



Patient preferences for stopping tyrosine kinase inhibitors in chronic myeloid leukemia

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ABSTRACT

Background

We used an interview-assisted survey of patients with chronic myeloid leukemia (CML) at a single tertiary care centre to explore patient reactions to and preferences for, and the risk-acceptability of, stopping tyrosine kinase inhibitor (TKI) treatment.

Methods

The study included patients with confirmed CML currently being treated with a TKI. The survey was conducted by structured interview using a standard form. Patient preferences were explored in a case-based scenario using 0%–100% visual analog scales and 5-point Likert scales. Data were analyzed using proportions for dichotomous variables and medians and interquartile ranges for continuous variables.

Results

Of 63 patients approached, 56 completed the survey. Participant responses suggest that the idea of stopping TKI use is appealing to many patients if there is a chance of long-term stable disease and a high probability of response upon restarting a TKI. Participants were more likely to stop their TKI as the risk of relapse decreased. Participants reported loss of disease control and failure of disease to respond to treatment as important concerns if they chose to stop their TKI.

Conclusions

Given the current 60% estimated rate of relapse after discontinuation of TKI therapy, most patients with CML chose to continue with TKI. However, at the lower

relapse rates reported with second-generation TKIs, participants were more undecided, demonstrating a basic understanding of risk. Contrary to our hypothesis, neither compliance nor occurrence of side effects significantly affected patient willingness to stop their TKI.

KEY WORDS

Chronic myeloid leukemia, tyrosine kinase inhibitors, patient preference

1. INTRODUCTION

The introduction of imatinib represented a paradigm shift toward targeted anticancer therapy in the treatment of cancer. In 2003, the results of the IRIS trial (International Randomized Study of Interferon and STI571) led to imatinib becoming the first-line treatment for newly diagnosed patients with chronic myeloid leukemia (CML)¹. The second-generation tyrosine kinase inhibitors (TKIs) nilotinib and dasatinib have been compared with imatinib and have demonstrated more rapid achievement of molecular responses^{2,3}. Whether a faster response to TKI therapy leads to a survival benefit is unclear. The most recent data from the DASISION trial, comparing dasatinib with imatinib, have not shown any overall or event-free survival benefits at 2 years of follow-up². However, the 3-year follow-up data from the ENESTnd trial comparing nilotinib with imatinib have demonstrated advantages in overall (CML-related deaths) and event-free survival⁴.

Therapy with a TKI is currently life-long therapy, requiring patients to take medication daily and to make frequent visits for monitoring. Side effects related to TKI therapy affect quality of life for many patients, and the most common side effect, edema, is reported at a frequency of 56% in treated patients¹. Daily adherence to TKI therapy is also challenging for a significant proportion of patients. Adherence is an important goal in treatment, and adherence

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rates of less than 90% have been demonstrated to correlate with a lower likelihood of achieving a major molecular response⁵. Since imatinib was approved, case reports, case series, and prospective trials have described patient outcomes after stopping treatment^{6–15}. The largest study, the STIM trial, demonstrated a relapse rate of 62% after 2 years off TKI treatment⁸. Preliminary results from a small trial of stopping a second-generation TKI demonstrated a lower relapse rate of 31% after 4 months¹⁶.

Although relapse rates and patient scenarios have differed significantly between publications, it appears that certain patients might be able to stop their TKI without relapse. However, no study has addressed patient concerns or preferences about stopping TKI therapy, which is an important consideration for the potential application of study results. In the present work, we explored the willingness of patients to stop their TKI therapy and, after stopping, the risk of relapse that would be acceptable to them. Patient preference studies are important for informing clinical decisions and understanding the preferences of cancer patients for treatment. They can also potentially influence future clinical practice.

2. METHODS

2.1 Patients

Adult patients (18 years of age and older) with cytogenetic and molecular Philadelphia chromosome–positive confirmed CML being treated with a TKI were approached for participation in this study during a 3-month period. Patients were approached during their regular follow-up appointments, and surveys were completed while they were in clinic. The study was approved by Western University's Research Ethics Board on Health Sciences Research Involving Human Subjects, Institutional Review Board (IRB 102646).

