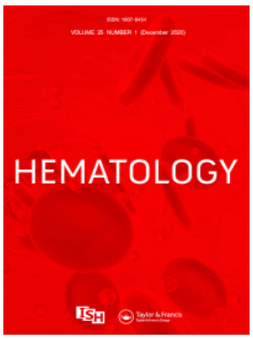

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Expert consensus definition of treatment intolerance in chronic myeloid leukemia in chronic phase

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ABSTRACT

Introduction: Chronic myeloid leukemia in the chronic phase (CML-CP) has undergone therapeutic transformation with the advent of BCR::ABL1 tyrosine kinase inhibitors (TKIs), improving 10-year survival rates from 20% to ~90%. These outcomes place increasing importance on maintaining quality of life (QoL), which can be compromised by adverse events (AEs) that may lead to decreased adherence or sub-therapeutic doses. Currently, there is no standardized definition of treatment intolerance, and treatment switches are based on individual physician practices.

Methods: A 13-member expert panel used a validated methodology (RAND/UCLA modified Delphi panel) to develop consensus on a definition of treatment intolerance in CML-CP. Panelists reviewed literature and provided 480 ratings on 96 unique patient scenarios that varied by TKI generation, line, and length of time on TKI treatment, frequency of AE interference on daily life, and TKI management strategies. Ratings were discussed at a meeting.

Results: After discussion, panelists agreed on 99% of scenarios. The group defined TKI treatment intolerance as patients whose AEs often interfered with daily activities, leading to TKI modifications. Panelists developed a tool to assess patient intolerance and recommendations for managing TKI therapy in the context of intolerance.

Discussion: Recognizing that treatment intolerance is influenced by laboratory findings, reported symptoms, and how patients experience their treatment, experts agreed on a patient-centered definition of TKI treatment intolerance in CML-CP. This definition represents a step forward in standardizing care for patients with CML-CP by presenting a balanced framework for managing TKI therapy, which will support shared decision-making.

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Introduction

Chronic myeloid leukemia (CML) in the chronic phase (CML-CP), the stage at which the majority of individuals with CML in Western nations are diagnosed, is characterized by the uncontrolled proliferation of maturing myeloid cells in the bone marrow, often with few symptoms [1]. Over the past 25 years, CML-CP has seen remarkable therapeutic advancements with the introduction of BCR::ABL1 tyrosine kinase inhibitors (TKIs). The six TKIs approved for CML in the United States (US) (imatinib [2], dasatinib [3], nilotinib [4], bosutinib [5], ponatinib [6], and asciminib [7]) have transformed CML from a fatal disease to a manageable condition, with a life expectancy approaching that of the general population. Since 2001, the 10-year survival rate has risen from 20% to ~90% [2], but maintaining these outcomes requires oral therapy, sometimes with difficulty. As a result, therapeutic focus has shifted towards maximizing quality of life (QoL) and reducing long-term toxicities.

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Despite TKIs' success, the definition of treatment intolerance remains underexplored. All TKIs can cause general early toxicities (e.g. rash, nausea, fatigue) and drug-specific toxicities (e.g. dasatinib-induced pleural effusion [8, 9], nilotinib-related dyslipidemia, and arterial thrombosis [10, 11]) that may necessitate treatment switches. More than a quarter of patients on first-line therapy and up to a third on second-line therapy require a TKI switch [12]. Yet no unified metric defines when toxicity become intolerable [13, 14]. Clinical trials have used differing definitions [13], inconsistently applied in clinical practice. Most research has focused on acute toxicities using the Common Terminology Criteria for Adverse Events (CTCAE), which defines intolerance as recurring grade 3 or 4 non-hematologic toxicity despite dose reduction and management [15]. However, lifelong daily therapy means even grade 1 or 2 toxicities can significantly impair QoL and require systematic management [16]. Moreover, treatment changes due to intolerance are subjective and influenced by patient and physician preferences.

Without a clear, standardized definition, clinicians and patients rely on individual judgment to determine whether side effects qualify as 'intolerance.' This inconsistency can delay switching or trigger premature changes, compromising care. To address this gap, we used a rigorous, reproducible process to derive consensus on defining treatment intolerance in US adults with CML-CP experiencing low-grade toxicity (i.e. no severe toxicities or serious complications requiring immediate intervention). The aim was to generate a standardized definition to improve treatment comparisons and guide clinical decision-making, prioritizing both efficacy and patient QoL.

Methods

This study used the RAND/UCLA modified Delphi panel method to define treatment intolerance in CML-CP (Figure 1). This formal group consensus process systematically and quantitatively combines expert opinions and evidence by asking panelists to rate, discuss, and re-rate items [17].

