# Management of Adverse Events Associated With Tyrosine Kinase Inhibitor Use in Adult Patients With Chronic Myeloid Leukemia in Chronic Phase: An Advanced Practice Perspective

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Authors' disclosures of conflicts of interest are found at the end of this article.

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**Abstract**

The tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, nilotinib, bosutinib, and ponatinib have drastically improved the life expectancies of patients with chronic myeloid leukemia in chronic phase (CML-CP). While survival outcomes are comparable across first-line TKIs, each TKI has a unique toxicity profile that should be considered before starting or managing any treatment. Furthermore, the safety and tolerability of TKIs are particularly important in CML-CP, as the majority of patients remain on treatment for several years or for life. Management of adverse events (AEs) is critical to ensure adherence to treatment and to maintain efficacy and quality of life; management should also be considered in the context of the patient's molecular response to therapy to avoid switching TKIs unnecessarily. We present case studies examining pleural effusion occurring with bosutinib and dasatinib, cardiovascular events associated with nilotinib and ponatinib, and myelosuppression, which is common across all TKIs. We discuss the management of these AEs based on international guidelines and present our collective experience for advanced practitioners to consider.

## CASE STUDIES

### Case Study 1: Pleural Effusion

An 82-year-old man was diagnosed with chronic-phase CML with baseline *BCR-ABL1* levels of 0.56% by FISH and cytogenetics revealing t(9;22). His medical history included coronary artery disease, atrial fibrillation, hypertension, and hypothyroidism. The patient had previously received

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three TKIs (nilotinib, dasatinib, and imatinib) within 1 year, but discontinued each due to AEs, mainly pleural effusions, before coming to the authors' institution. Therefore, his therapy was switched to bosutinib at a dose of 100 mg/day, which was increased to 200 mg/day.

After 1 year of treatment without side effects, the patient presented with shortness of breath. Chest x-ray showed a large right pleural effusion and small left pleural effusion. Thoracentesis drained 1.5 L of fluid and showed negative cytology. Infectious workup was negative. Treatment with bosutinib was withheld, the patient was started on diuretics, and symptoms improved. He remained off bosutinib and diuretics were withheld. One month later, pleural effusion reoccurred with CT showing moderate right and small left pleural effusions; thoracentesis was repeated and 650 mL of fluid was drained. There was no evidence of malignancy, infection, or pulmonary embolism. Bosutinib continued to be withheld as *BCR-ABL1* was negative and blood counts normal. Repeat chest x-ray at 2-month follow-up showed no effusions, and shortness of breath had resolved without the use of diuretics.

At 3-month follow-up, the patient's *BCR-ABL1* levels had increased to > 10% on the International Scale (IS); therefore, bosutinib was restarted at a lower dose (100 mg/day). After 2 months, the patient redeveloped shortness of breath, and chest x-ray showed large recurrence of pleural effusion. His *BCR-ABL1* was 0.02% IS and bosutinib was stopped. Thoracentesis drained 1.2 L of fluid, which was negative for infection and malignancy. The patient received supportive care with diuretics and symptoms resolved. The patient remained off bosutinib for 6 months with stable *BCR-ABL1*, after which the *BCR-ABL1* level increased to > 10% IS with normal blood counts. Therefore, the patient started treatment with ponatinib 15 mg/day with low-dose aspirin; he has remained in chronic phase with normal blood counts and stable *BCR-ABL1* with last level at 0.0046% IS.

**Case Study 2: Pleural Effusion**

A 43-year-old woman with CML was initially treated with imatinib and achieved complete molecular response (CMR). She developed imatinib intolerance (persistent headache) and switched to dasatinib while in CMR after receiving imatinib for 9 years. She remained in CMR with dasatinib and appeared to tolerate it well. After approximately 2 years of treatment, the patient presented to the emergency department with complaints of hand swelling, increasing abdominal girth, and shortness of breath. CT of the chest showed bilateral pleural effusions. She had a thoracentesis with 700 mL of fluid removed; assessment of fluid showed no evidence of malignancy, and infectious workup was negative. She was discharged on furosemide, and dasatinib was continued without interruption. At an outpatient follow-up visit 4 weeks later, the patient had no recurrent symptoms and had discontinued furosemide at home. She continued dasatinib and maintained CMR without recurrent pleural effusions for 2 additional years.