2.2 Survey

Our survey was conducted by structured interview using a standard form. Interviews were conducted by interviewers not involved in the participant's care, and anonymity of the responses was emphasized. Interviews lasted approximately 25 minutes, with roughly half that time being spent to explain the relevant clinical data when obtaining consent for the study and to conduct the structured part of the interview (case scenario, Appendix A). Interviewers were able to rephrase and clarify questions as needed. The survey consisted of 5 demographic questions, 2 questions about TKI adherence, 6 about side effects, 1 about considerations for stopping the drug, and 1 about motivation for treatment adherence.

A hypothetical situation was then presented. The question explained basic information about TKIs and

recent research into stopping treatment. In brief, the scenario suggested that approximately 40% of CML patients with undetectable disease who stop their TKI do not relapse after 3 years off treatment⁸. We informed patients that most people who relapse after stopping respond to their TKI after restarting. After being read the scenario, patient preferences with respect to relapse rates were explored using a 0%–100% visual analogue scale describing the rate of relapse after stopping (2 questions) and a 5-point Likert scale ranging from “absolutely stop”¹¹ to “absolutely not stop”¹⁵ (4 questions). Concerns about stopping treatment were elicited (6 questions).

2.3 Statistical Analysis

Data were analyzed using proportions for categorical variables, including patient responses on the Likert scales. Medians and interquartile ranges (IQRs) were calculated for continuous variables. For the proportions, 95% confidence intervals (CIs) were calculated using the normal approximation method. Pearson chi-square tests were used to test the influence of demographic variables and the responses to the scenario-based questions about willingness to stop TKI therapy. The demographic information used in the chi-square analysis included education, age, sex, annual income, drug coverage, payment concerns, adherence, and side effects. A Mann–Whitney *U*-test was performed to test whether willingness to stop TKI therapy was related to duration of disease. For statistical tests, a *p* value of 0.05 or less was considered significant. The statistical analysis was performed using the IBM SPSS Statistics application (version 20: IBM, Armonk, NY, U.S.A.).

3. RESULTS

Between July 1 and September 30, 2012, 56 patients with CML participated in our study. For various reasons (such as lack of time to complete the survey), 7 patients who were approached did not participate. Table 1 shows the demographic information for the final study group. Mean time from CML diagnosis was 4.9 years (IQR: 1.7–6.8 years). Medication adherence of 75% or less was reported by 21% of participants. Daily side effects of TKI therapy were reported by 25% of participants, with 9% reporting side effects more than 50% of the time, and 66% reporting side effects less than 50% of the time.

Of the 56 participants, 40 (71.4%; 95% CI: 58.5% to 81.6%) indicated that they would be willing to stop their TKI if they were monitored by a sensitive test to detect relapse. Participants indicated that a median relapse rate of 25% (IQR: 10%–50%) would be acceptable to consider stopping their TKI. The median acceptable relapse rate increased to 30% (IQR: 18%–60%) when it was emphasized that most patients respond well after restarting TKIs. We observed no difference

TABLE 1 Demographics and tyrosine kinase inhibitor (TKI) use in the study population with chronic myeloid leukemia (CML)

Variable	Value
Patients (n)	56
Mean age (years)	52.8
Sex [n (%) men]	30 (53.6)
Education level [n (%)]	
Did not finish high school	19 (33.9)
Completed high school	13 (23.2)
Postsecondary	23 (41.1)
Declined response	1 (1.8)
Household income [n (%)]	
<\$50,000	28 (50.0)
\$50,000–\$100,000	21 (37.5)
\$100,000–\$200,000	5 (8.9)
>\$200,000	1 (1.8)
Declined response	1 (1.8)
Payment for CML medication [n (%)]	
Private insurance	36 (64.2)
Provincial coverage	18 (32.1)
No drug insurance plan	2 (3.6)
TKI used [n (%)]	
Imatinib	33 (58.9)
Nilotinib	11 (19.6)
Dasatinib	12 (21.4)
Adherence to TKI [n (%)]	
100% of the time	43 (76.8)
75% of the time	11 (19.6)
50% of the time	1 (1.8)
Side effect frequency [n (%)]	
Daily	14 (25)
>50% of the time	5 (8.9)
<50% of the time	37 (66.1)
Disease control [n (%)]	
Complete molecular response (>3 log reductions)	44 (78.6)