The panel consisted of 13 experts: nine hematologists/oncologists, one pharmacist, one advanced practice registered nurse, one PhD researcher specializing in patient-reported outcomes in CML, and one patient with CML-CP. Clinicians averaged 13 years of experience in practice, treating approximately 200 patients with CML annually.

This study was funded by Novartis Pharmaceutical Corporation and was double-blinded. While work was ongoing, all but the moderator and panel chair were blinded to the sponsor's identity, and vice versa.

Figure 1. Modified Delphi panel methodology.

Unblinding occurred after results were submitted for conference presentation [18]. The sponsor had no input on the methodology or findings. Panelists were compensated for their participation. As modified Delphi panels do not involve human subjects as defined in 45 CFR parts 46 [19], institutional review board approval was not required.

Panelists reviewed a summary of the relevant literature on CML-CP treatments, including first-, second-, and third-line TKIs, common toxicities, and strategies for long-term management. A targeted search of the PubMed database was conducted. The search strategy and a reference list of the studies reviewed is provided in the Supplementary Appendix. The quality of the evidence was not formally appraised.

Through individual phone interviews to discuss CML-CP and TKI treatments, panelists collaboratively developed 96 unique patient scenarios varying by the clinical characteristics outlined in Table 1. Scenarios included patients with hematologic and non-hematologic laboratory abnormalities (CTCAE v5.0 grades 1-3) [20] on any line of therapy. All patients in these scenarios had confirmed CML-CP, were adherent to TKI therapy, had no TKI resistance or serious complications requiring immediate intervention, experienced AEs that impacted QoL despite supportive care, and had been on therapy for at least three months (as experts agreed that changes should not be made within the first three months of therapy initiation).

For each scenario, panelists gave five ratings (Table 2), totaling 480 questions total. Using a 1-to-9 scale, panelists rated the appropriateness of modifying TKI therapy – ranging from no change, to dose hold or reduction, to switching or discontinuing after prior modifications. Panelists also rated whether they would consider the patient intolerant to therapy, before and after a hold or dose reduction.

Ratings were completed before and after a professionally moderated virtual panel meeting in June 2024. During the meeting, panelists received a document showing their individual ratings alongside the group's

Table 1. Clinical characteristics in patient scenarios.

Characteristic	Definition[a]
Treatment goal	• Treatment-free remission; these patients may have an eventual goal of discontinuing therapy. • Patients on chronic therapy; these patients are likely to remain on therapy for the rest of their lives.
Generation of TKI therapy	• First generation [1G], including imatinib. • Second generation [2G], including dasatinib, nilotinib, bosutinib. • Third generation [3G]), including ponatinib, asciminib, or panelist-preferred 3G agent.[b]
Line of TKI therapy	• First-line • Later-line (anything beyond first-line e.g. second, third, fourth, etc.)
Length of time on TKI therapy	• Short (e.g. 3–6 months) • Intermediate (e.g. 12–18 months) • Long (e.g. 2+ years)
Frequency with which AEs[c] interfered with a patient's daily activities within the past week	Content of the item stem was informed by the 'Patient Reported Outcomes Measures Information System [PROMIS] – Ability to participate in social roles and activities' scale [21] • Rarely • Sometimes • Often
Grade of laboratory abnormalities	CTCAE v5.0 definitions for non-hematologic and hematologic laboratory abnormalities: • Grade 1 • Grade 2 • Grade 3

TKI, tyrosine kinase inhibitor; AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.
[a]Except for the grade of laboratory abnormalities, definitions developed by panelists for the purpose of this study.
[b]At the time of the panel meeting (June 2024), panelists agreed to classify asciminib as a 3G agent. However, some clinicians consider this to be an allosteric inhibitor [22, 23]. Furthermore, a study published after the panel meeting supported the use of asciminib as a first-line agent [24], prompting the FDA to grant accelerated approval for its use in adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML-CP) in October 2024 [25].
[c]Panelists agreed that it was appropriate to consider the extent to which AEs interfered with daily activities rather than a specific description of an AE.

Table 2. Rating scales.

