Management of chronic myeloid leukemia with tyrosine kinase inhibitors: adverse events, toxicities and therapy dosing

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Abstract

Targeted therapies have made a near-normal lifespan an attainable goal for many patients with chronic phase chronic myeloid leukemia. Most patients require years of therapy and not everyone may be able to discontinue treatment permanently without recurrence of the leukemia. *BCR*::*ABL1* targeted tyrosine kinase inhibitors, including ATP binding site and allosteric inhibitors that bind to the myristoyl pocket, are associated with treatment-emergent adverse events that may compromise quality of life and well-being. Although alternative treatment options exist, side effects may persist, or new ones occur after a therapy switch. Using a case-based approach, this review examines the incidence of non-hematologic and hematologic treatment-emergent adverse events with specific therapies, provides guidance on adverse event management, and describes the impact of therapy dose reduction on efficacy and tolerability.

Introduction

For the majority of patients with chronic phase (CP) chronic myeloid leukemia (CML) successful treatment with tyrosine kinase inhibitors (TKI) abrogates the risk of CML-related death and leads to a near-normal lifespan.[1] Therapies include TKI targeting the ATP binding site such as the first-generation TKI imatinib; the second-generation TKI dasatinib, nilotinib, bosutinib, flumatinib (in China) and radotinib (in South Korea); the third-generation TKI ponatinib and olverembatinib (in China); and asciminib, the allosteric inhibitor engaging the myristoyl pocket.[2-13] The treatment landscape continues to evolve with the approval of asciminib extended to first- and second-line therapy of CP CML in the USA, Canada, Japan, and a recommendation for approval by the European Medicines Agency. In addition, there are ongoing trials of new inhibitors. Tolerability, as measured by frequency, severity, and duration of adverse events (AE) and time to discontinuation, are important secondary endpoints of ongoing clinical trials. Asciminib has demonstrated an excellent tolerability profile for specific AE. However, imatinib with its excellent long-term safety profile, and second-generation TKI with potency in resistant CML remain essential treatments. From a cost perspective, imatinib, dasatinib and, more recently, nilotinib and bosutinib are now available as generic therapies.

Given excellent overall survival (OS) and the long duration of treatment, optimizing health-related quality of life (HRQOL), which includes perception of both physical and mental health over time, is a crucial component of care. Minimizing treatment-emergent adverse events (TEAE) and avoiding organ-damaging toxicities are paramount. Successful therapy discontinuation, also known as treatment-free remission, is one long-term strategy to eliminate TEAE. In addition to a definitive and detailed review by Lipton and colleagues, organizations such as the European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) provide detailed guidance on the management of TEAE.[14-16] The importance of communication between healthcare providers and patients to optimize tolerability and HRQOL is highlighted by the CML Survey on Unmet Needs (CML SUN) study, a large mixed-methods approach study, which included qualitative interviews and quantitative surveys of 361 CP CML patients and 198 physicians from 11 countries.[17]

In this study only 67% and 55% of patients were satisfied that their current treatment maintained or improved their QOL and had no or manageable side effects, respectively. Impacts on physical well-being, social life, work life, and mental health were frequent. Using a case-based approach, this review discusses the incidence of and management strategies for specific non-hematologic and hematologic TEAE. These are summarized in Tables 1-3 for all approved therapies.[2-11,14,16,18-33] Because therapy dose reduction, when possible, is also an important strategy to reduce TEAE, outcomes on lower than standard dosing are also reviewed.

Case 1

The patient is a 64-year-old male with low-risk CP CML according to his EUTOS long-term survival (ELTS) score.[34] His past medical history is notable for hypertension, hyperlipidemia, type 2 diabetes mellitus and cardiovascular disease. A drug-eluting stent to the left anterior descending artery was placed 5 years prior to the diagnosis of CML. Imatinib 400 mg daily was started first-line 24 months ago. After 12 months of therapy *BCR*::*ABL1* transcripts were 0.05% International Scale (IS) consistent with a major molecular response (MMR, *BCR*::*ABL1* transcripts ≤0.1% IS) and after 18 months *BCR*::*ABL1* transcripts have declined to 0.008% IS (MR4, *BCR*::*ABL1* ≤0.01% IS). The patient shares with you that he struggles with fluid retention, including both periorbital and peripheral edema, muscle cramps at least once weekly, and intermittent nausea despite anti-emetic therapy. The patient has perceived some improvements in peripheral lower extremity edema with the use of knee-high compression stockings. Electrolytes, including calcium, potassium, and phosphate, are within normal limits. The patient is interested in future imatinib discontinuation but given the persistence of TEAE and the need for several more years of therapy, he asks about imatinib dose reduction or alternative therapies. The patient shares that he would prefer to continue imatinib, if possible. He is planning on retiring in 9 months and the low cost of generic imatinib in the USA has relieved some of his anxiety about medication costs.

Imatinib dose reduction in chronic phase chronic myeloid leukemia: impact on non-hematologic treatment-emergent adverse events and outcomes

In the IRIS study that led to approval of imatinib as frontline therapy, superficial edema, nausea, and muscle cramps were reported in 59%, 49%, and 49% of patients, respectively (Table 1).[24,25] Imatinib dose reduction can improve both the frequency and severity of TEAE, as was documented in a recent Chinese single-center, retrospective study of 716 patients receiving imatinib as initial therapy.[35] Among 198 patients whose dose was reduced to 200 or 300 mg daily due to TEAE, the frequency of all grade TEAE, of which edema, gastrointestinal discomfort, fatigue, and muscle spasm were the most common, decreased from 86% to 46%[35] These findings are similar to those in earlier retrospective studies in which it was observed that TEAE improved in 62.2% of patients with MR4 or MR4.5 (*BCR*::*ABL1* ≤0.003% IS) whose dose of imatinib was reduced to 300 mg daily.[36,37] Among patients with MR4 or MR4.5, almost all maintained or deepened response after imatinib dose reduction to 300 mg daily. The prospective UK phase II cohort study DESTINY examined the impact of a 50% dose reduction for 12 months (with planned interim analysis) prior to TKI discontinuation.[38,39] Entry criteria included TKI therapy for at least 3 years and MMR or MR4 for at least 1 year prior to enrollment. Among 174 CP CML patients, 148 reduced imatinib dose to 200 mg daily, ten reduced dasatinib to 50 mg daily and 16 reduced nilotinib to 200 mg twice daily. The median duration of TKI use was 7.7 years and 6.5 years in the MMR and MR4 cohorts, respectively. In the interim analysis after dose reduction, nine patients (18.75%) in the MMR cohort and three patients (2.48%) in the MR4 cohort lost MMR. Within the first 3 months after dose reduction, improvements of periorbital edema, rash, nausea, diarrhea, lethargy, and hair thinning were reported. MMR or deeper molecular responses were achieved again by all patients restarting therapy for molecular recurrence. Among patients with MR4 who maintained MR4 for 12 months after dose reduction, recurrence-free survival was 72% (95% confidence interval: 64-80) after TKI discontinuation, supporting that treatment-free remission for patients in MR4 was not compromised by dose reduction prior to stopping therapy.[38] Both the single-center study from China and another retrospective real-world practice review of 298 cases, including 90 patients receiving imatinib, reported no difference in the probability of remaining in MMR on reduced imatinib dosing for patients in either MMR or MR4 at the time of dose reduction.[35,40] The achievement of MR4, MR4.5 or treatment-free remission was also not compromised.[35] However, conclusions from these studies on the efficacy of 200 mg imatinib dosing in patients in MMR, but without deeper responses, are limited by small numbers of patients. The impact on subsequent treatment-free remission remains unclear in this group and could be compromised; thus, caution is warranted.