in the mean acceptable relapse rate for stopping TKI when comparing patients who had achieved a major molecular response (defined as a > 3 log reduction in Bcr-Abl transcripts) with those who had not (28.6% vs. 29.2%, $p = 0.93$).

Study participants were also presented with a range of hypothetical rates of relapse (20%, 40%, 60%, 80%) and asked to indicate the likelihood that they would stop their TKI at those rates. The rate of response to this question was 54 of 56 participants. The number of patients willing to stop their TKI was inversely related to the risk of relapse (Figure 1). Most participants reported that they would experience fears of CML relapse and drug resistance if they decided to stop their TKI (Table II), and 45% would

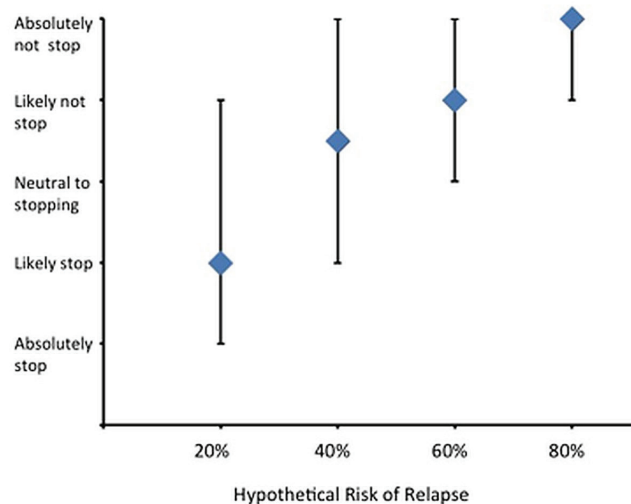


FIGURE 1 Median responses, with interquartile ranges, to the scenario question “If risk of relapse was ‘X%’ how likely would you be to stop your TKI [tyrosine kinase inhibitor]?”

be concerned about their ability to afford treatment should they need to restart a TKI after stopping. Fear of disappointing family or friends was expressed by 21% of participants. Of the full 56 participants, 53 responded that they would be “very likely” to take their TKI every day if their CML relapsed after stopping (94.6%; 95% CI: 85.4% to 98.2%). The Pearson chi-square test did not show any significant associations between willingness to stop a TKI and education level, age, income, insurance coverage for medications, or self-reported compliance and frequency of side effects (Table III). By Mann–Whitney U -test, duration of disease was not associated with willingness to stop TKI therapy ($p = 0.35$).

4. DISCUSSION

The results of studies that are reporting on stopping TKIs are intriguing and have the potential to change clinical practice in the management of CML. If the follow-up data from the STIM study suggest that stopping TKI use is a safe approach, it appears that some CML patients would consider that option. Our results suggest that the idea of stopping a TKI is appealing to many CML patients, particularly if the chance for sustained disease remission and the probability of disease control upon restarting a TKI are high. Understandably, many patients reported fears about loss of CML control and the possibility of disease resistance upon restarting TKI therapy after stopping treatment. A significant proportion of patients also reported concerns about paying for TKI therapy again after a trial of stopping, although re-institution of TKI therapy is currently covered for most patients in our province in the case of treatment interruptions. Interestingly, approximately 20% of patients reported

TABLE II Concerns about stopping tyrosine kinase inhibitor in the study population with chronic myeloid leukemia [CML ($n = 56$)]

Concern	Answered yes		
	(n)	(%)	(95% CI)
Fear of			
CML going out of control	45	80.4	68.2 to 88.7
Not responding to treatment if CML relapses	39	69.6	57.9 to 81.2
Having more drug side-effects if CML relapses	26	46.4	35.4 to 61.2
Being unable to afford treatment if CML relapses	25	44.6	33.0 to 58.5
Disappointing family or friends by stopping	12	21.4	13.0 to 34.4
Not getting adequate follow-up by physician	5	8.9	4.0 to 19.6

fears of disappointing family or friends with a trial of stopping TKI therapy. That finding might reflect the broader impact of cancer on a family or social group and possibly pressure exerted by friends and family to remain well.

