Symptoms Following Discontinuation of Tyrosine Kinase Inhibitor (TKI) Therapy After Achieving an Adequate Response in Patients With Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

CML-046

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Background

- In the past decades, chronic myeloid leukemia (CML) has been transformed from being a fatal condition to being managed as a chronic disease[1,2]
- This advance is largely due to the advent of tyrosine kinase inhibitors (TKIs), the current standard of care for patients with newly diagnosed, Philadelphia chromosome positive CML (Ph+ CML) and in patients with Ph+ CML resistant or intolerant to prior therapy[3]
- Until recently, the National Comprehensive Cancer Network (NCCN) advised lifelong therapy for Ph+ CML patients responding to TKIs, even for those in chronic phase
  (Ph+ CML-CP) achieving sustained deep molecular remission[3]
- Lifelong therapy may not be feasible or preferable in all patients given its high cost and resource intensive nature
- This has prompted several clinical trials to assess the impact of TKI therapy discontinuation (e.g., STOP studies) on the risk of relapse or recurrence, particularly in patients who had maintained deep molecular response[4,5,6,7]
- Based on the safety and efficacy findings of these studies, the NCCN updated their practice guidelines for CML (CML, V1.2017) in November 2016 to include recommendations on TKI therapy discontinuation[3]
- Additionally, in December 2017, the US product label for TKI therapy nilotinib was updated to include treatment-free remission (TFR) data[8]
- TKI therapy discontinuation in eligible patients with an adequate response (i.e., TFR) is a new goal in Ph+ CML-CP
- In clinical trials, some patients experienced symptoms following TKI therapy discontinuation, notably musculoskeletal pain.[9,10,11,12] However, there is a lack of information regarding symptoms following TKI therapy discontinuation in real-world settings.

Objective

- The objective of this study was to assess symptoms following TKI therapy discontinuation in patients achieving an adequate response in US clinical practice, outside of clinical trials

Materials and Methods

Data Source

- This study was a retrospective chart review study
- Between June 6 and October 2 of 2017, patient-level data were collected from patient charts using an online form completed by US oncologists/hematologists during routine clinical practice **(Figure 1)**
  - Data collection was conducted before the release of the updated NCCN practice guidelines and nilotinib US product label advising TKI therapy discontinuation practice
- Oncologists/hematologists from various practice settings were recruited from an existing nationwide panel of physicians in the US. Oncologists/hematologists were eligible to participate in the study if, since January 2013 (i.e., date from which molecular response monitoring on the international scale [IS] became a more standard procedure/more commonly available), they were responsible for treatment decisions and follow-up for at least 1 adult patient with Ph+ CML-CP who received a TKI and for whom they had access to molecular monitoring results reported on the IS at some point during therapy, as well as complete information on the CML-related care from the Ph+ CML-CP diagnosis for ≥2 years, unless the patient died within 2 years
- Data were extracted for adult patients diagnosed with Ph+ CML-CP who initiated a TKI as first-line therapy, not as part of a clinical trial, between January 2006 and March 2014
  - Patients meeting these selection criteria constituted the ***All-Comer Sample***
- Oversampling was conducted to collect additional charts of patients meeting an additional sample selection criterion of a TKI therapy discontinuation after achieving an adequate response (per physician's assessment)
  - These additional patients constituted the ***Oversample***
- Patients from the All-Comer Sample with a TKI therapy discontinuation after achieving an adequate response (per physician's assessment) and those from the Oversample were combined for all analyses
  - These patients with a TKI therapy discontinuation constituted the ***TKI Therapy Discontinuation Cohort***

Outcomes and Statistical Analyses

- The main outcome measured was symptoms following TKI treatment discontinuation **(Table 1)**
  - The type of symptoms, severity, treatments recommended or prescribed, and treatment alleviation were characterized at the patient-level
- All statistical analyses were descriptive

Figure 1: Questions Relating to Symptoms Following TKI Therapy Discontinuation Completed by Participating Oncologists/Hematologists

Question 1: Following discontinuation of TKI therapy, did the patient experience any symptoms (select all that apply)?