The timing of dose reduction is also important. For some patients dose reductions early in treatment, particularly within the first 12 months, may compromise outcomes especially for lower potency therapies such as imatinib. In the phase II Japan Adult Leukemia Study Group CML202 study overall survival and event-free survival in patients receiving 400 mg *versus* 300 mg daily were not statistically significantly different.[41] However, patients receiving imatinib doses <300 mg daily had inferior response rates and survival outcomes. In the retrospective single-center study from China, a shorter duration of MMR (<23 months)

Table 1. Incidence of therapy-associated treatment-emergent adverse events of Interest.

Type of TEAE	TEAE incidence, %											
	Imatinib[a,b,c,d]		Dasatinib[e,f,g,h]		Nilotinib[i,j,k l]		Bosutinib[m,n,o]		Ponatinib[p,q.r.s]		Asciminib[t,u,v]	
	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4	All	G3/4
Non-hematologic												
Gastrointestinal												
Nausea	49.5	1.3	10	-	22	2	37	-	29	0.7	12	0.6
Vomiting	22.5	2	5	-	15	<1	21	1	19	1.5	<10	-
Diarrhea	45.4	3.3	22	1	19	1	75	9	20	0.7	13	-
Constipation	11.4	0.7	1-10	-	20	<1	13	-	42	2.6	<10	-
Dyspepsia	18.9	0	1-10	-	10	-	13.4	0.7	-	-	-	-
Cardiovascular												
Congestive cardiac failure	0.1-1	-	2	<1	-	-	1-10	-	3.1	-	1.9	-
Hypertension	0.1-1	-	1-10	-	10	1	10	5	42	30	14	7
Arterial occlusive events[w]	3.6	-	5	-	24.8	-	7.5	-	14-31	6-17	5.1	-
Pulmonary arterial hypertension	0.01-0.1	-	5	1	U	-	1-10	-	-	-	-	-
QT prolongation	-	-	<1	-	0.4-4.1	<1	1-10	U	-	-	0.9	-
Fluid retention												
Superficial edema	59.9	1.5	14	-	9	<1	15	-	3.8-17	<3.7	<10	-
Pleural or pericardial effusion	<6.9	<1.3	28	3	2.2	0.7	6	0.7-4.4	9	-	2.1	-
Musculoskeletal pain												
Muscle cramps	49.2	2.2	5	-	12	-	-	-	14	-	-	-
Musculoskeletal pain	47	5.4	14	-	15	<1	1-10	-	11	1.5	24-25	1.5-2.6
Joint pain/arthralgia	31.4	2.5	7	-	22	<1	18	1	61	9	13	0.6
Myalgia	24.1	1.5	7	-	19	<1	1-10	-	24	1.1	<25	-
Dermatology												
Rash	40.1	2.9	14	-	38	<1	40	2	75	9	18-19	0.6
Dry skin	6.7	0.5	1-10	-	12	-	-	-	42	3.3	-	-
Other												
Osteopenia/osteoporosis	-	-	P	-	-	-	-	-	-	-	-	-
Headache	37	0.5	14	-	32	3	22	1	43	3.3	14-21	0.5-1.9
Abdominal pain	36.5	4.2	11	-	15-18	2	39	2	54	11	14	0.5
Nasopharyngitis	30.5	-	-	-	27	-	13.4	0.4	12	-	<15	-
Hemorrhage	28.9	1.8	8	1	2.9	1.1	1-10	-	23	3	<10	-
Venous thromboembolism	-	-	-	-	-	-	-	-	6	5.8	-	-
Fatigue	38.8	1.8	11	<1	23	1	33	1	44	3.7	18-20	0.6-1
Hematologic												
Anemia	44.6	3.1	90	10	38	3	22	4.5	35	14	24-37	2-2.5
Neutropenia	60.8	14.3	65	21	43	12	12.3	7.5	55	22	43-46	12-22
Thrombocytopenia	56.6	7.8	70	19	48	10	35.8	14.2	65	31	46-48	12-24
Biochemical												
AST or ALT elevation	43.2	4.7	-	<1	47-72	1-4	25.7-33.6	10.4-20.9	35-41	3.6-6	21-26	0.6-1.9
Total bilirubin elevation	-	0.9	-	1	59	4	6.3	-	13	0.9	12	-
Increased lipase	-	-	-	-	28	9	20.9	13.4	40	14	15-37	4.5-10
Hyperglycemia	-	-	-	-	50	7	42	2.7	54	7	-	-
Decreased phosphate	-	10	-	7	-	8	54	9	34	10	18	6
Increased potassium	-	1	-	-	-	2	23	-	20	2.2	48	2.1
Decreased potassium	-	2	-	-	-	<1	24	-	-	-	11	-

Continued on following page.