**Case Study 3: Cardiac and Vascular Disorders**

A 78-year-old man with a history of hypertension, hyperlipidemia, and coronary artery disease with stent placement began initial treatment for CML-CP with nilotinib, the TKI most readily available to the patient at the time. He achieved major molecular response (MMR) but developed atrial fibrillation. After 2 years of treatment with nilotinib and after his primary care provider, cardiologist, and oncologist further reviewed his cardiac history, the patient switched to dasatinib and his arrhythmia resolved. With close monitoring (electrocardiograms at baseline, 1 week after TKI initiation, and every 3 months thereafter), the patient has remained on dasatinib with continued remission and no cardiac events for 2 years.

**Case Study 4: Myelosuppression and Cytopenias**

A 54-year-old man with CML-CP achieved molecular response with dasatinib 100 mg once daily but started to experience thrombocytopenia 6 months into treatment with platelet levels as low as $35 \times 10^9$/L (grade 3). Given the patient's stable response (but not MMR) to dasatinib, the dosage was reduced to 50 mg once daily. The patient remains with moderate thrombocytopenia (platelet count 70–80 $\times 10^9$/L; grade 1). He also continues with a molecular response on the reduced dose.

Chronic myeloid leukemia in chronic phase (CML-CP) is a myeloproliferative disorder characterized by a reciprocal chromosomal translocation resulting in the constitutively active tyrosine kinase, BCR-ABL1 (Jabbour & Kantarjian, 2018). Tyrosine kinase inhibitors (TKIs) that specifically target BCR-ABL1 have dramatically improved the survival outcomes for patients with CML-CP, with life expectancies approaching those of the general population (Bower et al., 2016; Sasaki et al., 2015).

Currently, four TKIs are approved in the United States for the first-line treatment of CML-CP: the first-generation TKI imatinib (Gleevec), and the second-generation TKIs dasatinib (Sprycel), nilotinib (Tasigna), and bosutinib (Bosulif; Bristol-Myers Squibb Company, 2018; Novartis Pharmaceuticals, Inc., 2018a, 2018b; Pfizer Inc., 2017). Dasatinib, nilotinib, and bosutinib are also approved for later-line therapy, as is the third-generation TKI ponatinib (Iclusig) for T315I-positive disease (ARIAD Pharmaceuticals, Inc., 2020). Overall survival is largely similar for patients receiving first-line imatinib, dasatinib, and nilotinib, possibly due to the efficacy of second-generation TKIs used as subsequent therapies in patients who discontinued imatinib (Cortes et al., 2016a; Hochhaus et al., 2016; Hughes et al., 2014).

Most patients with CML-CP require TKI treatment for several years or for life to prevent disease progression. Long-term treatment increases the risk of adverse events (AEs), which not only raises health concerns, but also impairs quality of life for many patients (Efficace et al., 2011). Therefore, the appropriate management of AEs is critical to maintain quality of life and to avoid switching therapies unnecessarily before disease progression. Furthermore, AEs may be associated with lower adherence to treatment, which can lead to suboptimal response or loss of response (Eliasson et al., 2011; Ibrahim et al., 2011; Marin et al., 2010; Noens et al., 2009).

Three types of treatment responses can be evaluated in CML-CP: complete hematologic response, consisting of complete normalization of peripheral blood counts (with leukocyte count $< 10 \times 10^9$/L and platelet count $< 450 \times 10^9$/L), no immature cells in the peripheral blood, and no signs and symptoms of disease; complete cytogenetic response (CCyR), in which no Philadelphia chromosome-positive metaphases are detected in the bone marrow by cytogenetic analysis or fluorescence in situ hybridization (FISH); and molecular response according to results from quantitative polymerase chain reaction for *BCR-ABL1* at predefined chronological milestones (National Comprehensive Cancer Network, 2020). As achievement and maintenance of response is critical, a patient's current treatment response will largely influence AE management strategies.

Tyrosine kinase inhibitors are generally well tolerated. Adverse events associated with TKI use are typically mild or moderate in intensity, and either spontaneously resolve or can be easily treated (Steegmann et al., 2016). While some AEs, such as gastrointestinal events and myelosuppression, are common across TKIs, each TKI has a distinct safety profile that should be considered when selecting treatment and managing associated AEs. Clinically relevant AEs of particular interest that have been frequently reported with TKI use are shown in Table 1, although cross-trial comparisons should be made with caution due to differences in patient populations, trial design, and follow-up time. Management strategies for AEs that commonly occur with TKIs based on our experience in clinical practice can be found in Table 2. In this article, we present multiple case studies of adult patients with CML-CP, with the aim of discussing strategies for the management of notable AEs associated with TKI use based on our experience.

