

RESEARCH ARTICLE

Understanding and Challenges in Taking Tyrosine Kinase Inhibitors among Malaysian Chronic Myeloid Leukemia Patients: A Qualitative Study

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Abstract

Background: In Malaysia, the treatment for chronic myeloid leukemia (CML) has long been delivered under the Malaysian Patient Assistance Program (MYPAP), but research on identifying factors contributing to non-adherence to tyrosine kinase inhibitors (TKIs) is still limited. The current study explored understanding and challenges of Malaysian CML patients in taking imatinib and nilotinib. **Methods:** Semi-structured, face-to-face interviews were conducted with 13 CML patients receiving treatment at a public tertiary care center, and were analyzed using the content analysis approach. **Results:** The patients generally demonstrated inadequate knowledge, particularly of the natural history and staging of CML, the function of TKIs, and the methods used for monitoring the effectiveness of treatment. A number of them also had experiences of withholding, skipping or altering the treatment, mainly due to the life-disturbing adverse drug effects (ADRs), forgetfulness, and religious and social issues. Besides, most of them were found having limited skills in managing the ADRs, and not using prompts as reminders to take the medications. Furthermore, even though nilotinib was generally perceived as better tolerated as compared with imatinib, the inconvenience caused by the need to take it twice daily and on an empty stomach was constantly highlighted by the patients. **Conclusion:** While TKIs are widely used for CML treatment in Malaysia, the findings have revealed a lack of patient education and awareness, which warrants an integrated plan to reinforce medication adherence.

Keywords: Antineoplastic agents- chronic myelogenous leukemia- imatinib mesylate- Malaysia- medication adherence

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Introduction

Chronic myeloid leukemia (CML), a clonal myeloproliferative disease, is characterized by the presence of the Philadelphia chromosome and the resulting fusion oncogene (BCR-ABL). The transcript of oncogene, in turn, encodes a tyrosine kinase which impairs the normal growth of hematopoietic cells (Granatowicz et al., 2015). Approximately 85% to 90% of CML patients are diagnosed during the chronic phase (Baran and Saydam, 2012); nevertheless, without proper management, rapid progression of CML to the accelerated and fatal blast phases could take place in three to five years (Granatowicz et al., 2015). To date, the global prevalence of CML is approximately 10-12/100,000, which is projected to increase steadily following the use of new treatment and the increasing life expectancy of general population (Hoglund et al., 2015).

Apart from allogeneic hematopoietic cell transplantation, one of the major breakthroughs in CML treatment was the introduction of tyrosine kinase inhibitors (TKIs) (Firwana et al., 2016). Imatinib, the first-generation TKI, has demonstrated superiority with

improved cytogenetic, hematologic and major molecular responses in comparison with interferon and conventional chemotherapy (Roy et al., 2006). With the increasing recognition of pathogenesis of CML, new-generation TKIs with enhanced potency, such as nilotinib and dasatinib, have also been developed and commonly used in imatinib-resistant and -intolerant patients (Jabbour et al., 2006; Lang et al., 2015). Currently, CML has been considered more like a chronic illness, in which patients treated with TKIs are likely to have a near-normal life expectancy (Jayakar, 2014).

However, despite the effectiveness of TKIs, adherence to such treatment among CML patients remains suboptimal (Noens et al., 2009; Gater et al., 2012; Yood et al., 2012; Noens et al., 2014). The reported adherence to TKIs widely ranged from 19% to 100%, mainly due to the different methods of measurement (Darkow et al., 2007; Noens et al., 2009; Marin et al., 2010; Ganesan et al., 2011; Ibrahim et al., 2011; Noens et al., 2014). The possible contributory factors to non-adherence to TKIs also vary, ranging from patients' knowledge and characteristics (Darkow et al., 2007; Marin et al., 2010; Eliasson et al., 2011), communication with physicians

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(Eliasson et al., 2011), drug choice (Trivedi et al., 2014), dosage (Darkow et al., 2007), clinical status (Darkow et al., 2007; Almeida et al., 2016), to lifestyle (Eliasson et al., 2011). It is noteworthy that the majority of the existing studies on adherence to TKIs have been quantitative in design; hence, the information on the underlying feeling, values and perceptions that influence the drug-taking behaviors of CML patients is limited. Furthermore, the only few qualitative studies addressing this issue have focused merely on imatinib, and thus did not provide information on behavioral changes in patients after switching the treatment to new-generation TKIs (Chen et al., 2011; Eliasson et al., 2011; Wu et al., 2015).