[a]O'Brien SG, *et al*. N Engl J Med. 2003;348(11):994-1004. [b]Druker BJ, *et al*. N Engl J Med. 2006;355(23):2408-2417. [c]Hochhaus A, *et al*. N Engl J Med. 2017;376(10):917-927. [d]Imatinib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. *https://www.novartis.com/us-en/sites/novartis_us/files/gleevec_tabs.pdf* Accessed August 1, 2025. [e]Shah NP, *et al*. Haematologica. 2010;95(2):232-240. [f]Kantarjian HM, *et al*. Blood. 2012;119(5):1123-1129. [g]Cortes, JE, *et al*. J Clin Oncol. 2016;34(20):2333-2340. [h]Dasatinib tablets. Prescribing information. Bristol Myers Squibb; 2024. *https://packageinserts.bms.com/pi/pi_sprycel.pdf* Accessed August 1, 2025. [i]Based on nilotinib 300 mg twice daily cohort; Saglio G, *et al*. N Engl J Med. 2010;362(24):2251-2259. [j]Based on nilotinib 300 mg twice daily cohort; Hochhaus A, *et al*. Leukemia. 2016;30(5):1044-1054. [k]Based on nilotinib 300 mg twice daily cohort; Kantarjian H, *et al*. Leukemia. 2021;35(2):440-453. [l]Nilotinib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. *https://www.novartis.com/us-en/sites/novartis_us/files/tasigna.pdf* Accessed August 1, 2025. [m]Cortes JE, *et al*. J Clin Oncol. 2018;36(3):231-237. [n]Brümmendorf TH, *et al*. Leukemia. 2022;36(7):1825-1833. [o]Bosutinib. Prescribing information. Pfizer; 2024. *https://labeling.pfizer.com/showlabeling.aspx?id=884* Accessed August 1, 2025. [p]Cortes JE, *et al*. N Engl J Med. 2013;369(19):1783-1796. [q]Cortes JE, *et al*. Blood. 2018;132(4):393-404. [r]Cortes J, *et al*. Blood. 2021;138(21):2042-2050. [s]Ponatinib. Prescribing information. Takeda; 2024. *https://www.iclusig.com/sites/default/files/2023-02/iclusig-prescribing-information.pdf* Accessed August 1, 2025. [t]Hochhaus A, *et al*. N Engl J Med. 2024;391(10):885-898. [u]Hochhaus A, *et al*. Leukemia. 2023;37(3):617-626. [v]Asciminib. Prescribing information. Novartis Pharmaceuticals Corporation; 2024. *https://www.novartis.com/us-en/sites/novartis_us/files/scemblix.pdf* Accessed August 1, 2025. [w]Veltmaat L, Cortes JE. Blood. 2024;143(10):858-865. Information on treatment-emergent adverse events (TEAE) is extracted from prescribing information and clinical trial data that led to the Food and Drug Administration's approval for front-line use (including initial and long-term follow-up data, when available). Where reports vary, ranges are reported. TEAE for nilotinib are based on reports of 300 mg twice daily dosing. We acknowledge that incidence rates vary between studies, including those for the same drugs in later-therapy lines. G3/4: grade 3 or 4; AOE: arterial occlusive event; AST: aspartate transaminase; ALT: alanine transaminase; P: reported in pediatric patients; U: unknown frequency.

prior to dose reduction was also associated with a higher incidence of loss of MMR.[35]

For patients with loss of molecular response (e.g., loss of MMR or loss of complete cytogenetic response, *BCR*::*ABL1* ≤1% IS) on a reduced dose, a change in therapy should be considered if therapy dose cannot be re-escalated, especially if treatment-free remission is a goal.[42] Alternative therapy should also be considered if TEAE persist on a reduced dose, as long-term HRQOL is critical. Lastly, the impact of dose reduction in patients with high-risk features, such as high clinical risk scores and/or specific molecular features (e.g., additional cytogenetic abnormalities, *ASXL1* mutations), and/or slow *BCR*::*ABL1* transcript decline is unknown. As these features are associated with poorer molecular response and failure-free survival, these patients may be at risk with early dose reduction.[43-48]

Case 1 outcome

The patient had only recently achieved MR4, 6 months before the visit. After discussion, his imatinib dose was reduced to 300 mg daily. Edema and nausea improved with this dose reduction to 300 mg daily. MR4 was maintained and MR 4.5 achieved 12 months later with imatinib 300 mg daily. A plan was made to discuss further imatinib dose reduction to 200 mg daily followed by discontinuation if response is maintained and the patient completes at least 4-5 years of therapy.[15,38,39]

Case 2

The patient is a 61-year-old female with a past medical history notable for hypertension managed with losartan and a new diagnosis of low ELTS risk CP CML. She works long hours as a litigator and strongly prioritizes becoming eligible for TKI discontinuation. She is interested in front-line treatment with a second-generation TKI because the cumulative incidence of deep molecular response is higher.[4] You discuss the increased risk of pleural effusion with standard dosing of dasatinib and that the risk is higher in older patients.[4,49] The patient is worried about side effects such as diarrhea, headache, and pleural effusion and asks whether a lower dose of dasatinib may be started preemptively without compromising outcomes.

Second-generation tyrosine kinase inhibitor dosing: impact on non-hematologic treatment-emergent adverse events and outcomes - dasatinib

Retrospective analyses and comparative analyses have supported improved tolerance and sustained efficacy of lower dasatinib doses.[40,50] A significant toxicity of dasatinib is pleural effusion. In the front-line phase III DASISION study, by 5 years pleural effusion was seen in 28% of dasatinib-treated patients *versus* 0.8% of imatinib-treated patients.[4] As second-line therapy, the cumulative incidence of pleural effusion by 7 years was 28% for patients receiving 100 mg daily on the CA180-034 dose-optimization study of dasatinib.[3] Retrospective studies of lower dasatinib dosing (50 mg and 70 mg) have supported efficacy and improved tolerance.[51-53]

Prospective data supporting the initiation of 50 mg daily in newly diagnosed predominantly low- and intermediate-risk (Sokal score) CP CML patients is provided by a US single-arm study of 81 patients with a median age of 47 years (range, 19-84 years).[54-56] At 12 months the cumulative incidence of complete cytogenetic response was 94%, MMR was 79%, MR4 was 52% and MR4.5 was 43%; the corresponding figures at 60 months were 98%, 95%, 83%, and 82%, respectively.[56] Given the absence of randomized data for 100 mg *versus* 50 mg daily, propensity score analysis was used to compare patients treated with low-dose dasatinib (N=77) to a historical cohort that received 100 mg daily (N=77).[57] No statistically significant differences in molecular responses, event-free survival or overall survival were seen, but fewer TEAE were observed in the 50 mg group. More patients receiving standard-dose *versus* lower-dose dasatinib interrupted treatment within the first 12 months (N=40 [52%] *vs.* 5 [7%], respectively) and more patients discontinued

therapy (10% *vs*. 3%, respectively). Pleural effusions of any grade were seen in 21% *versus* 5% of patients treated with 100 mg and 50 mg, respectively (*P*=0.02).

