Adherence and Coping Strategies in Outpatients With Chronic Myeloid Leukemia Receiving Oral Tyrosine Kinase Inhibitors

Jochen Hefner, PhD, Eva-Johanna Csef, MS, and Volker Kunzmann, PhD

Purpose/Objectives: To assess adherence and coping strategies in outpatients with chronic myeloid leukemia (CML) on oral tyrosine kinase inhibitors (TKIs).

Design: Prospective, descriptive.

Setting: An interdisciplinary oncology outpatient clinic in Germany.

Sample: 35 outpatients with CML on oral TKIs.

Methods: Adherence and coping strategies were assessed with questionnaires. Clinical data were extracted from medical charts.

Main Research Variables: Adherence rates, main coping strategies, and frequency and contents of single coping strategies.

Findings: 18 patients showed adherence according to the applied screening instrument. Main coping strategies were spirituality and search for meaning. The two single items most frequently specified were adhering to medical instructions and trusting in the medical personnel involved.

Conclusions: The low adherence rate of 51% most likely resulted from using the Basel Assessment of Adherence Scale as the questionnaire of choice. The relevance of spirituality and search for meaning has not been shown previously in outpatients with CML. Most patients wish to obey medical instructions accurately and put trust in their oncologists; this introduces a resource that should gain relevance considering the increasing number of oral anticancer drugs.

Implications for Nursing: Nurses are encouraged to routinely assess adherence and spiritual needs in outpatients with CML. Spirituality and search for meaning represent pivotal coping needs in this group, which has an excellent prognosis. Oncology nurses may help provide tailored support, thereby ameliorating care for these patients.
patients are considered comparable to the general population in contrast to the previously often lethal outcome (Gambacorti-Passerini et al., 2011). Even for patients showing resistance to first-line therapy, their life expectancy may improve because of modern TKI alternatives (Kantarjian et al., 2006; Shah et al., 2014; Talpaz et al., 2006).

When oral TKIs were introduced, given all their benefits, high adherence rates were a foregone conclusion. However, in their 15 years, adherence rates have been as low as 60% (Noens et al., 2009); other studies have revealed a similar rate of nonadherence of at least 30% (Al-Dewik et al., 2016; Lam & Cheung, 2016; Winn, Keating, & Dusetzina, 2016). Low adherence rates undoubtedly result in unfavorable sequelae (Breccia, Efficace, & Alimena, 2011; Jabbour, Kantarjian, Eliasson, Cornelison, & Marin, 2012; Santoleri et al., 2016; Wu et al., 2010). Adherence in patients taking oral anticancer drugs seems to be influenced by a variety of factors, such as sociodemographic or medical variables (Mathes, Pieper, Antoine, & Eikermann, 2014; McCue, Lohr, & Pick, 2014; Verbrugghe, Duprez, et al., 2016). However, results of the respective, heterogeneous studies should be cautiously considered as indicators for factors that may influence adherence (Mathes et al., 2014). As early as 2001, scientists proposed focusing more on patients’ perceptions and favored qualitative studies to understand this (Verbrugghe, Duprez, et al., 2016; Vermeire, Hearnsaw, Van Royen, & Denekens, 2001). Studies regularly mention adherence-related factors, such as fears and anxieties, hopes, beliefs in medication, and trust in healthcare providers (Guilhot et al., 2013; Johnson, 2015; Verbrugghe, Timmers, et al., 2016; Wu et al., 2015; Yagasaki, Komatsu, & Takahashi, 2015). All authors stress that a trusting relationship between a patient and his or her healthcare providers allows open communication, thereby representing a key factor to potentially ameliorate the patient’s situation and adherence (Al-Barrak & Cheung, 2013; Breccia et al., 2015; Chen, Chen, Huang, & Chang, 2014; Eliasson, Clifford, Barber, & Marin, 2011; Johnson, 2015; Verbrugghe, Duprez, et al., 2016; Verbrugghe, Timmers, et al., 2016).

