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ORIGINAL ARTICLE

High adherence of patients with multiple myeloma who receive treatment with immunomodulatory drugs (IMIDS) in hematology/oncology group practices in Germany

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Abstract

Purpose Immunomodulatory drugs (IMIDS) have changed the treatment and outcome of patients suffering from multiple myeloma. However, with the oral administration adherence becomes an issue. Since there is no "gold standard" in measuring adherence, we assessed the adherence of myeloma patients with the help of different data sources.

Methods All patients who have been receiving IMIDS for at least 3 months were eligible. Computer assisted personal interviews of patients and, if possible, their caregivers were carried out. Attending oncologists evaluated the patient's adherence with the help of a standardized questionnaire. In addition, a retrospective analysis of prescription data was conducted. All data were analyzed statistically using SPSS.

Results One hundred myeloma patients, 35% female, 65% male, with a median age of 70 years (37–86) were interviewed. Prescription data could be evaluated in terms of adherence in 78 patients (78%), 56 caregivers could be questioned (56%). Ninety-seven percent of patients rated themselves as adherent in taking IMIDS. Data from treating oncologists, caregivers and prescriptions supported this result. IMID therapies were rated as very effective and significant, toxicities were acceptable and dosing regimens simple/uncomplicated.

Conclusions Myeloma patients seem to be highly adherent to IMID treatments.

Keywords Multiple myeloma · Adherence · Compliance · Immunomodulatory drugs · IMIDS · Outpatient treatment

Introduction

Multiple myeloma (MM) comprises 1% of all cancers and 13% of hematologic malignancies [1]. The treatment of MM has been rapidly evolving [2] due to the introduction of autologous stem-cell transplantation and novel agents [3]. In the past 10 years, effective agents (immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies) have been approved, which expanded the therapeutic armamentarium greatly and changed treatment and outcome dramatically [2]. Thalidomide, lenalidomide, and pomalidomide are considered immunomodulatory drugs (IMIDS) and have to be administered orally. However, with the oral administration adherence becomes an issue which is crucial for the success, safety and effectiveness of the therapy [4]. Adherence rates of less than 80% were associated with poorer survival in breast cancer patients taking tamoxifen [5], similar results were found in various studies on chronic myeloid leukemia [6–8]. Accordingly, Greer et al. summarize in their recently published review that poor adherence to oral cancer agents is consistently associated with lower likelihood of response to therapy and higher mortality [9].

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Patients are optimally adherent if no doses are missed, no extra doses are taken, and no doses are taken in the wrong quantity or at the wrong time [10]. The terms adherence and compliance can be used synonymously [10, 11]; persistence, defined as continuing treatment for the prescribed duration [12], should be distinguished [10, 11].

Despite a substantial number of studies investigating adherence with medication taking, there is still no "gold standard" method in measuring adherence [13–20]. Self-report instruments are cheap, easy to use, and uncomplicated to score [13] but fraught with difficulties, including recall issues and reluctance to admit nonadherence [10, 21–23]. For pill counts, patients are required to return unused pills at each next visit [13] but like self-reports they may be inaccurate and open to manipulation [10, 21]. Rates of prescription refills are objective and easy to obtain but a prescription refill is not equivalent to ingestion of medication [24]. Drug levels in blood or urine or other physiological parameters may be more effective, but are subject to individual differences because of pharmacokinetic factors [21] and for most oral anticancer drugs the available markers are not fully validated or sensitive and reliable enough to assess adherence [13]. Electronic monitoring may provide the best estimate of patient adherence [13]; however, it is expensive and not always feasible in daily practice [10, 13]. In summary, there are serious problems with each method for generating valid and reliable data to give an accurate estimate of the extent of adherence [15].