Data supporting an even lower starting dose in older Japanese patients were reported in a prospective single-arm, multicenter study, DAVLEC.[58] Fifty-two newly diagnosed CP CML patients with a median age of 77.5 years were enrolled. Dasatinib was started at 20 mg daily and dose escalation was permitted at 3, 6, and 9 months. MMR was achieved at 12 months in 60% (N=31/52) of evaluable patients and 44% (N=23) of patients continued 20 mg daily. MR4 and MR4.5 were achieved in 27% and 14%, respectively. Whether this very low-dose approach is as effective in patients of other ethnic/racial backgrounds remains unknown and further studies are needed. Alternative dosing strategies, such as intermittent TKI dosing, are also feasible and do not appear to compromise efficacy.[59,60] Lastly, dose optimization using a therapeutic drug monitoring approach is an appealing patient-centered approach to maximize efficacy and minimize TEAE; however, such approaches are not currently clinically available at most centers.[61]

Second-generation tyrosine kinase inhibitor dosing: impact on non-hematologic treatment-emergent adverse events and outcomes - nilotinib and bosutinib

For other second-generation TKI, the risk of specific TEAE can be mitigated by using lower doses. Nilotinib use is associated with an increased risk of cardiovascular, cerebrovascular, and peripheral arterial events, collectively termed arterial occlusive events, and the risk is associated with the dose used. At the 5- and 10-year follow-ups of the first-line randomized phase III ENESTnd study, arterial

Table 2. Recommended management for non-hematologic treatment-emergent adverse events of interest.

Non-hematologic TEAE	Clinical interventions		TKI therapy modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional comments[a,b]
	Non-pharmacological[a,b]	Pharmacological[a,b]		
Gastrointestinal				
Nausea	Diet modification +/- hydration Refer to gastroenterologist and dietitian	Anti-emetic	Dose reduction (with close monitoring) or switch TKI if persistent	Diet modification: smaller, more frequent meals, take medication with food (except nilotinib [capsule formulation] and asciminib), avoid spicy/fatty food
Vomiting				
Diarrhea		Anti-diarrheal		Hydration: oral hydration for lower grade toxicities but intravenous hydration may be indicated for more severe cases
Constipation		Laxative		Acid reducer: antacid > histamine H2 receptor antagonists > proton pump inhibitors, select based on drug-drug interactions
Dyspepsia		Acid reducer		
Cardiovascular				
Congestive cardiac failure	Refer to cardiologist	-	Dose reduction or switch TKI if persistent	-
Hypertension	Diet/lifestyle modification Refer to cardiologist Refer to vascular surgery for peripheral arterial disease	Guideline-directed therapy optimization[c,d,e,f,g]	Switch TKI for severe or persistent hypertension not responding to antihypertensive medications (more common with ponatinib and asciminib)	Lifestyle modification: consider a low sodium diet Guideline-directed therapy optimization[c,d] Select therapy with consideration of drug-drug interactions
Arterial occlusive events			Switch TKI whenever possible for the onset of new arterial and/or vascular adverse events (more common with nilotinib	Guideline-directed therapy optimization[c,e,f,g] Select therapy with consideration of drug-drug interactions
Pulmonary arterial hypertension	Monitor for shortness of breath/fainting Refer to cardiologist or pulmonary vascular specialist	Diuretic +/- corticosteroid +/- sildenafil	Switch TKI (more common with dasatinib)	-

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Non-hematologic TEAE	Clinical interventions		TKI therapy modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional comments[a,b]
	Non-pharmacological[a,b]	Pharmacological[a,b]		
Cardiovascular				
QT prolongation	Monitor for hypokalemia/ hypomagnesemia	Minimize/avoid concurrent QT prolonging medications Correct electrolytes if needed	Switch TKI if persistent (more common with nilotinib)	-
Fluid retention				
Superficial edema	Monitor for weight gain, peripheral and periorbital edema, bloating	Diuretic	Dose reduction (with close monitoring) or switch TKI if persistent	Lifestyle modification: consider compression stockings (lower extremity edema)
Pleural or pericardial effusion	Monitor for shortness of breath, chest pain, or cough Echocardiogram to assess LVEF, elevation of PASP and presence of pericardial effusion Refer to pulmonologist for consideration of thoracentesis Refer to cardiologist for consideration of pericardiocentesis	Diuretic +/- corticosteroid	Dose reduction or switch TKI for recurrence (more common with dasatinib)	-
Musculoskeletal pain				
Muscle cramps	Ensure adequate hydration, consider tonic water (muscle cramps) Assess creatine kinase	Electrolyte (potassium/ calcium) supplementation	Dose reduction (with close monitoring) or switch TKI if persistent	Lifestyle modification: hydration, correct electrolyte abnormalities, and light exercise if able
Musculoskeletal pain				
Joint pain/arthralgia				
Myalgia				
Dermatology				
Rash	Topical moisturizers, particularly after shower or bath Consider referral to dermatologist	Antihistamine +/- corticosteroid (topical)	Dose reduction (with close monitoring) For rash that requires interruption of treatment, consider TKI switch if the rash recurs after re-starting treatment	Lifestyle modifications: avoid prolonged sun exposure and avoid prolonged bathing in hot water Antihistamine/corticosteroid / antibiotic: topical antihistamine or corticosteroid can be considered for low-grade toxicity. Short-term systemic corticosteroid and/or systematic antibiotic can be considered in severe cases in consultation with a dermatologist Topical moisturizer: alcohol-free moisturizers. In addition, for dry skin, moisturizers with exfoliants such as ammonium-lactate, lactic acid, salicylic acid, or urea may be considered (can cause burns and dermatology consultation is recommended)
Dry skin				