In Malaysia, CML treatment has primarily been delivered under the Malaysian Patient Assistance Program (MYPAP), which was launched by the pharmaceutical company in collaboration with the Ministry of Health (Pharmaceutical Association of Malaysia, 2011). Both imatinib and nilotinib, which are respectively used as the first- and second-line treatment as listed in the National Drug Formulary, have been provided free of charge to CML patients. However, to date, there is still a lack of information on patients' experiences with such long-term treatment. Therefore, the current study was designed to explore their understanding and challenges in taking both drugs, which could eventually affect their adherence and thereby the treatment outcomes.

Materials and Methods

Design and Setting

This qualitative study was undertaken at the Sultanah Bahiyah Hospital, a public tertiary care center, which provides multidisciplinary medical services for approximately 2.1 million residents in Northern Malaysia. The study protocol was approved by the Medical Research Ethics Committee, Malaysia, under the protocol number NMRR-16-463-29772. At the time of the study (1st of March to 31st of May 2016), a total of 52 CML patients were actively followed up at the hematology clinic, and were treated with either imatinib (n=45) or nilotinib (n=7).

Recruitment of Participants

To be included in the current study, a patient had to (i) have a confirmed diagnosis of CML; (ii) be followed up at the hematology clinic during the study period and (iii) be treated with either imatinib or nilotinib for at least three months. Excluded patients were those who had hearing or cognitive impairment, or those who were unable to communicate in the Malay language. The list of patients who fulfilled the inclusion criteria, along with information on their scheduled clinic appointment dates, were obtained from the electronic Hospital Information System (e-HIS). The participants were recruited using the purposive sampling method. They were approached by one of the investigators (pharmacist) at the hospital pharmacy, and were subsequently briefed on the study information. Informed consent was obtained from each participant prior to data collection.

Data Collection

First, each participant was surveyed on their sociodemographic information, including gender, age, ethnicity, and level of education, by using a self-administered questionnaire. Besides, the information on the type of TKI received, duration of TKI treatment and the number of concomitant medications received was obtained from the e-HIS. Subsequently, each participant was interviewed by one of the investigators in a patient counseling room adjacent to the hospital pharmacy. All interviews were conducted in the Malay language, and each session took approximately 30 to 45 minutes to complete. A semi-structured questionnaire (Appendix I) was used to guide the interviews. It was developed based on the existing literature (Darkow et al., 2007; Marin et al., 2010; Eliasson et al., 2011; Ibrahim et al., 2011; Trivedi et al., 2011; Chen et al., 2014; Wu et al., 2015; Almeida et al., 2016), and was pre-tested with three patients receiving TKIs to enhance the credibility the findings (Squires, 2008).

Data Analysis

All interviews were audio-recorded and transcribed verbatim. The transcripts were compared with the notes taken during the interviews for discrepancies, and were then independently analyzed by two investigators using the content analysis approach (Gale et al., 2013). Constant comparison was made between interviews, and the recruitment of participants was continued until data saturation was achieved (Jeanfreau and Jack, 2010; Gale et al., 2013). As all the interviews were conducted in the Malay language, the transcripts were independently translated by two bilingual researchers (pharmacists Lim YM and Eng WL) into English. Subsequently, the translation was validated by another bilingual research officer (Chan HK) (Squires, 2008). The themes, subthemes and quotes selected to exemplify each theme were agreed by all the investigators.

Results

Over the three-month study period, 13 eligible patients (P1-P13) were identified and agreed to participate in this study. The majority of them were male (n=8), Malay (n=10), middle age (mean, 47.8 years) and had received tertiary education (n=8). Nine of them were treated with imatinib, while four received nilotinib, with an average treatment period of 2.6 years. Two major themes (understanding about disease and treatment, and challenges in taking TKIs), which were further divided into nine subthemes, emerged from the interviews.

Theme 1: Understanding about disease and treatment *Understanding about CML*

The participants generally perceived CML as a cancer of the white blood cells, and frequent blood tests were necessary to monitor their disease progression. Besides, physical discomfort and bleeding were cited as the most common symptoms of CML.

"I am unsure of what chronic myeloid leukemia is exactly, but I know that my white blood cell count is

abnormally high, and both my red blood cell and platelet counts are low. Occasionally, I have experienced physical discomfort, too. Also, patients are likely to have blood coagulation disorders. That is why we are all required to undergo a blood test before tooth extraction.” (P6; imatinib)

However, the natural history and staging of CML were not well comprehended by the participants.

“It is related to increasing white blood cell count... White blood cells keep eating the red blood cells.” (P8; imatinib).

Understanding about TKIs

Despite the poor understanding about how TKIs help in their conditions and the methods used for monitoring the treatment outcomes, most participants still demonstrated a high level of confidence with the efficacy of the treatment.

“According to my doctor, if I do not take the medication, my white blood cell count will increase.” (P6; imatinib).