However, the results of our study also suggest that many patients would likely prefer to continue their TKI, given the currently estimated relapse rate of 60% after stopping imatinib⁸. A small study reporting on discontinuation of second-generation TKIs suggests that the rate of relapse might be even lower after stopping treatment with those agents, being reported to be 31% in a group of 16 patients after a median follow-up of 15 months¹⁶. Based on our results, more patients might be interested in attempting a treatment interruption at that reported lower rate. The increasing willingness to stop TKI use as risk of relapse declines suggests that our group of patients understand basic concepts related to risk.

Men appeared to be more likely than women to stop their TKI therapy given the scenario presented. We found no other socioeconomic characteristics that correlated with willingness to stop TKI therapy, although it is difficult to accurately determine such associations because of the relatively small sample size.

In Canada, government drug benefits provide coverage for TKIs in all patients with CML, perhaps explaining why drug coverage was not associated with willingness to stop those agents. We had hypothesized that self-reported compliance and frequency of side effects would be associated with a patient's willingness to stop their TKI, but that was not the case. Medication adherence in our group was suboptimal, and approximately 20% of patients reported taking TKI only 75% of the time or less. However, that rate of adherence seems to be comparable to the rate in another study that reported adherence of less than 90% in approximately one quarter of CML patients⁵.

TABLE III Influence of demographics on likelihood of stopping tyrosine kinase inhibitor

Variable	df	Pearson chi-square	p Value ^a
Education	3	4.98	0.17
Age	1	0.38	0.55
Sex	1	3.74	0.05
Annual income	4	3.32	0.51
Insurance coverage for medications	4	2.54	0.64
Payment concerns	3	4.74	0.09
Adherence	2	1.34	0.51
Side effects	4	4.79	0.31

^a Significant at $p < 0.05$.

Because most patients reported only minor side effects, it is possible that patient fear of disease recurrence outweighs “nuisance” complaints. Catastrophic side effects, such as cancer recurrence, have been shown to disproportionately influence patient choice even when the risk is very small¹⁷.

The relatively wide range of responses to our questions about patient willingness to stop a TKI indicates that a prescriptive approach to decision-making about stopping would not be appropriate for this group. Ultimately, the choice to stop a TKI should involve shared decision-making between the patient and the clinician, which has been reported to be the approach preferred by most patients with cancer¹⁸. Conveying risk in treatment decisions is complex and is influenced by patient–physician communication and relationship¹⁹. These interactions are also affected by physician beliefs about quality of evidence, which influences how information about risk is conveyed to patients. Objective standardized patient education and decision tools could be useful adjuncts in such circumstances²⁰.

In consideration of the influence of the physician–patient relationship, a researcher outside the circle of care conducted the interviews in this study, and information given was based on a standardized information letter and survey form. Although this approach reduced interviewer-related influence, we acknowledge that interviewer factors might potentially have biased responses. There are also some limitations in our study design. This single-centre study had a limited number of participants, potentially leading to the bias that might arise when patients are all being seen by a single group of physicians. To minimize that influence, CML patients from all hematologists practicing at our centre were approached for inclusion in the study.

Our results can help to inform planning for future clinical trials in CML treatment discontinuation. Given the more rapid molecular response seen with second-generation TKIs, and applying the same criterion used in the STIM trial, recruitment for future trials might

be better than predicted by our survey results. We believe that the results from our study can also potentially be used to inform future discussions with patients who are considering stopping their TKI, which, currently, should be attempted only in the context of a clinical trial.