For the Non-pharmacological and Pharmacological Clinical interventions, TKI therapy modification, and Additional comments sections, we have adapted some recommendations from Lipton JH, *et al*. Blood Rev. 2022 56:100968 and National Comprehensive Cancer Network chronic myeloid leukemia guidelines version 1.2026 - July 16, 2025. [a]Lipton JH, *et al*. Blood Rev. 2022:56:100968. [b]National Comprehensive Cancer Network. Chronic myeloid leukemia (version 1.2026). *https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf* Accessed August 1, 2025. [c]Whelton PK, *et al*. J Am Coll Cardiol 2018;71:e127-e248. [d]Mancia G, *et al*. J Hypertens 2023;41:1874-2071. [e]Gornik HL, *et al*. Circulation. 2024;149(24):e1313-e1410. [f]Bushnell C, *et al*. Stroke. 2024;55(12):e344-e424. [g]Rao SV, *et al*. Circulation. 2025;151(13):e771-e862. TEAE: treatment-emergent adverse events; TKI: tyrosine kinase inhibitor; LVEF: left ventricular ejection fraction; PASP: pulmonary arterial systolic pressure.

occlusive events were reported in 7.5% and 16.5% *versus* 13.4% and 23.5% *versus* 2.1% and 3.6% of patients receiving nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, or imatinib 400 mg daily, respectively.[5,30] The ENESTswift trial provides support for a lower dosing approach for second-line nilotinib at 300 mg twice daily, compared to the approved dosing of 400 mg twice daily, for intolerant, but not resistant CP CML patients.[62] The NILO-RED observational study demonstrated the feasibility and safety of nilotinib dose reduction to daily dosing.[63] Among 81 patients in MMR, MR4, or MR 4.5 nilotinib was reduced to 450 mg once daily (86.6%), 400 mg daily (10.4%) or 300 mg daily (3%) and only two patients lost MMR on their reduced dose. Although unknown, it is possible that additional nilotinib dose reduction could further limit arterial occlusive events.

Bosutinib dosing at 400 mg daily or higher is associated with high rates of nausea, diarrhea, and increases in aspartate aminotransferase and alanine aminotransferase.[22] A comprehensive retrospective review of a phase I/II study of bosutinib in later lines reported the impact of bosutinib dose reduction in second-line or third-line treatment of CP CML.[64] Dose reductions were associated with improvements in diarrhea (33% 400 mg, 54% 300 mg), nausea (26% 400 mg, 29% 300 mg), and vomiting (9% 400 mg, 23% 300 mg). Among patients with a complete cytogenetic response or MMR prior to bosutinib dose reduction, only 2% of second-line and no third-line patients lost this response. In the randomized phase III BFORE study comparing first-line bosutinib to imatinib, after bosutinib dose reduction to 300 mg daily, 45.1% achieved MMR and 17.1% maintained MMR for more than 6 months.[7,32,65] TEAE, including diarrhea, thrombocytopenia, nausea, vomiting, and anemia, were reported to decrease by >10%. Based on these observations, an incremental dose increase approach is recommended by expert panels.[66] Typically, bosutinib is initiated at 200-300 mg daily and the dose is escalated based on molecular response. The safety of this approach was supported by several studies. In the phase II GIMEMA BEST study, 63 CP CML patients initiated bosutinib at 200 mg daily as second-line therapy and escalated at 2-week intervals to 300 or 400 mg daily.[67,68] Less diarrhea and nausea were reported with this approach. Notably, most patients remained on low-dose therapy with 73% and 6% remaining on 300 mg and 200 mg daily, respectively. At 12 months the MMR rate was 59%. By 36 months the probability of achieving or maintaining MMR was 78%, MR4 was 54%, and MR4.5 was 46%. The BODO study, which also examined an incremental bosutinib dose increase strategy, likewise reported good efficacy with 79% of patients achieving MMR.[69]

Although dose reduction is an effective strategy to reduce TEAE, there are several toxicities for which a change in therapy is the preferred approach (Table 2). These TEAE include arterial occlusive events, recurrent pleural effusions (dasatinib), pulmonary hypertension (dasatinib), severe hypertension (ponatinib, asciminib) not responsive to antihypertensive therapies, enterocolitis, neurotoxicity, or other immune-mediated adverse events (e.g., pericarditis, myocarditis, nephritis).[70,71]

Case 2 outcome

The patient started dasatinib 50 mg daily and *BCR*::*ABL1* transcripts declined to 1.5% IS after 3 months of therapy. MMR (0.04% IS) and MR4 (0.009% IS) were achieved at 9 and 12 months, respectively. The first months of treatment were characterized by fatigue and grade 1 thrombocytopenia with platelet counts ranging from 111-135x10^9/L. The patient also complained of headaches once per month, but no diarrhea or nausea. Fatigue improved substantially after 4 months of therapy. Platelet counts remained in a similar range and dasatinib 50 mg daily was continued.

Case 3

The patient is a 52-year-old female diagnosed with CP CML with a high-risk ELTS score. Her complete blood count at presentation showed a white blood cell count of 345x10^9/L, hemoglobin of 8.3 g/dL, platelet count of 125x10^9/L, and 2% circulating blasts; the spleen was palpable at 10 cm below the costal margin. A bone marrow aspirate was consistent with CP CML; 3% blasts were detected by flow cytometry; and grade 2 reticulin fibrosis was reported. Conventional cytogenetics demonstrated t(9;22)(q34;q11.2) in all 20 cells examined; no additional cytogenetic abnormalities were detected. Dasatinib 100 mg daily was started but the patient developed severe thrombocytopenia (platelets 21x10^9/L) with persistent moderate anemia (hemoglobin 8.1 g/dL) and mild neutropenia (absolute neutrophil count 1.3x10^9/L). Dasatinib was withheld for 4 weeks and restarted at a reduced dose of 50 mg daily once the platelet count recovered to 75x10^9/L; 4 weeks later platelets had decreased to 18x10^9/L and dasatinib was withheld again. A bone marrow examination 6 months after diagnosis showed CP CML with no evidence of cytogenetic or molecular response, but no clonal cytogenetic evolution. Next-generation sequencing revealed a T315I mutation. Ponatinib was started at 15 mg daily due to severe thrombocytopenia and the patient was referred to the local academic center for assistance with management.

Strategies for the management of severe hematologic toxicity

Hematologic toxicities are common after therapy initiation for all approved TKI, and rates are substantially higher in patients with accelerated or blast phase.[72] The incidence of all grade cytopenias has ranged from 30-90% across studies of CP CML; grade 3/4 toxicity is more uncommon and has been reported in 10-30% of newly diagnosed CP CML patients on therapy (Table 1).[18-23] It is difficult to compare risk of ane-

mia, neutropenia, or thrombocytopenia between individual drugs although two larger meta-analyses focused mainly on CP CML patients have attempted to do so.[73,74] Both studies identified more frequent cytopenias with dasatinib than with other TKI, either all grade[74] or grade 3/4.[73] Increased rates of cytopenias were also observed with higher drug doses.