1. Yes, musculoskeletal pain
2. Yes, gastrointestinal symptoms
3. Yes, neurologic or psychiatric symptoms
4. Yes, other, specify _____
5. No

Question 2: Rate the severity of the symptom(s) following TKI therapy discontinuation and indicate if any treatment was recommended or prescribed to alleviate the symptoms.

Symptom	Severity	Was the symptom also observed before discontinuation?	Treatment (select all that apply)		Did the treatment alleviate the symptom?
			Treatment you recommended (OTC)	Treatment you prescribed	
Musculoskeletal pain	1. Grade 1 2. Grade 2 3. Grade 3 4. Grade 4 5. Grade 5 6. Other, specify _____	1. Yes 2. No	1. No OTC treatment 2. Painkillers 2a. Acetaminophen (e.g., Tylenol) 2b. Other, specify _____ 3. Nonsteroidal anti-inflammatory drugs (NSAIDs) 3a. Ibuprofen (e.g., Advil) 3b. Naproxen 3c. Other, specify _____ 4. Ice/heat 5. Other, specify _____ 6. Information not available	1. Painkillers 1a. Acetaminophen (e.g., Tylenol) 1b. Opioid-containing medications 1c. Other, specify _____ 2. NSAIDs 2a. Ibuprofen (e.g., Advil) 2b. Naproxen 2c. Other, specify _____ 3. Steroids (e.g., prednisone or dexamethasone) 4. Re-initiate same TKI, same dose 5. Re-initiate same TKI, lower dose 6. Initiate a different TKI 7. Other, specify _____ 8. No treatment prescribed	1. Yes 2. No
Gastrointestinal symptoms	1. Grade 1 2. Grade 2 3. Grade 3 4. Grade 4 5. Grade 5 6. Other, specify _____	1. Yes 2. No	1. H2 blockers 2. PPIs 3. Motility drugs 4. Painkillers 5. Other, specify _____ 6. No treatment prescribed		1. Yes 2. No
Neurologic or psychiatric symptoms	1. Grade 1 2. Grade 2 3. Grade 3 4. Grade 4 5. Grade 5 6. Other, specify _____	1. Yes 2. No	1. Painkillers 2. Gabapentin 3. Lyrica 4. Antidepressants 5. Anti-anxiety agents 6. Anti-seizure drugs 7. Other, specify _____ 8. No treatment prescribed		1. Yes 2. No
Other	1. Grade 1 2. Grade 2 3. Grade 3 4. Grade 4 5. Grade 5 6. Other, specify _____	1. Yes 2. No	1. Other, specify _____ 2. No treatment prescribed		1. Yes 2. No

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Results

PATIENT CHARACTERISTICS

- A total of 157 oncologists/hematologists participated in the chart review study and 146 patients (All-Comer Sample: 25, Oversample: 121) constituted the TKI Therapy Discontinuation Cohort
- These patients had a median (IQR) age of 58 years (44–67) and almost all had their TKI therapy discontinued in first line (99%) (**Table 2**)

Table 2. Patient Characteristics and Clinical Profile

	TKI Therapy Discontinuation Cohort (N=146)
Age at Ph+ CML-CP diagnosis (years)	
Mean [SD]	54 [16]
Median [IQR]	58 [44–67]
Female, N (%)	71 (48%)
Race/ethnicity, N (%)	
White - Non-Hispanic/Latino	92 (63%)
Black or African American - Non-Hispanic/Latino	30 (21%)
Hispanic/Latino	20 (14%)
Other	4 (2%)
Insurance type at TKI therapy initiation as first-line therapy for Ph+ CML-CP, N (%)[1]	
Commercial/private insurance	83 (57%)
Medicare	43 (30%)
Medicaid	29 (20%)
Military insurance (VA or active military)	3 (2%)
No insurance	2 (1%)
Unknown/Not sure	1 (1%)
ECOG performance status at diagnosis, N (%)	
Grade 0 - 1	136 (93%)
Grade 2+	10 (7%)
Year of first-line TKI therapy initiation, N (%)	
2006 -2008	16 (11%)
2009 - 2011	49 (34%)
2012 - 2014	81 (55%)
First-line TKI therapy, N (%)	
Dasatinib	30 (21%)
Imatinib	100 (69%)
Nilotinib	16 (11%)
TKI therapy duration before discontinuation (years)	
Mean [SD]	3 [2]
Median [IQR]	3 [2–4]