5. ACKNOWLEDGMENTS

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6. CONFLICT OF INTEREST DISCLOSURES

RK, DS, ICY, AX, and KHJ have no conflicts to disclose. CH has received honoraria from Novartis, and ALL has received honoraria from Pfizer, Leo Pharma, and Boehringer Ingelheim.

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APPENDIX A: SURVEY OF PATIENT PREFERENCES FOR DISCONTINUING TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA

Demographics

Unique ID: _____

Age: _____ years

Gender (please circle 1): Male Female

What is your highest education level completed:

- Did not finish high school
- High school
- College/university
- Post-secondary/graduate school
- Prefer not to say

What is your household income?

- <25,000
- 25,000–50,000
- 50,000–100,000
- 100,000–200,000
- >200,000
- Prefer not to say

How do you pay for your medications?

- Drug plan with 100% coverage
- Drug plan with partial coverage (you pay a portion)
- Drug plan with complete coverage up to maximum
- Provincial coverage (over 65 years old, disability, etc.)
- No drug plan (I pay for medications out of pocket)
- Do not know

Please rate your concern about payment for the medications you take for CML (please circle one):

No	Minor	Very
concern	concern	concerned

Tolerance of drugs for CML

Which statement best describes your feelings about medication for CML?

Taking medication every day for CML is:

- Simple and easy and I remember 100% of the time
 - Simple but sometimes hard to do and I remember about 75% of the time (3 days out of 4)
 - Is a nuisance and I skip or forget doses about 50% of the time
 - Is a major nuisance and I frequently skip or forget doses (more than half the time)
-

In most months I miss or skip my medication

- Never
- 1 to 5 days
- 6 to 10 days
- 11 to 15 days
- >16 days per month

I experience side effects from my medications

- Daily
- At least 50% of the time (> 15 days per month)
- About 25 to 49% of time (at least 1 week or 7 days per month)
- Less than 10 to 24% of time (3 to 6 days per month)
- Never

My Most Common Side Effects is/are (please indicate all applicable answers):

	Nil	Minor	Tolerable	Tolerable but I adjust my activities or take medications for it	Intolerable
Nausea or vomiting or other gastrointestinal upset	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle cramping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swelling or fluid retention (face or legs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (please list)					

Side effects are bothersome enough that I ...

- Skip doses of medication regularly (more than 50% of the time)
- Skip doses of medication occasionally (5 days per month)
- Consider stopping drug if alternative were available
- Consider stopping drug

Have you ever thought about stopping your medication?

- Never
- Sometimes
- Often
- Usually
- All the time

What worries you most about TKIs?

- Day to day side effects
- Unknown side effects that may occur with long term use
- Drug costs
- Fear of losing response to this medication
- I have no concerns about taking this medication

Other—Please specify:

What prevents you most from stopping you medication?

- My doctor's strong recommendation that I stay on it
- My fear of the disease CML going out of control
- My family's concern about my disease

Other—Please specify:

Patient Preference

Scenario

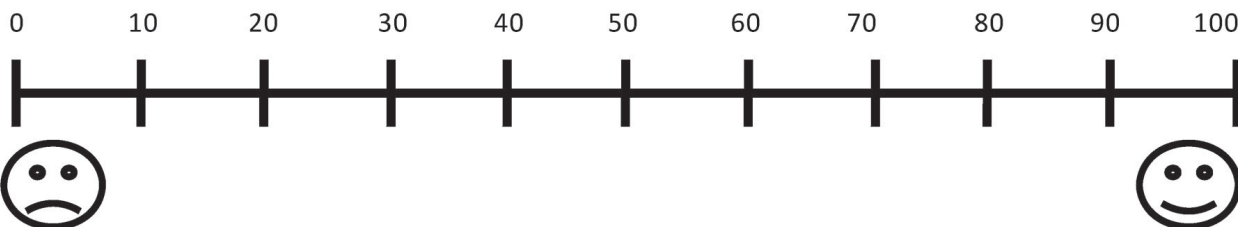
The success of drugs like Imatinib (Gleevec), Dasatinib (Sprycel) and Nilotinib (Tasigna) called tyrosine kinase inhibitors (TKIs) in treatment of chronic myeloid leukemia has dramatically improved the control of this disease in the past decade. Lifelong TKI therapy for patients with CML with regular monitoring is currently the accepted standard of care. This means that your doctor may have told you that you have to stay on this treatment indefinitely.