The mechanisms of severe hematologic toxicity while on TKI therapy have not been fully elucidated. Although targeting of PDGFRA and cKIT by imatinib, for example, may directly suppress normal hematopoiesis, interactions between CML cells, the bone marrow microenvironment, and normal hematopoietic cells are also salient.[75-77] Clinically, severe cytopenias are more frequently observed in the setting of a higher burden of CML. Earlier pre-clinical studies demonstrated that *BCR*::*ABL1*-positive stem/progenitor cells not only outcompete normal hematopoietic cells but also create a suppressive environment for normal hematopoiesis through the secretion of specific cytokines that favor expansion of myeloid cells over other lineages and may even create an environment favoring apoptosis of normal hematopoietic stem/progenitor cells versus *BCR*::*ABL1*-positive cells.[78,79] Anemia and thrombocytopenia at presentation, as seen in this patient, may also be a risk factor for more severe cytopenias on treatment.[80] Factors associated with myelosuppression include bone marrow fibrosis and the appearance of Philadelphia chromosome-negative clonal evolution on therapy, as has been described for trisomy 8.[81] Age-related clonal hematopoiesis with somatic mutations in *TET2* or *DNMT3A* may also play a role. For isolated grade 1 or 2 hematologic toxicity, therapy may be continued with close monitoring. Management for patients with grade 3/4 hematologic toxicity , when recurrent, is problematic (Table 3). Prescribing information recommends that therapy be withheld when the absolute neutrophil count is $<1.0\times10^9$/L or platelet count is $<50\times10^9$/L.[18-23] Therapy is resumed once the absolute neutrophil count or platelet count is above these thresholds again.

Early studies provided evidence that patients receiving imatinib and requiring dose reductions for myelosuppression and/or grade 3/4 anemia have poorer cytogenetic response

Table 3. Recommended management of hematologic, biochemical, and other therapy-associated treatment-emergent adverse events of interest.

Type of TEAE	Clinical interventions		TKI therapy modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional comments[a,b]
	Non-pharmacological[a,b]	Pharmacological[a,b]		
Hematologic				
Anemia	Monitor for new shortness of breath or fatigue	For grade 3 or 4, erythropoiesis-stimulating agents may be considered	Dose reduction (with close monitoring) or switch TKI if persistent. Cross-intolerance is common	Monitor complete blood counts regularly
Neutropenia	Monitor for infection symptoms	For grade 4, granulocyte colony-stimulating factor may be considered		
Thrombocytopenia	Monitor for bruising, bleeding	For grade 4, thrombopoietin receptor agonists may be considered		
Biochemical				
AST or ALT elevation	Monitor for jaundice / brown urine Monitor liver function tests	Minimize/avoid concurrent medications with risk of hepatotoxicity	Dose reduction (with close monitoring) or switch TKI if persistent	-
Total bilirubin elevation				
Increased lipase	Monitor for abdominal pain Consider imaging by contrast enhanced CT or MRI	-	Dose reduction (with close monitoring) or switch TKI if persistent, (most common with nilotinib, ponatinib, and asciminib)	-
Hyperglycemia	Monitor blood glucose at baseline and periodically Refer to endocrinologist	If diabetic, optimize antidiabetic medications	Dose reduction (with close monitoring) or switch TKI if persistent (most common with nilotinib)	-
Decreased phosphate	Monitor electrolytes	Correct electrolytes	Dose reduction (with close monitoring) or switch TKI if persistent	-
Increased potassium				
Decreased potassium				

Continued on following page.

Type of TEAE	Clinical interventions		TKI therapy modification (conditions not resolved despite optimal clinical intervention)[a,b]	Additional comments[a,b]
	Non-pharmacological[a,b]	Pharmacological[a,b]		
Other				
Osteopenia/osteoporosis	Vitamin D level at baseline and periodically	Data for bone-modifying agents are limited	-	-
Headache	Sleep hygiene, caffeine management Consider referral to neurologist (e.g., headache clinic)	Acetaminophen-based therapy or NSAID if needed	Dose reduction (with close monitoring) or switch TKI if persistent	-
Abdominal pain	Monitor liver function tests, amylase and lipase Imaging studies	Determined by etiology	Dose reduction (with close monitoring) or switch TKI if persistent	-
Nasopharyngitis	Monitor for signs/symptoms of infection Refer to otolaryngologist	Over-the-counter pain relievers and/or antiinflammatory medications	Dose reduction (with close monitoring) or switch TKI if persistent	-
Hemorrhage	Monitor for signs/symptoms of bleeding	-	-	-
Venous thromboembolism	Monitor signs/symptoms of thrombosis	Anticoagulation based on patient-specific factors (e.g., renal function)	-	-
Fatigue	Lifestyle modification	No data to support the use of stimulant medications	Dose reduction (with close monitoring) or switch TKI if persistent	Lifestyle modification: maintain active lifestyle (routine exercise) if physically able

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rates.[82,83] However, a retrospective review of dose reductions and interruptions of second-generation TKI therapies reported no impact on response rate, perhaps because of the increased potency of second-generation TKI and, as discussed earlier, the efficacy of TKI at lower than standard recommended doses.[84] However, failure-free survival was worse for patients unable to continue therapy. For the rare group of patients with *BCR*::*ABL1* transcripts persistently >10%, repeatedly withholding therapy for recurrent cytopenias may contribute to limited molecular response and poorer outcomes. The pattern may recur after switching to another therapy.[74] Recurrent cytopenias may also be a sign of disease progression and a bone marrow examination is indicated in this setting. For the rare patients with recurrent severe cytopenias who cannot receive consistent TKI therapy, the NCCN and ELN suggest consideration of allogeneic hematopoietic cell transplantation.[15,16,85] For patients who are not eligible for transplantation, a recent study highlighted that continuation of low-dose therapy, compared to no therapy, may limit the risk of disease progression.[86]