Question	Scale
After supportive measures have been attempted	
1. Appropriateness of making no change to the TKI	1 = inappropriate, 9 = appropriate
2. Appropriateness of holding or dose reducing the TKI	1 = inappropriate, 9 = appropriate
3. Rate the patient's intolerance to therapy	1 = tolerant, 9 = intolerant
After supportive measures AND a hold or dose reduction have been attempted	
4. Appropriateness of switching or discontinuing TKI	1 = inappropriate, 9 = appropriate
5. Rate the patient's intolerance to therapy	1 = tolerant, 9 = intolerant

TKI: tyrosine kinase inhibitors.

median and range (example in the Supplementary Appendix). Discussion focused on areas of disagreement, defined as ≥2 ratings of 1–3 and ≥2 of 7–9 for the same scenario [21]. Items without disagreement were classified into three categories based on their median scores (1–3, 4–6, 7–9). Second-round ratings were analyzed to develop consensus statements, as presented below.

Results

Following the discussion, agreement was reached on 99% ($N = 474/480$) of ratings compared to 83% ($N = 400/480$) in the first round. The following statements summarize how the panel defined TKI treatment intolerance and related management strategies. They are intended to guide, not supersede, clinical judgment in treating adult patients with CML. Users should consider each patient's individual circumstances and share decision-making with patients and caregivers. Every case is different, and it would be impossible to include all clinical scenarios.

Definition of treatment intolerance and management of TKI

While the panel considered various clinical scenarios that may impact the definition of treatment intolerance (see Methods section), they ultimately agreed that two key factors define treatment intolerance: (1) how often AEs interfere with a patient's daily activities (rarely, sometimes, often) and (2) the grade of laboratory abnormalities (grades 1, 2, 3).

The panelists also agreed that increasing AE interference with daily activities signifies increasing intolerance to TKI treatment (Table 3).

Similarly, panelists agreed that patients with more severe (i.e. ≥grade 3) laboratory abnormalities – hematologic and non-hematologic – could be considered intolerant to TKI treatment (Table 4).

The panel emphasized that AE features alone don't define treatment intolerance. Rather, because most patients require lifelong TKI therapy, a patient's own perspective on how AEs interfere with their daily activities is central to defining intolerance. Common AEs (e.g. nausea, fatigue, joint pain, shortness of breath, and periorbital/ankle edema) may or may not interfere with daily activities depending on the individual. 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 another. One patient may not feel joint pain, muscle pain, or muscle spasms that limit movement interfere with their daily activities, whereas another patient

Table 3. Definition of TKI intolerance based on non-laboratory AEs.

Frequency of AEs interference with daily activities within the past week	Intolerance to TKI therapy	Appropriateness of making a change to TKI therapy[a]
Rarely	Tolerant to treatment	Appropriate to keep TKI treatment unchanged
Sometimes	May be intolerant to treatment	May be appropriate to make modifications to TKI therapy depending on patient and physician discussion (e.g. goal of therapy, line and generation of treatment, and length of time on current treatment could be considered)
Often	Intolerant to treatment	Appropriate to change TKI treatment (i.e. hold or reduce the dose if patient continues to respond to therapy, switch to another TKI treatment after a hold and/or dose reduction has been attempted)

TKI: tyrosine kinase inhibitors; AEs: adverse events.
[a]In all scenarios, panelists considered patients who had been on therapy for at least three months and did not experience serious complications that required immediate intervention.

Table 4. Definition of TKI intolerance based on laboratory abnormalities.

Grade of hematologic and non-hematologic laboratory abnormality[a]	Intolerance to TKI therapy	Appropriateness of making a change to TKI therapy[b]
Grade 1[c]	Tolerant to treatment	Appropriate to keep TKI treatment unchanged
Grade 2	May be intolerant to treatment	May be appropriate to make modifications to TKI therapy depending on patient and physician discussion (e.g. goal of therapy, line and generation of treatment, and length of time on current treatment could be considered)
Recurrent or persistent grade 3[d]	Intolerant to treatment	Appropriate to change TKI treatment (i.e. switch to another TKI treatment, hold, or reduce the dose if patient continues to respond to therapy)

[a]As defined by CTCAE v5.0.
[b]In all scenarios, panelists considered patients who had been on therapy for at least three months and are not experiencing serious complications that require immediate intervention.
[c]E.g. platelet count decreased LLN-75,000/mm^3, ALT increased up to 3xULN.
[d]For example, anemia requiring transfusion, pancreatic enzymes decreased/sequelae of absorption deficiency.
TKI: tyrosine kinase inhibitors.

may disagree. Similarly, fatigue relieved by rest may be manageable for a retired patient but not for someone more active.

Application of guidance in clinical practice

To apply this guidance, clinicians should directly ask patients: 'In the last week, how often did [*symptoms the patient reports*] interfere with your daily activities – rarely, sometimes, or often?' The patient's response informs intolerance status. There exist validated tools for use in clinical trials [22, 23]. Based on these, the panel developed a patient-centric assessment tool as a part of this project to elicit this information in routine clinical practice (Figure 2).