## DISCUSSION

### Case Studies 1 and 2: Pleural Effusion

In clinical trials, pleural effusion has occurred in patients treated with bosutinib in the first-line setting (2% at 1 year and 4% at 2.5 years in two phase III trials; Cortes et al., 2018a; Gambacorti-Passerini et al., 2014a) and later-line settings (5% at 2 years, 17% at 4 years in a phase I/II trial; Cortes et al., 2016b; Gambacorti-Passerini et al., 2014b). However, pleural effusion has been reported more frequently with dasatinib than other TKIs approved for first-line treatment of CML-CP and can develop any time during dasatinib treatment (Steegmann et al., 2016). The early phase III CA180-034 dose-optimization trial in patients with CML-CP resistant or intolerant to imatinib

**Table 1. Common Adverse Events Reported With TKIs in Patients With CML-CP in Key Trials**

| **Imatinib**[a] 400 mg qd n = 551 | **Dasatinib**[b] 100 mg qd n = 258 | **Nilotinib**[c] 300 mg bid n = 279 | **Bosutinib**[d] 400 mg qd n = 268 | **Ponatinib**[e] 45 mg qd[f] n = 270 |
|---|---|---|---|---|
| **IRIS** 5-year follow-up | **DASISION** 5-year follow-up[g] | **ENESTnd** 5-year follow-up | **BFORE** 1-year follow-up | **PACE** 5-year follow-up |
| *Most common any-grade non-hematologic AEs (%)* | | | | |
| Edema[h] (60)<br>Nausea (50)<br>Muscle cramps (49)<br>Musculoskeletal pain (47)<br>Diarrhea (45) | Pleural effusion (28)<br>Myalgia[i] (23)<br>Diarrhea (21)<br>Rash (13)<br>Headache (13)<br>Superficial edema (13) | Rash (38)<br>Headache (32)<br>Nasopharyngitis (27)<br>Cholesterol elevation (28)<br>Fatigue (23) | Diarrhea (70)<br>Nausea (35)<br>ALT increased (31)<br>AST increased (23)<br>Rash (20) | Rash[j] (47)<br>Abdominal pain (46)<br>Headache (43)<br>Dry skin (42)<br>Constipation (41) |
| *Any-grade AEs of special interest (%)* | | | | |
| Edema[h] (60)<br>Congestive heart failure (< 1) | Infections (33)<br>Pleural effusion (28)<br>Pulmonary hypertension (5)<br>Arterial ischemic events[k] (5) | Hypertension (10)<br>Peripheral edema (9)<br>Cardiovascular events[l] (8)<br>Symptomatic QT prolongation (2)<br>Pleural effusion (2)<br>Pulmonary hypertension (0) | Infections (44)<br>Hypertension (5)<br>Cardiac events[m] (5)<br>Vascular events[n] (4)<br>Peripheral edema (4)<br>Pleural effusion (2) | Hypertension (37)<br>Arterial occlusive events[o] (31)<br>Venous thromboembolic events[p] (6) |
| *Grade 3–4 hematologic abnormalities (%)* | | | | |
| Neutropenia (17)<br>Thrombocytopenia (9)<br>Anemia (4) | Neutropenia (29)<br>Thrombocytopenia (22)<br>Anemia (13) | Lymphopenia (13)<br>Neutropenia (12)<br>Thrombocytopenia (10)<br>Anemia (4)<br>Leukopenia (3) | Thrombocytopenia (14)<br>Neutropenia (7)<br>Anemia (3)<br>Leukopenia (1) | Thrombocytopenia (35)<br>Neutropenia (17)<br>Anemia (10) |

*Note.* AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MCyR = major cytogenetic response; MedDRA = Medical Dictionary for Regulatory Activities. Data are from key phase III trials assessing first-line treatment with imatinib (Druker et al., 2006), dasatinib (Cortes et al., 2016b; Jabbour et al., 2014), nilotinib (Hochhaus et al., 2016), or bosutinib (Cortes et al., 2018a), as well as the pivotal phase II trial of ponatinib for second-line or later treatment (Cortes et al., 2018b).