To date, the perception of patients with CML has not been studied in the broader context of coping strategies. Coping was defined by Weisman (1979) as “what one does about a perceived problem in order to bring about relief, reward, quiescence, or equilibrium” (p. 3). Lazarus and Folkman (1984) delivered a further definition of coping “as cognitive and behavioral efforts to manage demands as taxing or exceeding resources” (p. 19). The construct of coping with cancer represents a complex topic (Dunkel-Schetter, Feinstein, Taylor, & Falke, 1992; Parle, Jones, & Maguire, 1996; Richardson, Schüz, Sanderson, Scott, & Schüz, 2017); a normative classification of coping as being adaptive or maladaptive is impossible because of influencing factors, such as cancer stage, treatment options, or course of the disease (Salander & Windahl, 1999). As known from patients in an advanced stage of CML or within the hematologic stem cell transplantation setting, spirituality constitutes one of the most important coping resources (Sirilla & Overcash, 2013; Zaza, Sellick, & Hillier, 2005).

This pilot study aims to investigate adherence and coping strategies in German outpatients with CML treated with oral TKIs to generate the first results and innovative hypotheses for additional assessments and interventions.

The authors’ hypotheses were that, in outpatients with CML, adherence measured through a questionnaire would be low despite its relevance for the therapy outcome in responding patients and that it would be much higher in comparison when rated on a visual analog scale (VAS). The study of coping strategies was not driven by hypotheses because the authors intended to collect initial data on the topic. In a German population of CML outpatients treated with oral TKIs, monetary reasons for low adherence or coping strategies can be ruled out because of full insurance coverage of medical costs.

**Methods**

A prospective and descriptive study design was adopted for this explorative study. The dataset used belonged to a larger parent study (Hefner, Csef, & Kunzmann, 2016) in which outpatients with CML were screened for distress, adherence, and coping mechanisms. In 37 outpatients with CML, the authors already have shown that fear of progression provides a frequent source of distress, most often generated by fear (Hefner et al., 2016).

**Setting and Ethical Issues**

All participants were recruited from the outpatient clinic of the Medizinische Klinik und Poliklinik II affiliated with the University of Würzburg, Germany, where about 4,000 outpatients are treated annually by an interprofessional team (i.e., specialists of hematology-oncology and psychosomatic medicine). About 50–60 of these outpatients have CML. Newly diagnosed outpatients receive information about their disease and treatment in a one-on-one conversation with their doctor. Additional leaflets are handed out, and diaries are recommended to patients receiving oral anticancer drugs. Follow-up visits usually take place every three months, and results of laboratory findings and physical examinations are discussed with the doctor.

In the outpatient setting, adherence is not mandatorily assessed with questionnaires. With a shift toward
oral anticancer drugs, nurses at this institution predominantly care for patients who receive IV therapy and stay for several hours.

Requirements for inclusion in the current study were a documented CML diagnosis and treatment with oral TKIs. The major exclusion criteria were: being aged younger than 18 years, needing inpatient treatment, having obvious intellectual impairment, and having insufficient knowledge of the German language. Before enrollment, all participants were informed about the study and its goals and gave written informed consent. Participants then were asked to complete their questionnaires. All patients were briefed about the psycho-oncologic support program offered by the hospital. Assessments had a mean duration of 15 minutes and took place in an extra room at the outpatient clinic to provide privacy and confidentiality. The study was approved by the Ethics Committee for Medical Research in Würzburg, Germany, in accordance with the Declaration of Helsinki.

Measures

Sociodemographic data, including age, gender, and marital status, were obtained using an established questionnaire (Deck & Röckelein, 1999). Patients aged 60 years and older were defined as older adults (Hefner et al., 2016). Current TKI side effects and CML remission status were assessed during the patients’ visits. Side effects were defined as cytopenia grades 3–4, and all grades of fatigue, fluid retention, cardiopulmonary abnormalities, myalgia, arthralgia, nausea, vomiting, diarrhea, or rash (Hefner et al., 2016). Medical history was obtained from charts. Oral TKIs were categorized into first-generation (imatinib), second-generation (dasatinib, nilotinib, and bosutinib), and third-generation TKIs (ponatinib) (Hefner et al., 2016).