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 interfere with your daily activities? Rarely	Sometimes	Often	I did not experience this
Gastrointestinal				
Diarrhea	☐	☐	☐	☐
Constipation	☐	☐	☐	☐
Nausea	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐
Constitutional				
Fatigue	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Rash	☐	☐	☐	☐
Muscle spasms	☐	☐	☐	☐
Muscle pain (myalgia)	☐	☐	☐	☐
Joint pain	☐	☐	☐	☐
Shortness of breath, coughing, and/or chest pain	☐	☐	☐	☐
Swelling (edema)	☐	☐	☐	☐
[*List other symptoms as needed*]	☐	☐	☐	☐

Scoring for clinician use:

- *Patients can be deemed **intolerant** to treatment if one or more AEs **often** interfere with daily activities within the past week.*
- *Patients can be deemed **tolerant** to treatment if AEs **rarely** interfere with daily activities within the past week.*
- *Patients whose AEs **sometimes** interfere with daily activities within the past week **may be intolerant** to treatment. Further discussion between physician, patient, and caregiver will determine tolerance.*

Figure 2. Example of assessment tool.

Discussion

Thirteen experts convened to develop a standardized definition of TKI treatment intolerance in CML-CP. The panel agreed on a patient-centered definition, with the impact of AEs on daily life and the severity of laboratory abnormalities (graded by CTCAE v5.0 [20]) emerging as critical factors. Panelists agreed that treatment intolerance is defined by (1) how often AEs interfere with a patient's daily activities (rarely, sometimes, often) and (2) the grade of laboratory abnormalities (grades 1, 2, 3). This definition aligns with the FDA's 1998 definition of tolerability, which defined intolerance by the degree to which AEs can be endured [24]. The panel also agreed that therapy should continue unchanged in tolerant patients and should be modified (e.g. dose hold, reduction, or switch) when intolerance is identified. The RAND/UCLA Modified Delphi panel method was used to develop a definition of TKI treatment intolerance in CML-CP. The method is a validated and reliable tool for quantifying expert opinion and has been used to develop society guidelines [25], disease classification systems [26], research agendas, and quality improvement interventions [27, 28].

The panel emphasized individualized assessment and shared decision-making, recognizing that intolerance is shaped not only by symptoms and labs but also by patients' experiences. Published literature supports this approach. A recent systematic review found that integrating patient-reported outcomes helps identify needs, reduces mortality risk, and improves QoL within 12 weeks [29]. Another study showed that patients often hesitate to report treatment challenges, underscoring the importance of eliciting feedback [30]. Because most patients require lifelong TKI therapy, minimizing toxicity is essential. The panel's tool aims to help clinicians capture patient perspectives and manage therapy accordingly (see Figure S1 in the Supplementary Appendix for an example).

This definition builds on previous work. A 2010 review called for a consistent definition of imatinib intolerance to guide chronic toxicity management [13]. Similarly, the European LeukemiaNet guidelines recognized that even low-grade AEs could significantly affect QoL and adherence, advocating for a unified intolerance framework [14]. The definition may complement existing CML-specific tools, such as the M.D. Anderson Symptom Inventory and PROMIS variants [22, 23], by offering a CML-specific method to assess tolerability.

The patient-centric assessment tool developed as part of this panel (Figure 2) is meant to be used in routine clinical practice to facilitate conversation between patients and providers regarding treatment tolerability. It is intended to support clinical decision-making, not supersede it.

This study had limitations. While the Delphi method is validated for expert consensus, it does not capture the full variability of patient experiences. No patient data were collected; the panel relied on artificial clinical scenarios. The resulting definition reflects the views of 13 US-based experts. Further validation in real-world settings is needed. A second panel comprising mostly patients could provide valuable insight into the framework's real-world applicability. Treatment intolerance is also linked to available treatment options and will need updating as new therapies emerge. Thus, the panel recommends a periodic review and refinement of the definition of TKI intolerance to align with the changing TKI landscape. Finally, because had access to all six approved TKIs, the guidelines may not apply in countries with fewer options.

This definition represents a significant step in standardizing CML-CP care. By combining patient perspectives with objective laboratory criteria, it offers a balanced framework for managing TKI therapy and addresses an unmet need in CML-CP – supporting not just survival, but a fulfilling life while on therapy.

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Author contributions

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Data availability statement

The data that support the findings of this study are available from the corresponding author, MSB, upon reasonable request.

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