[a] All-cause AEs are reported for imatinib from the IRIS trial, except for congestive heart failure, which was drug related.
[b] All-cause AEs are reported for dasatinib, except for pleural effusion, myalgia, diarrhea, rash, headache, and superficial edema, which were drug related.
[c] All-cause AEs are reported for nilotinib.
[d] Treatment-emergent AEs are reported for bosutinib.
[e] Treatment-emergent AEs are reported for ponatinib.
[f] The starting dosage for ponatinib was 45 mg qd. Proactive dosage reductions to 15 mg qd for patients with MCyR or 30 mg qd for patients without MCyR were implemented due to an accumulation of arterial occlusive events.
[g] Myalgia, diarrhea, rash, headache, superficial edema, and infections are reported at 3-year follow-up.
[h] Includes peripheral and periorbital edema.
[i] Includes myalgia, muscle spasms, and musculoskeletal pain.
[j] Includes erythematous, macular, and papular rash.
[k] Includes cardiovascular events (4%), transient ischemic attack (1%), and peripheral arterial disease (0%).
[l] Includes ischemic heart disease (4%), peripheral artery disease (3%), and ischemic cerebrovascular disease (1%).
[m] Includes arrhythmias, most commonly electrocardiogram QT prolongation, atrial fibrillation, sinus bradycardia, and bradycardia (1% each).
[n] Includes cardiovascular (3%), peripheral vascular (1%), and cerebrovascular (0%) events.
[o] Based on MedDRA preferred terms related to vascular ischemia. Includes cardiovascular (16%), peripheral vascular (14%), and cerebrovascular (13%) events.
[p] Based on MedDRA preferred terms related to thrombosis.

showed that treatment with dasatinib 100 mg once daily vs. 70 mg twice daily resulted in significantly lower rates of pleural effusion (Shah et al., 2008); at 7 years' follow-up, drug-related pleural effusion was reported in 28% of patients receiving the now standard 100-mg once daily dosage of dasatinib (Shah et al., 2016). Similarly, in the phase III DASISION study in patients with newly

**Table 2. Management of Common Adverse Events Associated With TKIs Based on Clinical Experience**

| Adverse event | Management strategy |
|---|---|
| *Nonhematologic AEs* | |
| Nausea and vomiting | Take imatinib with food; antiemetics if needed |
| Diarrhea | Loperamide or diphenoxylate atropine |
| Fluid retention | Low-sodium diet, oral diuretics |
| Peripheral edema | Diuretics (furosemide) as needed |
| Periorbital edema | Steroid-containing cream, low-sodium diet, cold compresses |
| Pleural effusion | Observation if minimal; if intervention is needed, hold TKI and resume with or without a dose reduction when the effusion has improved; diuretics and corticosteroids are options; thoracentesis for large, symptomatic effusions |
| Skin rash | Symptomatic therapy (e.g., antihistamines), topical steroids, occasionally systemic steroids, minimize sun exposure |
| Muscle cramps | Oral magnesium may be beneficial, electrolyte (e.g., potassium) replacement if needed, tonic water, muscle relaxants/analgesics |
| Arthralgia, bone pain | NSAID (should be used with caution if platelet dysfunction is suspected, e.g., with dasatinib) |
| QT interval prolongation | If QTc > 480 msec, hold TKI, correct low potassium and magnesium levels with supplements, review concomitant medications; check electrocardiogram and resume TKI at same dose within 2 weeks if QTc is < 450 msec and within 20 msec of baseline or at reduced dose if QTc is 450–480 msec; monitor, discontinue upon reoccurrence (QTc > 480 msec) after dose reduction[a] |
| Elevated AST or ALT | Monitor if grade 1–2, hold TKI if grade 3 and restart at a lower dose when improved to grade ≤ 1 |
| Elevated bilirubin | Monitor if grade 1–2, hold TKI if grade 3 and restart at a lower dose when improved to grade ≤ 1. Elevated bilirubin is common with nilotinib, especially among patients with Gilbert syndrome; for those patients, continuation of therapy may be allowed in some cases in spite of grade 3 elevated bilirubin. |
| Elevated lipase or amylase (asymptomatic) | Monitor if grade 1–2, hold TKI if grade 3 and restart at a lower dose when improved to grade ≤ 1 |
| Hyperglycemia | More common with nilotinib than other TKIs; hold therapy if grade ≥ 3 and restart at a lower dose when improved to grade ≤ 1; no contraindication to use nilotinib in patients with diabetes mellitus; close monitoring and adjustment of hypoglycemic agents as needed |
| *Hematologic AEs* | |
| Neutropenia[b] | Hold TKI if grade ≥ 3 (ANC < 1 × $10^9$/L); restart at the same dose when improves to grade ≤ 1 (ANC ≥ 1.5 × $10^9$/L); dose reductions are recommended if neutropenia does not improve in 1–2 weeks or if recurrent |
| Thrombocytopenia[b] | Hold TKI if grade ≥ 3 (platelets < 50 × $10^9$/L); restart at the same dose when improves to grade ≤ 1 (platelets ≥ 75 × $10^9$/L); dose reductions are recommended if thrombocytopenia does not improve in 1–2 weeks or if recurrent |
| Anemia | Treatment interruption or dose reduction usually not needed; consider erythropoietin or darbepoetin[c]; transfusions rarely needed |