Adherence: The authors applied an adapted version of the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) (Cleemput & Dobbels, 2007) to assess adherence. This scale was originally invented to monitor adherence behavior in patients undergoing solid organ transplantation. In its first part, the scale focuses on four relevant medication-taking dynamics (i.e., taking, administration, regularity of intake, and presence of drug holidays during the four weeks preceding transplantation). When assessed, patients are asked whether they have skipped one or more doses, whether their daily time of medication intake varies by more than two hours, whether they have changed the dose without informing their doctors, or whether they have discontinued medication intake. One positive answer to any of these questions constitutes nonadherence. The second part of the BAASIS consists of a VAS ranging from 0 (completely nonadherent) to 100 (perfectly adherent), by which the patients can rate their own perceived adherence (Cleemput & Dobbels, 2007; Noens et al., 2009).

The scale has been adapted to several groups of patients. In patients with HIV, the BAASIS showed moderate to good validity compared with other monitoring options. More specifically, the VAS showed excellent sensitivity and specificity compared with electronic monitoring (64% and 77%, respectively) and pill count (89% and 82%, respectively) (Walsh, Mandalia, & Gazzard, 2002). In addition, combining the questionnaire with the VAS enabled prediction of virologic failure (Deschamps et al., 2008; Glass et al., 2008).

Another adapted BAASIS version already has been used in patients with CML by Noens et al. (2009). As in Noens et al.’s (2009) ADAGIO (Adherence Assessment With Glivec®: Indicators and Outcomes) study, the current authors used that adapted scale in the current study and also referred to it as BAAS.

Coping: Coping was assessed by the Freiburg Questionnaire of Coping With Illness (FKV) (Muthny, 1989, 1996). The FKV is a 35-item questionnaire with five primary dimensions: depressive coping, problemsolving behavior, distraction and self-valorization, religiousness and search for meaning, and extenuation and wishful thinking. The 35 items are scored on a Likert-type scale ranging from 1 (not at all) to

![Table 1. Sample Characteristics (N = 35)](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAIoAAAD2CAYAAAAJhLbjAAAAAX1BMVEVY1VQJcCNJIDc32wYAAAAAElFTkSuQmCC)
5 (very much). A high score in the FKV subscales indicates a strong tendency toward the concerned coping mechanism. Cronbach alphas for the single subscales range from 0.68–0.77 (Muthny, 1989, 1996), and several validity studies have been done for other cancers (Faller, Bülzebruck, Drings, & Lang, 1999; Faller, Kraus, Burth, & Zeigert, 1999).

### Statistical Analyses

Data were registered and analyzed using SPSS®, version 22.0. For descriptive analysis, data were expressed as median or mean and standard deviation. For tests of significance, mean differences of continuous variables among two subgroups were examined by t tests for independent samples. All tests of significance were two-tailed; p values of less than 0.05 were considered statistically significant. To examine the relationship between two independent categorical variables, Fisher’s exact test was performed.

### Results

Forty-five patients fulfilled the current study’s inclusion criteria. Eight patients declined participation, and 37 patients were enrolled, 35 of which fulfilled the questionnaires completely once during their medical visit.

The description of sociodemographic and medical characteristics of the 35 patients included in the current study is presented in Table 1. The mean age was 59 years (range = 22–87 years). The mean time since CML diagnosis was 76 months (range = 4–236 months), and the mean time since onset of TKI treatment was 69 months (range = 4–139 months).

The medication prescribed was imatinib in 24 patients; 11 were treated with second-generation TKIs (dasatinib or nilotinib). No significant group differences were seen regarding age, gender, or time course of disease or treatment. Within the second-generation TKIs group, four patients had to change to second-line TKIs because of former imatinib resistance. In another three patients, previous side effects were the reason for this change. The last four patients received second-generation TKIs as their first-line treatment.