CML: chronic myeloid leukemia; CP: chronic phase; ECOG: Eastern Cooperative Oncology Group; Ph+: Philadelphia chromosome positive; TKI: tyrosine kinase inhibitor, SD: standard deviation, IQR: interquartile range
[1] Physicians were able to select more than one option

SYMPTOMS FOLLOWING TKI THERAPY DISCONTINUATION

- Of the 146 patients for whom TKI therapy was discontinued after achieving an adequate response, 25/146 patients (17%) experienced symptoms following TKI therapy discontinuation with 2 patients having experienced ≥2 symptoms
- The most commonly reported symptom was musculoskeletal pain (12% [17/146]) **(Figures 2a & b)**
- Other symptoms included gastrointestinal (GI; 6% [8/146]) and neurologic/psychiatric symptoms (1% [2/146]) **(Figures 2a & b)**; no other symptoms were reported
- In most cases, symptoms were already present before TKI therapy discontinuation. Specifically, symptoms were already present in:
  - 41% (7/17) of patients with musculoskeletal pain
  - 63% (5/8) of patients with GI symptoms
  - 100% (2/2) of patients with neurologic/psychiatric symptoms
- All patients with symptoms following TKI therapy discontinuation received a treatment
- For the treatment of musculoskeletal pain **(Figure 3a)**:
  - 17/17 patients (100%) were recommended painkillers; 15/17 (88%) received acetaminophen (e.g., Tylenol) and 4/17 (24%) received opioid-containing painkillers
  - 8/17 (47%) were recommended NSAIDs in addition to pain killers
  - 2/17 (12%) were restarted on their initial TKI therapy
    - 1/17 (6%) at a lower dose
    - 1/17 (6%) at the same dose
    - No patients were initiated on a new TKI
  - 1/17 (6%) was prescribed steroids
  - No other treatments were received for musculoskeletal pain
- For GI symptoms, 6/8 patients (75%) were prescribed proton pump inhibitors (PPIs) and 4/8 (50%) H2 blockers **(Figure 3b)**; none received motility drugs, painkillers, or any other treatments
- For neurologic/psychiatric symptoms, 1/2 patients (50%) was prescribed anti-depressants and 1/2 (50%) gabapentin **(Figure 3c)**; none received anti-anxiety agents, anti-seizure drugs, pregabalin, painkillers, or any other treatments
- Treatment alleviated symptoms for most patients (musculoskeletal pain, 94%; GI, 88%; neurologic/psychiatric, 100%)

Figure 2a: Type of Symptoms Following TKI Therapy Discontinuation (N=146)