*Note*. For recommendations specific to each TKI, including rare but serious toxicities, please refer to the prescribing information for each agent or most current NCCN Guidelines. AE grades are based on the Common Terminology Criteria for Adverse Events Version 5.0 (National Institutes of Health, 2017). AE = adverse event; ANC = absolute neutrophil count; NSAID = nonsteroidal anti-inflammatory drug; QTc = QT corrected; TKI = tyrosine kinase inhibitor. Table adapted with permission from Cortes & Kantarjian (2012).

[a]Management strategy based on NCCN Guidelines for chronic myeloid leukemia (Version 2.2021).

[b]Specific cutoff levels for ANC and platelet counts vary by TKI. Please refer to the prescribing information or NCCN Guidelines for details for each agent.

[c]Treatment with erythropoietin and darbepoetin is investigational and not considered standard in this setting (Santos et al., 2011).

diagnosed CML-CP, at 5 years' follow-up, 28% of patients treated with dasatinib experienced drug-related pleural effusion compared with 1% of patients treated with imatinib (Cortes et al., 2016a). Despite the high incidence of pleural effusion with dasatinib in these trials, grade 3 to 4 pleural effusions were relatively uncommon (3%–5%; Cortes et al., 2016a; Shah et al., 2016). The same management strategies for pleural effusion can be applied regardless of the specific TKI associated with it.

In both case studies, the patients presented with shortness of breath, a common symptom of pleural effusion; in an analysis of 48 patients treated with dasatinib after imatinib failure who developed pleural effusion, all patients had dyspnea at the time of pleural effusion (Quintas-Cardama et al., 2007). Other common symptoms include dry cough, chest pain, and fatigue. Identified risk factors for pleural effusion include cardiac disease, hypertension, hypercholesterolemia, autoimmune disease, prior skin rash on imatinib or dasatinib, twice daily dosing (vs. once daily), and older age (de Lavallade et al., 2008; Porkka et al., 2010; Quintas-Cardama et al., 2007). In a recent multivariate analysis of patients treated with dasatinib from the DASISION and CA180-034 studies, advanced age was identified as a risk factor for pleural effusion, but not hypertension, history of autoimmune disease history of skin rash, or average daily dose.

Other factors not associated with risk of pleural effusion included, but were not limited to, baseline Euro (Hasford) risk scores, prior lung disease, smoking history, lymphocytosis, line of therapy, and major molecular response (MMR) at 12 months (Hughes et al., 2019a). Thus, in the first case study, the patient's age, history of coronary artery disease, and perhaps hypertension put him at greater risk of developing pleural effusion; in the second case study, the patient did not have any identified risk factors.

Management of pleural effusion is typically based on its size as estimated by chest x-ray and the severity of associated symptoms (Figure 1; Cortes et al., 2017; Steegmann et al., 2016). Small, asymptomatic pleural effusions (< 500 mL and typically observed as blunting of the costophrenic angles by x-ray) may only require close monitoring (Cortes et al., 2017). Small, symptomatic pleural effusions can be managed with temporary treatment interruption until the effusion improves or resolves; treatment can resume either at the same dose or at a lower level depending on the patient's symptoms, response to therapy, and risk factors. If the pleural effusion does not improve with TKI interruption, treatment with diuretics or a short course of corticosteroids is also an option in stable patients, depending on other comorbidities (e.g., cardiovascular conditions and diabetes) and medications. If symptoms do not improve, a CT scan should be conducted. As noted in both case studies, more severe pleural effusions (those that are large and cause difficulty breathing), may require thoracentesis with possible ultrasound for resolution. To investigate potential non-TKI–related causes of pleural effusion, fluid from thoracentesis should be tested for malignancies and infection; if thoracentesis is not performed, infection should be ruled out by other clinical assessments. Imaging should be performed immediately after thoracentesis, and the patient should be monitored every 2 to 4 weeks for improvement or resolution. In the case of recurrent pleural effusions, further dose reductions or switching to another TKI should be considered depending on severity, as was done in the first case study.