Due to these methodological difficulties, some authors concluded that only a combination of measures can maximize accuracy [20, 22, 24, 25]. Feiten et al. recently published results concerning adherence assessments of patients suffering from metastatic solid tumors [26]. Adherence was assessed from different perspectives (patient, oncologist, caregiver) and a retrospective analysis of prescription data was conducted [26]. We adapted this approach and investigated patients who suffered from MM and received treatment with an immunomodulatory drug (IMID) in hematology/oncology group practices in Germany.

The objective of the present study was an estimation of adherence with IMIDS in patients suffering from MM and receiving outpatient treatment. To the best of our knowledge, this is the first evaluation of adherence in this setting.

Methods

This study was conducted in seven hematology/oncology group practices in Germany at the following sites: Koblenz, Speyer, Mayen, Oldenburg/Delmenhorst, Neuwied, Mannheim, and Kaiserslautern. It was approved by the local ethics committees.

All patients who suffered from MM and have been receiving an immunomodulatory therapy (thalidomide, lenalidomide, pomalidomide) for at least 3 months were identified. Eligible patients were informed in detail by their oncologists and gave written informed consent prior to participation. The interviews were carried out by study nurses and lasted 5 to 10 min. The standardized computer-assisted questionnaire covered the following areas: handling of and attitudes to oral drugs in general, tolerability and efficacy of myeloma therapy, self-reported adherence, and handling of adherence problems.

For all eligible caregivers, additional interviews with the main topic patient's reliability with medication-taking were conducted. Caregivers had been identified by the patients during their interviews with the help of an open-ended question as to persons who support them in medication-taking. They had to agree to the conduction of the interview in writing after being fully informed.

A written survey of the attending oncologists with the topics tolerability and efficacy of the prescribed IMID and the reliability of the patient with medication-taking was performed for all investigated patients.

Tolerability and efficacy of IMIDS were evaluated by patients and attending oncologists with the help of a rating scale ranging from 1 to 100. "100" meant that the therapy was "very well tolerated" or "very effective" and "1" that the treatment was "not at all" tolerable or effective. Reliability of patients in medication-taking was assessed by the attending oncologists, the caregivers and the patients themselves using a scale ranging from "100," "very reliable' to "1," "not reliable at all."

In addition, a retrospective analysis of the medical treatment data was carried out for all patients, using medical records and checking prescriptions for deviations from the documented treatment regimen. Because a special prescription form is necessary to prescribe IMIDS in Germany (T-Rezept) and due to the prices of the drugs they are thought to be prescribed only by oncologists. As an assessment period, the previous 6 months were used.

The above-mentioned interviews of patients, caregivers, and the survey of attending doctors were developed according to existing literature. The questionnaires were used as adherence assessment in more than 120 patients suffering from metastatic solid tumors [26], but they are not formally validated so far.

The issue of adherence was thus classified from 3 or 4 different and independent perspectives per patient:

1. patient interview
2. survey of attending doctor
3. caregiver interview (if possible)
4. retrospective analysis of prescription data

Statistical analyses were performed using SPSS 19. Frequencies, medians, means, and standard deviations were calculated to describe the data. The degree of agreement

between patients' and oncologists' assessments was evaluated with the help of a Bland-Altman plot [27, 28]. No formal confirmatory hypothesis testing or statistical power calculations were pre-specified for the present exploratory study. The sample size of 100 patients was chosen for feasibility reasons.

Results

Demographics

A total of 108 patients suffering from MM and receiving an IMID were approached, 100 (93%) participated in the interviews. The median age was 70 years (37–86 years), 35% were female and 65% were male. In 66%, the partner was the main caregiver, 13% named children, 5% partner and children, 3% others, and 13% had no main caregiver. Fifteen percent lived alone, 81% lived together with someone else, and 4% did not respond to this question. Patients received IMIDS in the observation period as follows: lenalidomide 75%, pomalidomide 12%, thalidomide 7%, lenalidomide/pomalidomide consecutively 5%, and thalidomide/lenalidomide consecutively 1%.