Growth factors including granulocyte colony-stimulating factor for neutropenia, erythropoiesis-stimulating agents for anemia, and thrombopoietin receptor agonists for severe thrombocytopenia have been examined.[83,87-91] A retrospective single-center review of 608 CP patients treated with various imatinib doses (after interferon-α in 50% of cases) reported a >2 g/dL increase in hemoglobin in 80% of patients.[83] Thrombosis was seen in 8.5% of patients who received an erythropoiesis-stimulating agent *versus* 2.6% of those who did not (P=0.0025).[83] Early studies also supported the use of granulocyte colony-stimulating factor in patients with imatinib-induced neutropenia.[89] Preclinical studies even suggested that granulocyte colony-stimulating factor may enhance imatinib efficacy in quiescent CML stem cells.[92] However, a subsequent small clinical study of 30 patients showed no benefit from the combination, but no significant risks with granulocyte colony-stimulating factor use were identified.[93] A recent phase II study investigated the use of the thrombopoietin receptor agonist eltrombopag in CML patients with grade 3 or 4 thrombocytopenia.[90] Eltrombopag

was initiated at 50 mg/day, with dose escalation up to 300 mg daily allowed every 2 weeks. Fifteen patients with CML were enrolled. After a median of 18 months (range, 5-77 months), 12 of the 15 patients achieved a complete platelet response. The median peak platelet count among responders was 154x10^9/L (range, 74-893x10^9/L). Five patients could re-escalate the TKI dose and nine improved their response. One patient discontinued therapy due to toxicity (elevated transaminases). Non-occlusive deep venous thrombosis was reported in one patient receiving ponatinib with eltrombopag. Another study of 21 patients documented increases in platelet counts in 16 of 21 patients receiving eltrombopag, with four patients having adverse events.[91] The improvements in thrombocytopenia observed in CML patients enrolled in these studies were likely also due, in part, to the ability to continue CML therapy, achieve molecular response, and thus potentially remove the myelosuppressive effects of CML on normal hematopoiesis. The impact of longer-term use of eltrombopag in CML is unknown, but some concern may be warranted given reports of clonal evolution in aplastic anemia.[94]

Ponatinib dosing in chronic phase chronic myeloid leukemia

Ponatinib is approved for the treatment of T315I-mutated CML and for resistant or intolerant CML in later lines (generally ≥ third-line).[23] Ponatinib dose reduction is a crucial component of management because of the risk of arterial occlusive events with this drug. In the pivotal phase II PACE trial of heavily pre-treated and resistant CP CML patients overall survival at 5 years was 73% and progression-free survival was 53%.[8] Arterial occlusive events were reported in 26%, but a retrospective re-examination of the data estimated that the rate of arterial occlusive events was 17% based on independent cardiovascular adjudication.[95] Hypertension may occur soon after ponatinib initiation and contributes to the risk of arterial occlusive events and aggressive management in this setting is important.[23] In response to these observations, the phase II OPTIC study examined the impact of response-based dosing on outcomes.[9] This study randomized 283 patients 1:1:1 to three dosing cohorts: 45 mg, 30 mg, and 15 mg daily. There was a mandatory dose reduction to 15 mg daily upon achievement of *BCR*::*ABL1* ≤1% IS for the 45 mg and 30 mg cohorts. By 12 months *BCR*::*ABL1* ≤1% IS was achieved by 51.6%, 35.5%, and 25.3% of patients in the 45 mg, 30 mg, and 15 mg cohorts, respectively, and responses were maintained after dose reduction to 15 mg in 73% and 79% of patients of the 45 mg and 30 mg cohorts, respectively.[9] A dose-dependent impact on arterial occlusive events was observed, with 9.6% of patients in the 45 mg cohort experiencing an arterial occlusive event *versus* 3.2% in the 15 mg cohort. A recent analysis estimated that response-adjusted dosing reduced the risk of arterial occlusive events by ~60%.[96] For patients with T315I mutations, *BCR*::*ABL1* ≤1% IS was achieved by 12 months by 60% of patients in the 45 mg cohort *versus* 25% and 11% in the 30 mg and 15 mg cohorts, respectively. Consequently, close monitoring and dose escalation based on molecular response should be considered if lower doses of ponatinib are initiated.

Case 3 outcome

Ponatinib and high-dose asciminib (200 mg twice daily) are the only approved targeted therapies for CML with a T315I mutation.[19,23] *BCR*::*ABL1* transcripts prior to ponatinib initiation were 65%. Ponatinib dose was escalated to 30 mg daily after 3 weeks. Grade 3 thrombocytopenia recurred and ponatinib was withheld for 3 weeks. Hematopoietic cell transplantation was discussed but was not possible due to a lack of social and caregiver support. Eltrombopag was started at 50 mg and escalated to 100 mg daily after 2 weeks. Ponatinib was restarted at 15 mg and dosed continuously. Over a period of 4 months platelet counts slowly increased from 22x10^9/L to 82x10^9/L and concurrently *BCR*::*ABL1* transcripts declined from 21% to 1.34%. Over the next 2 months eltrombopag was tapered off, *BCR*::*ABL1* declined to 0.27% IS and platelet counts remained between 100-120x10^9/L. A MMR was achieved 3 months later and maintained with 2 years follow-up on continued ponatinib 15 mg daily.

Allosteric inhibitors and hematologic and non-hematologic treatment-emergent adverse events

Asciminib was approved by the Food and Drug Administration in 2021 for use in patients as third-line treatment or beyond based on the results of the phase III randomized ASCEMBL study which compared asciminib *versus* bosutinib.[10,19] Asciminib was approved at a higher dose of 200 mg twice daily for patients with T315I mutations based on the results of a phase I study.[97] Long-term follow-up, including emerging HRQOL data, from these studies demonstrate excellent tolerability, although rates of hematologic AE are similar to those with other TKI.[10,98,99] Front-line approval of asciminib is based on the phase III ASC4FIRST study which randomized patients to asciminib *versus* imatinib or second-generation TKI. Superior MMR rates at 48 weeks and 96 weeks were seen in patients receiving asciminib *versus* imatinib and *versus* all investigator-selected TKI (including patients receiving imatinib or second-generation TKI).[11,100] The tolerability of asciminib is highlighted by the lower rates of grade ≥3 TEAE reported in 38%, 44.4% and 54.9% of patients treated with asciminib, imatinib or second-generation TKI, respectively. At week 48 fewer patients discontinued therapy with asciminib due to TEAE (4.5% *vs.* 11.1% *vs*. 9.8%, respectively) and fewer patients required dose adjustments or treatment interruptions (30% *vs*. 39.4% *vs*. 52.9%, respectively). Relative to imatinib-treat-