### Case Study 3: Cardiac and Vascular Disorders

Various cardiovascular toxicities have been reported with nilotinib use. In a phase I dose-escalation study of nilotinib in patients with imatinib-resistant CML or acute lymphoblastic leukemia, QT prolongation in electrocardiograms (increases of 5–15 milliseconds) was reported (Kantarjian et al., 2006) and is reflected by a boxed warning on the U.S. Food & Drug Administration (FDA) label. Additionally, peripheral arterial occlusive disease has been reported with nilotinib in retrospective and prospective studies at a frequency of 1.1% to 16.7% (Aichberger et al., 2011; Giles et al., 2013; Larson et al., 2012; Le Coutre et al., 2011; Quintas-Cardama et al., 2012; Novartis Pharmaceuticals, Inc., 2018b); when the ankle–brachial index is assessed, the frequency increased to 26.0% to 35.7% (Kim et al., 2013). After 10 years of follow-up in the phase III ENESTnd trial in newly diagnosed CML-CP, more patients experienced cardiovascular events with nilotinib than imatinib (approximately 20% vs. 5%), with a similar inci-

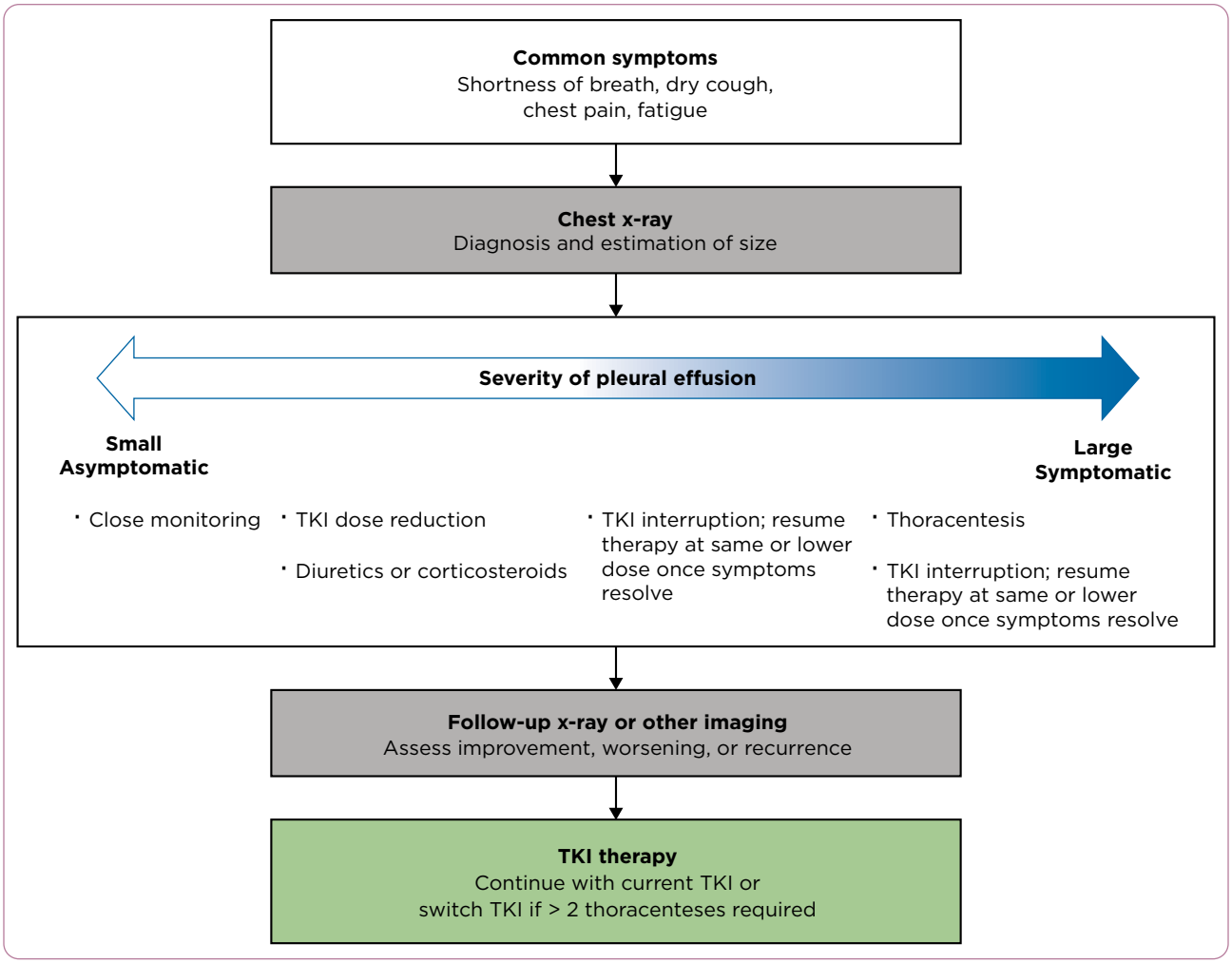


**Figure 1.** Management of pleural effusion associated with TKI use.

dence of cardiovascular events between the first 5 years of treatment and beyond 5 years (Hughes et al., 2019b). As expected, previous reports from this study demonstrated that patients with higher cardiovascular risk at baseline were more likely to experience a cardiovascular event while on therapy. Post baseline, more patients treated with nilotinib than imatinib had elevated glucose levels, as well as total cholesterol, low-density lipoprotein cholesterol, and glycated hemoglobin (HbA1c) levels above clinically relevant thresholds, which could contribute to cardiovascular risk (Hochhaus et al., 2016).

Increased risk of vascular events has also been a concern with ponatinib, which is indicated for second-line or later use. The boxed warning on the ponatinib label notes the risk of arterial occlusion, venous thromboembolism, heart failure, and hepatotoxicity, and use of ponatinib is restricted to patients with T315I-positive CML, and those for whom no other TKI is indicated (ARIAD Pharmaceuticals, Inc., 2020). In the 5-year follow-up of the pivotal phase II PACE trial, 31% of patients with CML-CP treated with ponatinib had