Furthermore, the physician-patient relationship appeared to be an important contributing factor to their confidence with the treatment, regardless of their knowledge about TKIs.

“I was shocked when I was first diagnosed with this disease, but my doctor gave me encouragement. He assured me that this medication will help me, so I felt more relaxed.” (P3; imatinib)

Theme 2: Challenges in taking TKIs

Adverse effects of TKIs

The participants, who took either imatinib or nilotinib, reported a number of adverse drug effects (ADRs), ranging from nausea, vomiting, itchiness, skin pigmentation, edema, weight loss, muscle weakness, mouth dryness, mouth ulcers, blurred vision, to temporary hearing loss. Although the ADRs were generally mild and tolerable, some participants still complained that their daily activities were significantly affected.

“Besides nausea and vomiting, I had ulcers in my mouth, which made it difficult for me to eat. Recently, I had blurred vision, too. My face was also swollen and itchy.” (P5; imatinib)

More importantly, some of the ADRs, such as nausea, vomiting and temporary hearing loss, had led several patients to withhold or alter their treatment.

“I was unable to hear for about a week, so I self-adjusted the dose. For example, if I was taking 200mg, I reduced it to 100mg during that week. I did not seek the consultation from doctors because my next clinic visit was 3 months after that.” (P6; imatinib)

Besides, minor ailments, such as cold and flu, were deemed as the ADRs of TKIs by some participants without referring to the physicians, resulting in self-adjustment of doses.

“I do not want to go to the doctor too frequently. I can judge it by myself, as I know my condition very well. If I have a flu or fever, I will reduce the dose by myself.” (P11; nilotinib).

Nevertheless, the majority of the patients chose to ignore the ADRs and continued the treatment, while some

also relied on certain self-designed coping strategies, which were believed to be effective, to reduce the symptoms.

“To prevent from vomiting, I usually take the medication with warm water, or mix it with milk to make it easier to swallow.” (P6; imatinib).

As far as the life-disturbing ADRs were concerned, all the participants, who had switched the treatment from imatinib to nilotinib, perceived that the latter was a better choice of drug, as it caused less severe nausea and vomiting.

“This medication is better because it does not cause severe nausea and vomiting. Therefore, I am able to do my work undisturbed.” (P4; nilotinib).

Forgetfulness

Occasionally, several participants forgot to take the TKIs. Anyhow, all of them claimed that they compensated for the missed doses as soon as they remembered.

“I sometimes missed a dose, but have never waited until the next day. Most of the time, I forgot to take the medication in the morning, and took it when I remembered in the afternoon or evening.” (P6; imatinib)

Although forgetfulness was almost inevitable, one of the participants highlighted the importance of getting help from family members.

“I have never missed a single dose. I have been following the schedule set by my doctor every day for two years. Even if I forget, my wife will remind me.” (P1; imatinib).

Traveling

Several participants tended to miss doses during traveling, especially when they unexpectedly needed to extend their stay in another country.

“I thought I had to go abroad only for two days, but instead I had to stay there for three days. I only brought the medications which were sufficient for two days of use” (P11; nilotinib).

Nonetheless, some of them managed to avoid missing any doses, mainly by ensuring that the amount of medications brought with them was more than what would be needed.

“If I go travelling, I will calculate the quantity of medications required, and will bring a few additional doses.” (P6; imatinib).

Religious and Social Issues

The Muslim participants disclosed that they had frequently skipped or changed doses of nilotinib, which needed to be taken twice daily, in order to fulfill their religious obligations during Ramadan (fasting month).

“I know it should be taken every 12 hours, but instead I have been taking it at 16-hour and 8-hour intervals during Ramadan. The doctor advised me not to fast; however, as a Muslim, fasting is one of the Five Pillars of Islam.” (P11; nilotinib).

Apart from that, active participation in social gatherings posed a barrier to adherence to nilotinib, which required patients to take it on an empty stomach.

“Sometimes, I went for a feast with my friends. By

6.30 pm, I should have taken my second dose. However, I had to take it later.” (P11; nilotinib).

Poor palatability and large tablet size

Several participants shared their unpleasant experiences with the poor palatability and large tablet size of imatinib, which made it difficult to swallow.

“This medication is very bitter and big, and difficult to swallow.” (P9; imatinib)

Poor appetite

One of the participants admitted that he had missed a few doses of imatinib, which should only be taken with food, due to poor appetite.

“I have been missing this medication about 2 to 3 times a month because of poor appetite. I need to take it with food, otherwise I will vomit again.” (P8; imatinib).

Concern over switching to a new TKI

A concern over the twice-daily dosing of nilotinib and the need for additional monitoring was expressed by one of the participants, who refused to switch his treatment from imatinib to nilotinib after receiving advices from the physician.