The majority of patients obtain a very good response and a proportion of patients have undetectable disease. The term undetectable disease generally means that we are unable to detect CML cells or CML genetic material using the most sensitive laboratory tests. The most sensitive DNA tests are currently not available at most centres, including the London Health Sciences Centre, since they are currently considered experimental at present times. Recent studies show that up to 40% of patients with undetectable disease can stop their TKI treatment without signs of relapse at 3 years. Furthermore, it appears that the 60% of patients who relapse after stopping their TKI treatment are able to restart their previous TKI treatment with good results.

Consider the following hypothetical questions. These are pretend questions and do not impact your current treatment with your own doctor. Given the choice and risk of relapse, we would like to understand if you would consider stopping TKI treatment.

1. Are you willing to stop your medication for CML if you are monitored closely with very sensitive blood tests (please circle one)?
 Yes No

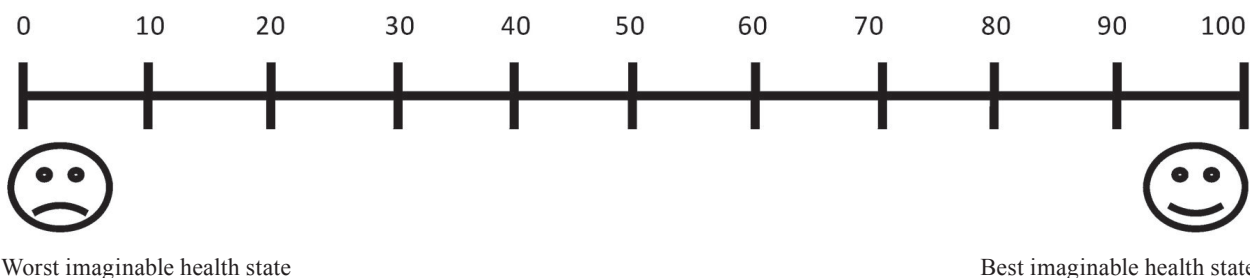
2. I would be willing to stop medication if the chance of relapse after stopping were:



Worst imaginable health state

Best imaginable health state

3. If my disease relapses after stopping medication, we know that almost all patients respond to restarting the same pills. Knowing this, I would be willing to stop medication if the chance of relapse after stopping were:



4. If my disease relapses after stopping medication and I were to restart a medication for CML, how likely are you to take your medications every day:

Very unlikely Unlikely Neither unlikely nor likely Likely Very likely

5. In the following questions, if the risk of relapse is different, how likely are you to stop medications for your CML?

If the risk of relapse were 20%?

I would absolutely stop I would likely stop I would be neutral I would likely not stop I would absolutely not stop

If the risk of relapse were 60%?

I would absolutely stop I would likely stop I would be neutral I would likely not stop I would absolutely not stop

If the risk of relapse were 40%?

I would absolutely stop I would likely stop I would be neutral I would likely not stop I would absolutely not stop

If the risk of relapse were 80%?

I would absolutely stop I would likely stop I would be neutral I would likely not stop I would absolutely not stop

6. Are any of the following factors concerns about stopping treatment? (Yes or No)

- Fear of the disease CML going out of control
- Fear that if the disease relapses you will not respond to treatment
- Fear that if the disease relapses you will not be able to afford treatment
- Fear that if the disease relapses you will experiences more side effects
- Fear that you will not get adequate follow-up by your doctor
- Fear that you will disappoint family or friends

CML = chronic myeloid leukemia; TKI = tyrosine kinase inhibitor.