According to the BAAS, 17 patients documented at least one of the four queried behaviors in the past four weeks and, therefore, were considered to be nonadherent. The most common relevant behavior was delaying a dose by more than two hours (n = 14) followed by occasionally omitting single doses (n = 4); one participant’s dose was reduced, but no medication was discontinued for any participant. On the contrary, VAS ratings of patients were high (X̄ = 99.3, SD = 2.38, range = 89–100).

Adherence was not correlated with age (p = 0.75), gender (p = 0.74), or marital status (p = 0.15). It also was not correlated with first- or second-generation TKIs (p = 0.15). In addition, adherence was not correlated with current side effects (p = 1.00). Finally, adherence in the current sample was not associated with elapsed time since the first diagnosis of CML (t[35] = 0.22, p = 0.82) or with the time since the onset of TKI therapy (t[35] = 0.76, p = 0.45).

The subscale of religiousness and search for meaning showed to be the dominant coping mechanism next to distraction and self-valorization, active problem-solving behavior, extenuation and wishful thinking, and depressive coping (see Table 2). No significant correlations were found between sociodemographic variables (age, gender, marital status) and coping styles (see Table 3). In addition, no significant correlations were found between current side effects or type of TKI and coping styles. After more than one year of TKI intake, patients used significantly fewer strategies of extenuation and wishful thinking or depressive coping.

Single-item analyses revealed that patients generally are eager to follow the physician’s orders exactly and that they are willing to trust the medical personnel involved. Items much less frequent concerned the disease, like fighting resolutely against it or accepting it as fate (see Table 4).

### Discussion

Despite the enormous clinical advantages of a regular intake of oral TKIs, adherence rates in patients with CML are reported to be low (Breccia et al., 2015; Efficace et al., 2012; Jabbour et al., 2012; Marin et al., 2010; Noens et al., 2009; Santoleri, Sorice, Lasala, Rizzo, & Costantini, 2013; Wu et al., 2015; Yood et al., 2012). These results are quite unexpected in light of the potential life threat of the malignant disease and the foreseeable, unfavorable health implications of nonadherence (Anderson et al., 2015; Breccia et al., 2011, 2015; Jabbour et al., 2012; Marin et al., 2010; Noens et al., 2009; Wu et al., 2010). In the current sample, the

### Table 2. Coping Strategies in Patients With Chronic Myeloid Leukemia on Oral Tyrosine Kinase Inhibitors (N = 35)

<table>
<thead>
<tr>
<th>Coping Style</th>
<th>X̄</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Religiousness and search for meaning</td>
<td>2.6</td>
<td>0.61</td>
<td>1.6–3.8</td>
</tr>
<tr>
<td>Distraction and self-valorization</td>
<td>2.43</td>
<td>0.83</td>
<td>1–4</td>
</tr>
<tr>
<td>Problem-solving behavior</td>
<td>2.41</td>
<td>0.74</td>
<td>1–4.4</td>
</tr>
<tr>
<td>Extenuation and wishful thinking</td>
<td>1.94</td>
<td>0.87</td>
<td>1–4.33</td>
</tr>
<tr>
<td>Depressive coping</td>
<td>1.79</td>
<td>0.71</td>
<td>1–4</td>
</tr>
</tbody>
</table>

Note. Scores ranged from 1 (not at all) to 5 (very much).
adherence rate of 51% according to the BAAS was alarmingly low, even when compared to former studies showing unexpectedly low rates of adherence in patients treated with oral TKIs (60%–80%) (Anderson et al., 2015; Breccia et al., 2015; Efficace et al., 2012; Jabbour et al., 2012; Marin et al., 2010; Noens et al., 2009; Santoleri et al., 2013; Wu et al., 2015; Yood et al., 2012). The majority of nonadherence (40%) resulted from a deviation of more than two hours from the daily time point of pill intake.

The self-rating on a VAS appeared to be much more favorable than the results of the aforementioned questions (89%–100%), a result that is in line with other reports (Noens et al., 2009). The authors assumed that the discrepancies shown between the four items of the questionnaire and the VAS were partly explained by the Hawthorne effect (a basic social desirability bias and an effect of being assessed) and that they point toward one of the basic difficulties in assessing adherence—the absence of a flawless gold standard (Partridge, Avorn, Wang, & Winer, 2002; Ruddy, Mayer, & Partridge, 2009). In addition, the discrepancy between the medical needs screened with the single items and the patients’ adherence perceptions as reflected by the VAS ratings may account for this obvious difference.