Fifty-six main caregivers with a median age of 66.5 years (30–84 years) could be questioned as well. Seventy-five percent were female and 25% were male. Sixty-six percent accompanied the patient always or almost always to the doctor, 11% most of the time, 21% seldom, and 2% never or almost never. Seventy-five percent assessed themselves as well informed about the patients' medications.

Assessment of medication-taking

According to treatment files, patients took 9 (1–20) different medications in median. Forty-three percent took their medications straight from the packaging. Fifty-six percent used a pill dispenser and prepared pills most often for a day (28%) or a week (24%) in advance. Forty-three percent were supported by another person, usually by reminding (27%) and/or by preparation in a pill dispenser (24%). Partner (84%) and children (9%) were the most important resources in supporting patients. Package leaflets of the pills were read by a little more than half of the patients (55%) and were mostly perceived as comprehensible, informative and helpful. Assessments of trained interviewers showed that 83% of patients were able to name their cancer medication (IMID) correctly and completely without any help. After presentation of personal prescription sheets, additional 10% identified their anticancer drug properly and completely; in 7%, the responses remained incomplete and/or incorrect. IMID dosing regimens were rated as very simple/uncomplicated by 74% of the patients and as simple/uncomplicated by 25%.

Efficacy, tolerability, and significance of myeloma therapies

Efficacy of IMID therapies was regarded as quite high by patients, physicians, and caregivers with mean values of 90, 84, and 89, respectively (standard deviations (SD) 15, 25, and 19). Tolerability was assessed similarly with means of 86 (SD 18; patients), 85 (SD 19; doctors), and 84 (SD 20; caregivers). Sixteen percent of therapies had to be discontinued, mostly due to toxicities and/or lacking efficacy. In 27% doses had to be modified, in 23% due to toxicities. Patients evaluated their myeloma therapies as highly significant for their own health. The mean value was 94 (SD 11) for the whole group with a range from 92 to 95 for all subgroups.

Estimation of adherence to IMIDS

Patients reported in 97% that they would take their medications always or almost always as prescribed. Accordingly, they rated themselves as highly reliable in taking IMIDS. The mean value was 98 (SD 5), the median 100, with a range from 70 to 100. No significant differences in subgroups such as sex, age groups (70 years or younger vs. 71 years or older) or number of prescribed drugs (up to 8 vs. 9 or more) could be observed. The mean values between these groups varied from 97 to 99.

From the oncologists' perspective, the patients were also considered to be highly adherent, the mean value was 98 (SD 10). However, adherence problems were documented by the treating physician in 4% of the patients' files. No differences in the assessments of different subgroups could be found, means varied between 97 and 98.

An adherence calculation with the aid of IMID prescriptions was possible only in 78 patients (78%) due to lacking data. For these patients, a mean drug availability of 99% was calculated. The respective IMID was prescribed for 6% of patients to 87–90%, for 8% to 91–94%, for 8% to 95–99%, and for 78% to 100% of the necessary number.

Main caregivers assessed patients' reliability in medication taking as very high, too. The mean value was 97 (SD 11).

Concordance of adherence assessments of patients and oncologists

A Bland-Altman plot (Fig. 1) assessing the degree of agreement between patients and oncologists ($n = 100$) showed a high concordance. The 95% interval covers an area that is usually considered still adherent.