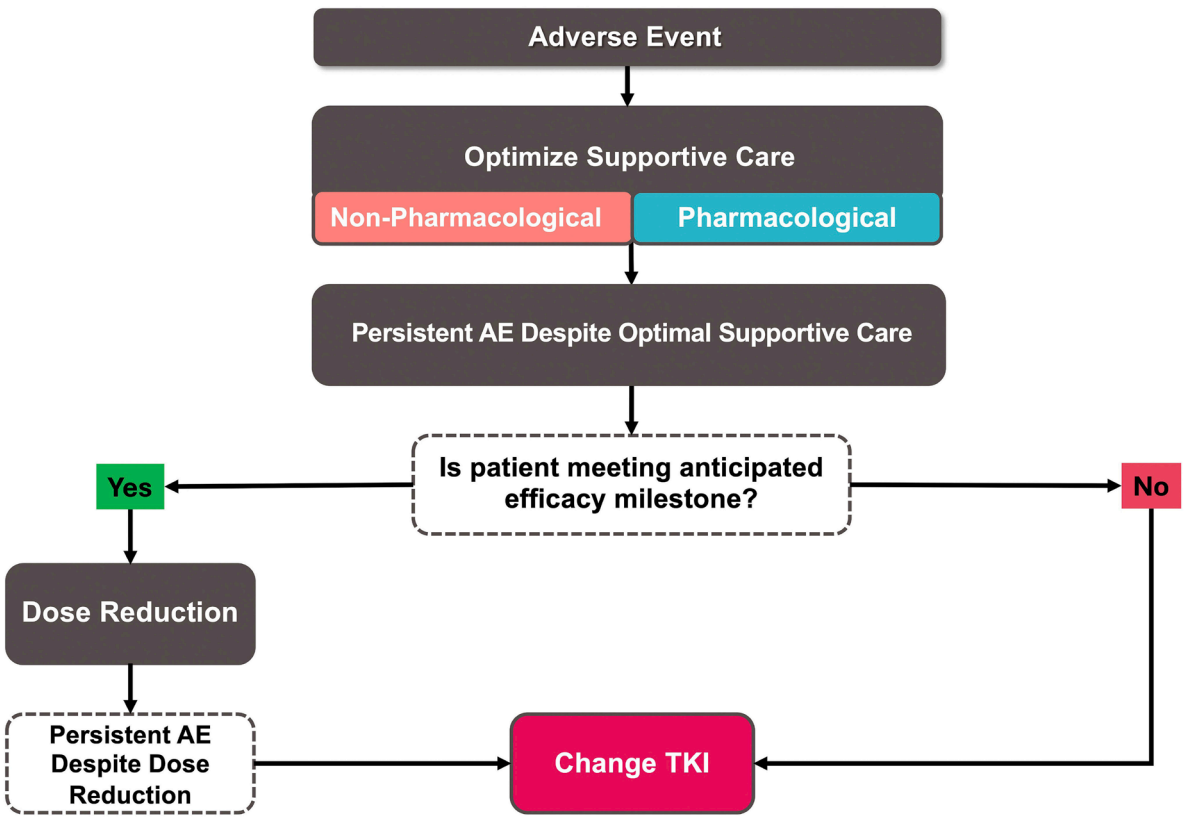

Figure 1. Overview of toxicity management. AE: adverse event; TKI: tyrosine kinase inhibitor.

ed patients, asciminib-treated patients had lower rates of diarrhea, nausea, muscle spasms, periorbital/face edema and relative to patients treated with second-generation TKI, asciminib-treated patients had lower rates of diarrhea, nausea, headaches, rash, and elevations of aspartate and alanine aminotransferases, and lipase. Pleural effusion is rare with asciminib, and the risk of arterial occlusive events appears low based on currently available data.[10,98] Other allosteric inhibitors are under evaluation in clinical trials, including TERN-701 and TGRX-678. These drugs represent an important advancement in limiting intolerances for CML patients on therapy.

For patients receiving imatinib or second-generation TKI, doses lower than recommended by prescribing information are a reasonable first-step strategy for management of TEAE. Recent reports have highlighted that for some patients serial intolerances on subsequent TKI may occur.[101] Whether this observation is true for asciminib is unclear. For patients struggling with TEAE and with slow molecular responses, asciminib is a good alternative choice. These observations are particularly relevant early in the treatment course when responses associated with overall survival are still being achieved. For patients with significant side effects on asciminib, there are limited data regarding outcomes on doses lower than the recommended starting dose.

Conclusion

Although therapy discontinuation is the goal of many patients and can lead to resolution of many TEAE and improvements in HRQOL, not all patients are able to stop and ~50% need to restart therapy due to molecular recurrence.[102-104] Consequently, strategies to limit TEAE without compromising response are crucial. Asciminib, given its efficacy and tolerability, is an important addition to the treatment arsenal. With the availability of generics, the cost of some TKI continues to decline steeply, which can reduce healthcare costs and help to limit patients' anxieties associated with high-cost drugs. New allosteric inhibitors are under evaluation in clinical trials and the future of CML treatment may include these drugs as well. Moreover, appropriate dose adjustment of imatinib, second-generation TKI and other third-generation TKI therapies to improve tolerance while maintaining efficacy remains a crucial part of CP CML management (Figure 1). The importance of dose selection is highlighted by ongoing clinical trials of novel CML therapies, which are examining more than one dose in expansion cohorts to identify more comprehensively the best dose that balances efficacy with tolerability. Nonetheless, caution is warranted if starting with lower doses in patients with higher risk CP CML with high clinical risk scores (e.g., ELTS score) or higher risk genetic features such as *ASXL1* mutations, which are associated with inferior molecular response and the acquisition of mutations in *BCR*::*ABL1*.[45-48] Continued awareness of therapy intolerances and toxicities experienced by patients coupled with shared decision-making between healthcare teams and patients can ensure optimal outcomes, improved HRQOL, and long-term safety.

Disclosures

VGO has been principal investigator for clinical trials for Novartis, Ascentage Pharma, Terns, and Shenzhen TargetRx and has provided consultancy services for Novartis, Terns, and Takeda. EB and IJH have no conflicts of interest to disclose.

Contributions

VGO wrote the manuscript and created the tables and figure. EB edited the manuscript. IJH edited the manuscript and created the tables and figure.

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