arterial occlusive events (cardiovascular, 16%; cerebrovascular, 13%; peripheral vascular, 14%), and 6% had venous thromboembolic events (Cortes et al., 2018b). Patients with a higher risk of arterial occlusive events included those with a history of ischemic heart disease, hypertension, diabetes, or hypercholesterolemia, and older patients (≥ 65 years). Additionally, serious cases of atrial fibrillation and angina pectoris were reported in 6% and 5% of patients, respectively. Further analysis of PACE and pooled data from additional ponatinib tri-

als suggested that arterial occlusive events were dose related (Dorer et al., 2016; Knickerbocker, 2014). Consistent with the European LeukemiaNet (ELN) guidelines, in clinical practice, the starting dosage of ponatinib is typically 30 mg or 15 mg once daily for CML-CP, depending on the patient's history and disease characteristics (Hochhaus et al., 2020). In our experience, the FDA-approved and NCCN-recommended initial dosage of 45 mg once daily is normally reserved for patients with acute lymphoblastic leukemia. To further evaluate the optimal starting dose for ponatinib in CML-CP, OPTIC, an ongoing phase II trial, is assessing the efficacy and safety of ponatinib dosages of 45, 30, and 15 mg once daily in patients with resistant CML-CP (ClinicalTrials.gov, 2019).

As recommended by the ELN, patients with high cardiovascular risk or a history of arteriovascular disease should avoid first-line nilotinib or later-line ponatinib if possible (Hochhaus et al., 2020); these agents should only be given to such patients after careful consideration of the expected benefits in efficacy vs. the safety risks. Therefore, prior to starting any TKI treatment, cardiac history and current status should be assessed and an electrocardiogram performed (Table 3). National Comprehensive Cancer Network Guidelines suggest referral to a cardiologist for patients with cardiovascular risk who are considering starting ponatinib (NCCN, 2020). Depending on the TKI, cardiovascular monitoring while on treatment may be necessary. Patients should also be monitored for fasting glucose, HbA1c, lipids, and creatinine. Additionally, actions should be taken to decrease cardiovascular risk. If a cardiac event does occur and resolves, TKI treatment can be continued if no new events occur.

