common to all patients with MM treated with lenalidomide. It is concerning that adherence rates above 0.8 have been found in so few patients, and it is necessary to investigate and further delve into the causes of lack of adherence, conceivably to be related more to tolerability than dosage. In spite of the low percentage of adherence, 56% of patients are still under treatment one year they started, proving that the tendency is to continue treatment with the same drug, also limiting dosage adjustments, which occurred in 16% of cases. Adherence to treatment is a multifactorial phenomenon influenced by social and financial factors, related to therapy, disease, the characteristics of a patient and the relationship with the health system in which the patient lives.[39] The study and knowledge of the levels and causes of non-adherence help identify fragile patients and implement corrective actions in order to maximize adherence levels and increase the probability of therapeutic success.[40,41] In this context, the awareness of having described a population of non-adherent patients should alert all health professionals, doctors, pharmacists, nurses and caregivers, to think about productive actions and adherence to treatment. The function of the pharmacist is key, as this professional interfaces with doctor and patient. Many experiences have informed improvement in adherence in the oncological field, through the use of different strategies put in place by pharmacists, such as the use of therapy diaries that include counseling and reminders,[42] text messaging,[43] direct calls on a periodic basis,[44–47] as well as specific patient support programs implemented by pharmacists in order to support the patient in understanding the correct modes of drug administration.[20] Such evidence underlines how important it is to measure adherence so as to put in place specific activities to support patients on the basis of the therapy at hand.

The datum on the median PFS described in the literature varies from a minimum of 9 to a maximum of 21 months.[48–52] Such broad data variability is attributable to a variety of factors, including patient's condition, disease, previous treatments, onset and management of adverse effects, and treatment adherence. The two pivotal trials on lenalidomide in the treatment of MM, MM009, conducted in North America, and MM010, in Europe, Australia and Israel, recorded a median PFS of 11.1 months and an OS of 29.6 months[8] and a median PFS of 11.3 months and an OS of 20.6 months, respectively.[7] One year after the start of treatment, patients in OS were 77% and 75% respectively in MM-009 and MM010. The data presented in the trials are similar to those described in real world, in this study, (OS = 89.3%), and confirm the effectiveness profile of lenalidomide in real world.

Limitations

This study has several limitations. First and foremost, being single-center it relies upon a relatively limited number of patients. It follows that the analyses and sub-classifications that have been performed have inherent structural drawbacks. Another limiting concern is the failure to describe the causes of non-adherence and the description of any adverse reactions.

Conclusions

The analysis of adherence in MM patients treated with lenalidomide one year from the beginning of therapy reveal a concerning lack of adherence. Data reported focused on low adherence data described in the study. This evidence should make us reflect on the fact that, beyond important issues, such as the therapies taken and the state of the disease, it is also important to focus attention on the assistance provided to patients, trying to describe and remedy non-adherence that contribute to therapy failure. Interesting studies will be carried out over longer periods in order to fully describe the journey of MM patients.

Key messages

What is already known on this subject

- Over the past decade the novel oral therapies have resulted in vast improvements in survival in Multiple myeloma (MM);
- No empirical data were about medication adherence in patients undergoing treatment for MM;

What this study adds

- Data on adherence and persistence in the treatment of Multiple Myeloma with lenalidomide in real world

Declaration of conflicting interests

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