In the current sample, adherence was not associated with sociodemographic variables or the time course of the disease or treatment. These results seem to contradict previous results (Klein, Geschwindner, & Spichiger, 2013); however, all current calculations were based on a small and heterogeneous sample. Regarding the most frequent single coping strategies according to the FKV, the authors can show for the first time that outpatients with CML tend to follow orders given by physicians accurately and put trust in the attending medical personnel (X = 4.46, SD = 0.66) and X = 4.4, SD = 0.7, respectively). As the patients’ responsibility to ensure regular medication intake increases dramatically with the shift toward oral chemotherapy (Foulon, Schöffski, & Wolter, 2011), patients show an invaluable disposition that is not sufficiently used when considering the low adherence rates in the current sample.

Considering the five superordinate coping strategies condensed in the FKV (i.e., religiousness and search for meaning, distraction and self-valorization, problem-solving behavior, extenuation and wishful thinking, and depressive coping), the authors also can show for the
first time the primary importance of religiousness and search for meaning in outpatients with CML (X = 2.6, SD = 0.61). In patients with advanced CML, 78%-93% consider spirituality and religiousness to be important aspects of coping (Alcorn et al., 2010; Balboni et al., 2007; Vallurupalli et al., 2012); however, this attitude never has been shown in patients with an excellent prognosis like in the current sample. The current results show that patients actually have the notion of being threatened by a potentially lethal condition, regardless of the likely favorable outcome, and they reconsider their purpose in life. A similar observation can be made in patients with a good prognosis in a much more intensive setting, like in those receiving hematologic stem cell transplantations (Sinclair et al., 2016). To the authors’ knowledge, these are nevertheless unique results in outpatients with CML.

Limitations

The current investigation shows numerous limitations. The small and heterogeneous sample allows only preliminary interpretations. The use of different TKIs over varying periods of time led to very small subgroups. Although the authors observed changes in coping strategies over time, sample sizes were so small that the authors could not draw any more conclusions. In addition, because of the small sample sizes, the authors refrained from computing correlations between adherence and coping strategies. Different therapy strategies before the onset of TKIs remained unstudied, as well as the administration of the latest TKIs, such as ponatinib or bosutinib. The authors used a cross-sectional design with a one-time assessment. Referring to a report that described possible stages of experience in patients with CML (Guilhot et al., 2013), additional studies should consider follow-ups in their design.

The assessment tool chosen to monitor adherence represents another limitation of the current study. Reviews describe seven different groups of assessment tools, all of which appear fraught with uncertainty: (a) patient-completed adherence scales, (b) healthcare providers’ interviews, (c) patient-reported adherence with diaries and calendars, (d) medication event monitoring, (e) automated voice response, (f) drug and metabolite assays, and (g) prescription databases (Patel et al., 2013). The authors chose a patient-oriented scale even though a well-validated scale designed particularly for oral anticancer drugs is lacking (Huang, Chen, Lin, & Chang, 2016). However, the authors chose the BAAS as a rapid screening tool to gain an understanding of daily routines or periodic prompts, which may be beneficial for adherence (Hall et al., 2016; Marin et al., 2010; Schneider, Hess, & Gosselin, 2011). Regarding the long half-life of TKIs, the two-hour deviation indicating nonadherence set in the current study may be misleading. A time delay does not necessarily compromise efficacy if the right dose per day is used (Noens et al., 2009). In any case, the current data suggest that medication intake has not been implemented as an integral part of daily life in CML outpatients.

