



UNITED STATES (US) EXPERT CONSENSUS ON DEFINING INTOLERANCE TO TYROSINE KINASE INHIBITOR (TKI) TREATMENT IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA (CML)

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INTRODUCTION

- Prevalence of CML has risen, in part due to the effectiveness of BCR-ABL1 TKI therapy at improving survival of patients with chronic phase (CP) CML.
- CML has been transformed from a fatal disease into a manageable condition.
- In addition to prolonging survival, the goals of CML therapy now include treatment-free remission (TFR), improving quality of life (QoL), and reducing long-term toxicities.
- There is no clear definition of treatment intolerance, making it difficult for clinicians to know when to recommend modifications to TKI therapy.

AIM

Define intolerance to CP-CML treatment.

- We developed an expert consensus-based definition of treatment intolerance in CP-CML to help inform clinical decision-making.

RESULTS

- Physician panelists had an average of 14 (range 4-24) years of experience and treated an average of 199 (range 30-600) patients in the past year.
- Panelists agreed on the majority of ratings defining treatment intolerance and TKI management strategies (Table 1).
- Panelists agreed that only the frequency with which AEs interfered with daily activities (rarely, sometimes, often) and the grade of laboratory abnormalities (Grade 1, 2, 3) has an impact on whether a treatment is considered tolerable and whether a change in TKI therapy should be made.
- The definition is for patients who are currently being treated with TKI therapy and in the absence of AEs would be continued on that therapy.

Table 1. Rating form results

N=480	Agreement			Disagreement % (n)
	Median ≥7-9 % (n)	Median ≥4-<7 % (n)	Median 1-<4 % (n)	
First-round	33 (156)	18 (88)	33 (156)	17 (80)
Second-round	34 (165)	30 (142)	35 (167)	1 (6)

Disagreement was defined as ≥2 panelist ratings of 1 to 3 and ≥2 panelist ratings of 7 to 9 within the same scenario. Percentages may not add to 100 due to rounding.

Expert consensus: Definition of intolerance

As AEs increasingly interfere with patient's daily activities, patients can be considered increasingly intolerant to TKI treatment:

- TOLERANT:** Patients can be deemed **tolerant** to treatment if AEs **rarely** interfere with daily activities within the past week. In these circumstances, panelists agreed it is appropriate to keep TKI treatment unchanged.
- INTOLERANT:** Patients can be deemed **intolerant** to treatment if AEs **often** interfere with daily activities within the past week. In these circumstances, panelists agreed it is appropriate to change TKI treatment (i.e., switch to another TKI treatment, hold, or reduce the dose if patient continues to respond to therapy).
- UNCERTAIN:** Patients whose AEs **sometimes** interfere with daily activities within the past week may be intolerant to treatment. In these circumstances, panelists agreed that it may be appropriate to make modifications to TKI therapy depending patient and physician discussion. Goal of therapy, line and generation of TKI treatment, and/or length of time on current TKI treatment could be considered.

Similarly, patients with more severe (i.e., ≥Grade 3) laboratory abnormalities (for both hematologic and non-hematologic laboratory abnormalities) can be considered intolerant to TKI treatment.

Importance of patient perspective

Specific AEs alone will not determine whether a patient tolerates treatment. Instead, panelists agreed that the patient's perspective on the degree to which the AE interferes with their daily activities is instrumental in a definition of intolerance.

Common AEs from TKI therapy (e.g., GI signs/symptoms [diarrhea, constipation, nausea, vomiting], fatigue, headache, rash, muscle spasms, myalgia, joint pain, shortness of breath/coughing/chest pain, edema) may or may not interfere with patients' daily activities based on individual circumstances.

For example:

- Mild nausea without loss of appetite may not interfere with the daily activities of one patient but may often interfere with the daily activities of a patient who works in the food industry.
- Joint pain, myalgia, or muscle spasms that limit movement may not interfere with the daily activities of a mostly sedentary patient but may often interfere with the daily activities of a young athlete.
- Fatigue relieved by rest may not interfere with a retired patient's daily activities but may interfere with the work of others.

To apply this guidance, it is crucial that clinicians elicit directly from patients the degree to which AEs interfere with their daily life. See Figure 1 for an example of a tool developed here by panelists to elicit this information.

METHOD

Double-blinded RAND/UCLA modified Delphi panel method:

- Panelists from the US with diverse backgrounds, selected by a panel chair, included: 8 hematologist/ oncologists, 1 hematologist, 1 pharmacist, 1 advanced practice provider, 1 PhD CML researcher specializing in patient reported outcomes, and 1 patient with CML.
- Panelists were provided with a literature review on current treatment of CML and strategies for managing TKI tolerability.
- Panelists completed 2 rounds of expert ratings using a rating form; live discussion in between.
- Second-round ratings formed the basis of expert consensus.

Rating form

- Developed in collaboration with panelists, consisted of 480 unique patient scenarios that varied by:
 - Goal of therapy
 - Line and generation of TKI treatment
 - Length of time on current TKI treatment
 - Whether supportive measures alone or with a hold/dose reduction in TKI therapy had been taken
- Frequency with which adverse events (AEs) interfered with daily activities in the past week (rarely, sometimes, vs. often interfered)
- Grade of laboratory abnormalities (Grade 1, 2, vs. 3)
- AEs were considered in aggregate.
- On a 1 to 9 scale, panelists rated: 1) the appropriateness of 3 different TKI management strategies (no change, hold or dose reduce, switch or discontinue), and 2) the patient's intolerance to therapy.
- Disagreement was defined as ≥2 panelist ratings of 1 to 3 and ≥2 panelist ratings of 7 to 9 within the same patient scenario.

CONCLUSIONS

- Experts agreed that the degree to which AEs (e.g., gastrointestinal, constitutional) interfere with patients' daily activities within the past week directly affect a definition of treatment intolerance.
- Prior to this study, there was no clear definition of treatment intolerance. This standardized definition will facilitate better comparisons across therapies and guide treatment decisions that prioritize both efficacy and patient QoL.
- To apply this guidance, **it is crucial that clinicians elicit directly from patients the degree to which AEs interfered with their daily life in the preceding 7 days.** The patient's answer will determine their treatment intolerance. A tool such as the one shown here (Figure 1) can be used to elicit this information.

Figure 1. Example of assessment tool

In the last week, how often did the following symptoms (if experienced) interfere with your daily activities – rarely, sometimes, or often? Check the box that best describes your experience.

Symptom	How often did the symptom <u>interfere</u> with your daily activities?			I did not experience this
	Rarely	Sometimes	Often	
Gastrointestinal				
Diarrhea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Constitutional				
Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Headache	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle spasms	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Muscle pain (myalgia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Joint pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shortness of breath, coughing, and/or chest pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Swelling (edema)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
[List other symptoms as needed]	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Scoring for clinician use: Patients can be deemed **intolerant** to treatment if one or more AEs **often** interfere with daily activities in the past week.