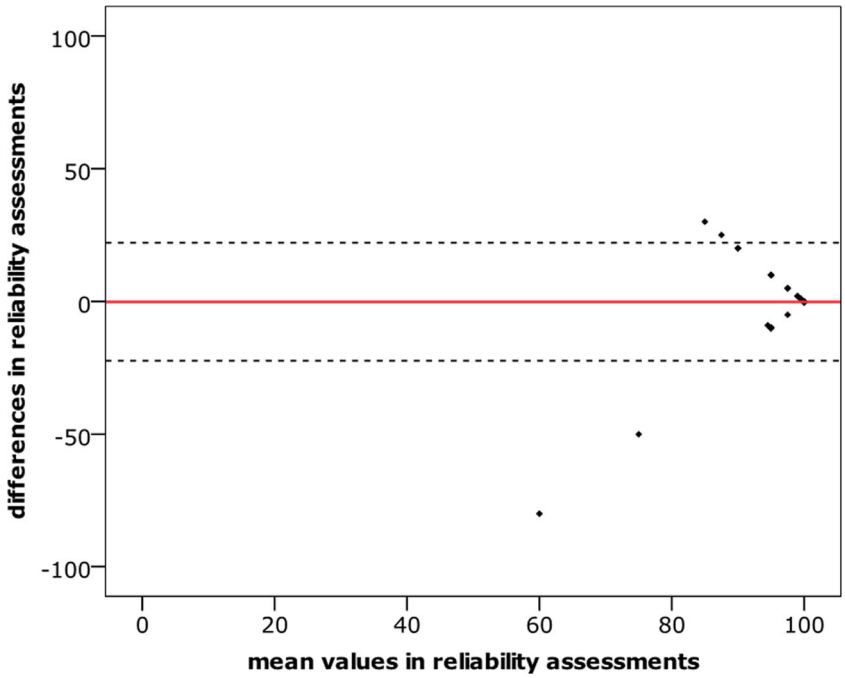

Fig. 1 Bland-Altman plot of the agreement between patients' and oncologists' evaluations ($n = 100$) of patients' reliability in medication-taking

Discussion

High adherence to IMIDS in myeloma patients—really?!

Patients rated themselves as highly reliable in taking IMIDS with a mean value of 98. But how valid is this finding? Indirect methods of assessing medication adherence, such as self-report, tend to yield higher estimates as compared with calculations based on pharmacy data or electronic medication event monitoring systems [9]. Our retrospective calculation, based on prescriptions, showed a mean drug availability of 99%. This does not mean that patients had taken their medication but at least they had enough drugs prescribed to take them in the right quantity. Based on convention, even a possession rate of 80% or more is considered adequate adherent [29]. The fact that such analyses were not possible in 22% of patients does not contradict this high rate.

Furthermore, from the oncologists' perspective, the patients were considered to be highly adherent as well. The mean value was 98, too, and there was only a small number of 4 patients who were thought to be nonadherent. The required combination of adherence measures to maximize accuracy [20, 22, 24, 25] can be considered as given and the results are similar. Furthermore, caregivers also assessed patients' reliability in medication taking as very high (mean 97) but these data were only available for about one half of the patients.

Assuming that the adherence of myeloma patients is indeed high, the question arises as to why it is so high? Cancer patients are often thought to be highly motivated by the gravity of their disease, with "too much to lose" by being nonadherent [18, 25, 30, 31]. Recent studies report adherence rates between 82.6 and 96.8% in patients suffering from metastatic disease [23, 26, 32, 33]; Arber et al. found 92.2% in myeloma patients receiving the, compared to IMIDS, much more complex CTD regimen (cyclophosphamide, thalidomide, dexamethasone) [34]. Potential barriers to adherence are, among others, treatment toxicities, regimen complexity and drug ineffectiveness [20]. IMID therapies in our cohort were rated as very effective by patients, doctors and caregivers (means 84–90). Toxicities were acceptable, only 16% of therapies had to be discontinued and in 27% doses had to be modified, mostly due to side effects. Furthermore, patients evaluated their myeloma therapies as highly significant for their own health (mean value 94) and dosing regimens as (very) simple/uncomplicated in 99%. The patients are seen by their doctors in a four-week rhythm (due to IMID prescriptions and maybe bisphosphonate therapy), so toxicities are closely monitored and dose adjustments can be easily made if necessary. An explicit monitoring of toxicities to implement timely dose adjustments or discontinuation has been regarded as a useful intervention strategy to ensure adherence [20].