Screening for coping strategies with the FKV-35 also revealed some limitations. Comparability with other studies is difficult because the bulkier FKV-102 mostly is used (Harrer, Mosheim, Richter, Walter, & Kemmler, 1993; Petz, Diete, Gademann, & Wallesch, 2001) or even completely different screening tools are applied. In addition, the corresponding studies focused on different types of cancer (Faller, Kraus, et al., 1999; Ghodraty-Jabloo, Alibhai, Breunis, & Puts, 2016; Koenigsmann, Koehler, Regner, Franke, & Frommer, 2006) or on associations to somatic outcome (Faller, Bülzebruck, et al., 1999; Faller & Schmidt, 2004; Pulgar, Garrido, Alcalá, & Reyes del Paso, 2012).

Implications for Nursing Research and Practice

The current study can be grouped with prior research on adherence to oral anticancer drugs in which adherence rates are much lower than intuitively expected (Al-Dewik et al., 2016; Lam & Cheung, 2016; Noens et al., 2009; Ruddy et al., 2009; Santoleri et al., 2016; Winn et al., 2016). Future research should aim at further clarifying the reasons behind the reported low adherence rates found in outpatients with CML. Within the current sample, the authors could not specify whether the low rates were based on somatic status, emotional states, lack of knowledge and information, or forgetfulness.

Many authors claim that communication problems between medical professionals and patients are responsible for low adherence rates (Al-Barrak & Cheung, 2013; Breccia et al., 2015; Chen et al., 2014; Eliasson et al., 2011; Guilhot et al., 2013; Jabbour et al., 2012; Johnson, 2015; Klein et al., 2013; Verbrugghe, Duprez, et al., 2016; Verbrugghe, Timmers, et al., 2016;...
Knowledge Translation

- Outpatients with chronic myeloid leukemia (CML) using oral anticancer drugs perceive themselves as being highly adherent, and most of them want to follow physicians’ orders exactly; in contrast, adherence rates focusing on medical needs are suboptimal.
- Spirituality and search for meaning were revealed as the most prevalent coping strategies, suggesting that having CML poses an existential plight to patients, regardless of its typically favorable outcome.
- Oncology nurses should routinely assess adherence and existential (spiritual) needs in patients with CML to optimize comprehensive cancer care.

Verbrugghe, Verhaeghe, Lauwaert, Beeckman, & Van Hecke, 2013; Wu et al., 2015; Yagasaki et al., 2015). The current findings support this view, revealing a discrepancy between low adherence rates and patients’ willingness to follow medical instructions according to the FKV. Results of the BAAS show that perceived adherence (VAS scale) differs very much from adherence aspects based on medical needs (items 1–4). The low adherence rates likely are a result of the advantage of the oral application of the anticancer drug, leading to shorter contacts with medical personnel (particularly nurses) at the institution. Therefore, the authors suggest that oncology nurses should routinely assess adherence in patients receiving oral anticancer drugs. In addition, they should reinforce the medical needs of adherence even in patients who perceive themselves as adherent.

Conclusion

The current study is the first to describe spirituality and search of meaning as the most prevalent coping strategy in outpatients with CML. Additional efforts should focus on correlations between spirituality and quality of life, distress, or even medical outcomes in outpatients with CML, because such correlations have been reported in other cancer settings (Balboni et al., 2013; Sinclair et al., 2016; Whitford & Olver, 2012). In clinical practice, oncology nurses are encouraged to routinely assess spiritual needs in outpatients with CML. Feasible screening instruments, such as the BAAS, may help to facilitate a focus on these topics and to overcome potential communication barriers on the side of healthcare professionals (Balboni et al., 2014; Hall et al., 2016; Phelps et al., 2012; Sinclair et al., 2016). Fears of offending patients by asking for religious or spiritual needs described elsewhere are unlikely (Sinclair et al., 2016). To the authors’ understanding, nurse specialists may play a pivotal role within the community of healthcare providers by building trustworthy and cooperative relationships with outpatients receiving oral anticancer drugs for CML. These professionals represent the ideal personnel to provide spiritual counseling and support or initiate additional assistance.

References

Cleemput, I., & Dobbels, F. (2007). Measuring patient-reported outcomes in solid organ transplant recipients: An overview of


with the Freiburg questionnaire of illness coping [Article in German]. Rehabilitation, 35(2), IX–XVI.