“Doctor recommended the new medication to me, but I did not want to change. This medication (imatinib) only requires blood monitoring, but doctor will also need to monitor my liver if I take the new medication (nilotinib). Besides, I cannot take any food for two hours before and one hour after taking that medication (nilotinib), meaning a total of three-hour fasting. I prefer this medication (imatinib) which I can take whenever I wish to.” (P6; imatinib)

Discussion

To the best knowledge of the investigators, this is the first study adopting a qualitative approach to explore the knowledge of Malaysian CML patients and their experiences in taking TKIs, which could have an impact on the long-term diseases control. Different from other qualitative studies focusing only on imatinib (Chen et al., 2011; Eliasson et al., 2011; Wu et al., 2015), this study also disclosed the challenges in taking nilotinib, as well as the reasons for refusal of switching the treatment from first- to second-generation TKIs.

Notwithstanding the fact that the majority of the participants had received tertiary education, they generally had limited knowledge of CML and its treatment. They perceived CML as a malignancy related to the changes in blood cell count, and believed that TKIs were an effective treatment for their conditions. However, their comprehension of other critical aspects of the disease, including its natural history and staging, the function of TKIs, and the methods used for monitoring the effectiveness of treatment, was limited in general. Although a good physician-patient relationship could improve the patients' confidence with the treatment (Gopichandran and Chetlapalli, 2015), it is still crucial for the healthcare professionals to provide them with all the information necessary so as to reinforce medication

adherence.

Apart from that, the participants were apparently lacking in awareness of the possible consequences of, either intentionally or unintentionally, withholding, skipping or altering the treatment. In response to the ADRs of TKIs which remarkably affected the quality of life, the participants were also found to either ignore them or relied on some non-proven, self-designed coping strategies. Rather, they should be educated that most of the mild, non-hematological ADRs of TKIs, such as nausea, vomiting, edema, and skin rashes, can be effectively controlled via a range of pharmacological or supportive measures (Deininger et al., 2003; Valent, 2011). Even if the ADRs were severe and intolerable, they need to recognize that dose interruption or adjustment can only be conducted after seeking advices from the physicians (DeAngelo, 2012).

Besides, in parallel with a number of studies (Chen et al., 2011; Eliasson et al., 2011; Wu et al., 2015), forgetfulness, traveling and poor palatability of TKIs were all found to be the barriers to medication adherence. Interestingly, the majority of the participants was found to refer to taking TKIs as an important part of their daily routine, but did not use any prompts, except for having a family member to remind them. It is therefore suggested that an intervention could be made to increase their commitment to the treatment; for example, by introducing the use of dosing boxes or alarms (Eliasson et al., 2011). Aside from that, intensifying education, medication counseling and post-consultation communication with patients are potential strategies for optimizing their adherence (Chen et al., 2011).

In addition, consistent with a previous study suggesting that switching to nilotinib may lead to less severe ADRs (Cortes et al., 2016), the participants who took nilotinib in this study were generally more satisfied with the current treatment, mainly attributable to the better controlled nausea and vomiting. Nevertheless, the inconvenience caused by the twice-daily dosing of nilotinib and the need to take it on an empty stomach was still constantly highlighted, particularly by the Muslim participants, and by those who had an active social life. Hence, besides the safety profile and efficacy of TKIs, the physicians should also take the patients' perspectives into consideration when evaluating the best treatment choice for each individual.

The major limitation of this study is that it only included CML patients actively followed up at the hospital, who were also likely to have better awareness of their health conditions and treatment. Additionally, the single-center design and the use of purposive sampling method for patient recruitment might limit the generalizability of the study findings. Besides, the economic burden posed by TKIs was not captured in this study, as the medications were provided free of charge to the patients under the MYPAP.

In conclusion, this study has revealed that Malaysian CML patients generally had limited knowledge of their health conditions and treatment. The findings have also provided important insights into the challenges in taking TKIs, some of which had led the patients to withhold, skip

or alter their treatment. Therefore, immediate attention, particularly from physicians and pharmacists, and an integrated plan to improve awareness and medication adherence among the patients are warranted.

Appendix I

Semi-structured Questionnaire

1. Could you tell me what chronic myeloid leukemia (CML) is?
2. Could you tell me how your CML is treated and monitored?
3. Do you know what your medication is?
Probes: oral tyrosine kinase inhibitor, imatinib, nilotinib.
4. Do you have any unpleasant experience with the treatment?
Probes: side effects, taste, inconvenience.
5. What are the strategies you use to cope with the unpleasant experience?
6. What are the problems that could cause you to skip a dose or stop the treatment?
7. Is there anything else that you wish to talk about?

Conflict of Interest Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors declare that there is no conflict of interest.

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