However, most studies have shown a number of patients who may need specific interventions to ensure adherence, too [23]. Based on independent data sources in our population, a small group of about 4% of patients can be found who seem to be at risk for nonadherence. Identifying potential barriers to adherence for these patients will be extremely important and if these barriers are not modifiable an alternative therapy should be considered [20].

Consistently high adherence across subgroups

No substantial differences between male and female or younger and older patients could be observed, neither from the patients' nor from the oncologists' perspectives. But one has to take into account that subgroups were rather small, i.e., only 35 female patients took part in the interviews and it would have been difficult to find significant differences. We did not calculate statistical power a priori but it is obvious that we did not have a sufficient sample to investigate subgroups in detail. Due to a very small number of patients living alone ($n = 15$), we did not analyze this subgroup although it is known that patients living alone are less adherent [35]. However, our results do not contradict the findings of other studies that demographic variables are poor indicators of adherence [15]. Polypharmacy as another adherence diminishing factor [20] was analyzed more closely.

High adherence despite polypharmacy

In our population, patients had to take nine different drugs in median. Other studies found that older patients with cancer take a median number of medications of 5 to 9.1 [36]. The use of five or more medications regularly has been a frequently used definition for polypharmacy while a very high number of medications, such as ten or more, has been defined as "excessive polypharmacy" [36]. In this respect, polypharmacy was an issue in 82% of our patients and in 42% even "excessive polypharmacy." One can easily imagine that single doses could be missed or that overdosing could be an issue. Sharma et al. found accordingly in their review that the more medications a patient is taking, the more likely a patient is to be nonadherent [36]. However, we found a very high adherence rate in these patients notwithstanding the high number of prescribed drugs.

Practical implications

In routine care, it is of utmost importance to detect patients with low adherence as early as possible [37] why clinicians should integrate assessments of medication adherence into clinical practice. Even single question self-report questionnaires could be helpful for it has been found that they correlate fairly well with medication event monitoring systems [9]. In addition, self-assessments could be cross-checked by treating oncologists. In patients who may be at risk, i.e. where discrepancies in the assessments could be observed, a follow-up evaluation could help to guide recommendations to improve the patient's medication-taking behavior [9]. Furthermore, given the Hawthorne effect, a systematic monitoring of patient pill-taking may be as well an effective way to improve adherence and persistence [10]. Because nonadherence often may be intentional rather than non-intentional patients must have a good understanding of their therapy and their medications in order to be adherent [29]. In this sense, adherence implies a collaborative approach to decision-making, ideally with mutual agreement between patient and doctor [9].

Methodological considerations

To the best of our knowledge, this is the first evaluation of adherence in patients suffering from MM and receiving treatment with IMIDS in hematology/oncology group practices. In a recent review of 51 papers on rates/correlates of adherence to oral antineoplastic therapy [9], only one was included which investigated, among others, two myeloma patients [38]. Two recently published papers deal with the adherence of myeloma patients receiving panobinostat [39] and CTD [34]. However, adherence with IMIDS is reported in one abstract only which concludes that adherence "was not optimal" in 63 myeloma patients [40].

The strength of our project is the population of unselected real-life patients in a multicenter outpatient context and the different measurement methods. But there are limitations which have to be considered. First of all, a retrospective analysis of prescription data is difficult and there are too many cases in which adherence could not be assessed adequately due to missing data. Secondly, we could only manage to survey about 50% of all caregivers. The high adherence rate we found has to be replicated, ideally using other methods of measurement, i.e., medication event monitoring systems. Further investigations should consider communication aspects and evaluate for example if treatment decisions were mutually agreed in a sense of shared decision making and how this process affects adherence.

Conclusions

Myeloma patients who are treated in hematology/oncology group practices are highly adherent to immunomodulatory therapies (IMIDS). Measuring adherence with different methods is feasible and leads to concordant results but has some pitfalls to be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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