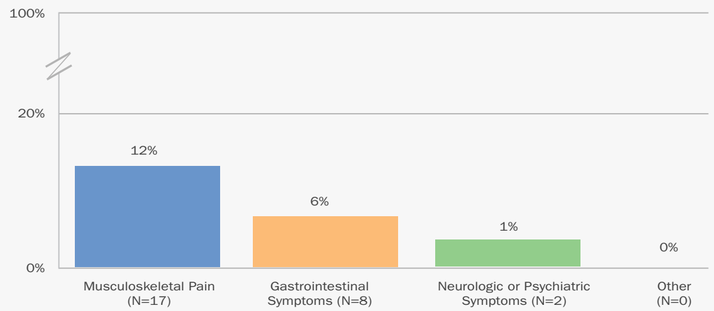


Figure 2b: Severity of Symptoms Following TKI Therapy Discontinuation

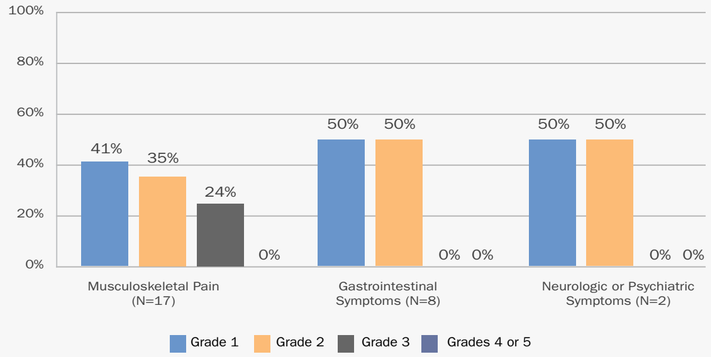
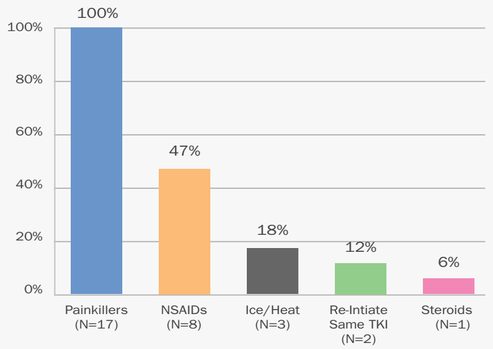
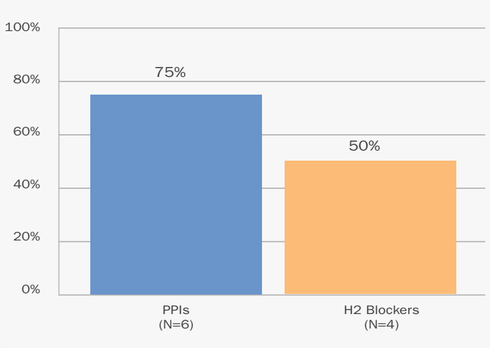


Figure 3a: Treatments for Musculoskeletal Pain (N=17)



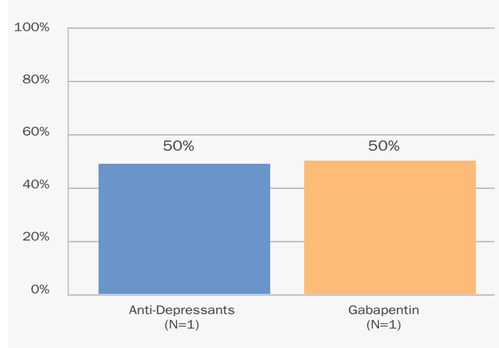
NSAIDs: Non-steroidal anti-inflammatory drugs, TKI: tyrosine kinase inhibitor

Figure 3b: Treatments for Gastrointestinal Symptoms (N=8)



PPIs: Proton pump inhibitors

Figure 3c: Treatments for Neurologic/Psychiatric Symptoms (N=2)



LIMITATIONS

- This study may be subject to potential biases, including a selection bias and a recall bias
- Data collection was conducted before the update of practice guidelines with recommendations for TKI therapy discontinuation. TKI therapy may have been discontinued under suboptimal conditions
- Generalizability may be limited by the sample size and the retrospective design of the study

CONCLUSIONS

- Symptoms following TKI therapy discontinuation after achieving an adequate response (per physicians' assessment) were observed in 17% of patients with Ph+ CML-CP in US clinical practice, outside of clinical trials
  - The most commonly reported symptom was musculoskeletal pain followed by GI symptoms
- Although a small proportion of patients experienced symptoms following TKI therapy discontinuation, the majority of these symptoms were already present before discontinuation, were largely of low severity, and were alleviated by medication

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