**Case Study 4: Myelosuppression and Cytopenias**

Neutropenia, thrombocytopenia, and anemia are commonly reported with TKI use. However, myelosuppression is thought to reflect the therapeutic effects of TKIs, as the recovery of normal hematopoiesis from suppression by the leukemic clone may be delayed (Henkes et al., 2008). In randomized trials of imatinib, dasatinib, nilotinib (300 mg twice daily), and bosutinib in the first-line setting, grade 3 to 4 hematologic toxicities reported at the primary analysis included neutropenia (7%–21%), thrombocytopenia (6%–19%), and anemia (3%–10%; Cortes et al., 2018a;

**Table 3. Cardiovascular Assessments for Patients Receiving TKIs for CML-CP**

| Assessment | Imatinib | Dasatinib | Nilotinib | Bosutinib | Ponatinib |
|---|---|---|---|---|---|
| *Baseline* | | | | | |
| Clinical CV assessment | Y | Y | Y | Y | Y |
| Blood pressure | Y | Y | Y | Y | Y |
| Fasting glucose | AI | AI | Y | AI | Y |
| Fasting lipids | AI | AI | Y | AI | Y |
| Electrocardiogram | Y | Y | Y | Y | Y |
| Echocardiogram | AI | AI | AI | AI | AI |
| Ankle–brachial index | AI | AI | AI | AI | AI |
| *1-month follow-up* | | | | | |
| Clinical CV assessment | AI | Y | Y | AI | Y |
| Blood pressure | AI | AI | AI | AI | Y |
| *3- to 6-month follow-up*[a] | | | | | |
| Clinical CV assessment | Y | Y | Y | Y | Y |
| Blood pressure | AI | AI | Y | AI | Y |
| Fasting glucose | AI | AI | Y | AI | AI |
| Fasting lipids | AI | AI | Y | AI | Y |
| Electrocardiogram | AI | AI | Y | AI | Y |
| Echocardiogram | AI | AI | AI | AI | AI |
| Ankle–brachial index | AI | AI | AI | AI | AI |

*Note.* Assessments should be performed more frequently in patients with high cardiovascular risk or if clinically indicated. AI = as indicated; CV = cardiovascular; Y = yes. Table adapted with permission from Barber et al. (2017)
[a]Follow-ups should continue every 3–6 months and at least yearly for patients in stable condition.

Kantarjian et al., 2010; Saglio et al., 2010). In the later-line setting with ponatinib, the frequency of grade 3 to 4 neutropenia, thrombocytopenia, and anemia was 14%, 32%, and 6%, respectively (Cortes et al., 2013).

Myelosuppression commonly occurs within the first 4 to 6 weeks of treatment, with the highest incidence of grade 3 to 4 cytopenias at the start of treatment initiation (Steegmann et al., 2016). As myelosuppression may lead to infection and hemorrhagic events, cytopenias should be closely monitored; prophylaxis is generally not required.

As demonstrated in the case study, most hematologic effects of TKIs can be improved or are reversible by dose reduction or treatment interruption, although the possible effect on efficacy should be considered. Thus, as recommended by the ELN, blood counts should be monitored weekly during the first 4 to 6 weeks of treatment, every 2 to 4 weeks until month three, and every 3 months thereafter in the absence of grade 2 to 4 cytopenias (Hochhaus et al., 2020; Steegmann et al., 2016). In clinical practice, this schedule may vary slightly; for example, blood counts may be monitored weekly during the first month, every two weeks during the second month, and monthly thereafter if the patient is stable.

Specific recommendations for the management of myelosuppression associated with each TKI can be found in their respective package inserts (ARIAD Pharmaceuticals, Inc., 2020; Bristol-Myers Squibb Company, 2018; Novartis Pharmaceuticals, Inc., 2018a, 2018b; Pfizer Inc., 2017) or in the NCCN Guidelines (2020). In general, treatment should be withheld in the case of severe cytopenias (absolute neutrophil count < $1 \times 10^9$/L [grade ≥ 3]; platelet count < $50 \times 10^9$/L [grade ≥ 3]) until the absolute neutrophil count returns to ≥ $1.5 \times 10^9$/L (grade ≤ 1) and platelet count ≥ $75 \times 10^9$/L (grade ≤ 1); TKI treatment can be resumed at the same dose, although dose reductions may be recommended if blood counts do not improve within 1 to 2 weeks or if the cytopenias reoccur. Additionally, transfusional support may be used as needed. In patients with persistent cytopenia who do not require transfusional support, withholding treatment may not be necessary if the patient is monitored closely.

## IMPLICATIONS FOR THE ADVANCED PRACTITIONER

As exemplified by the case studies, each TKI has a distinct safety profile to consider when selecting treatment and managing AEs. While general recommendations can be made, each patient must also be treated on an individual basis. It is especially key to consider the patient's comorbidities, which may increase the risk of developing a particular AE. For patients with current or prior lung disease or other risk factors for pleural effusion, TKIs other than dasatinib may be more appropriate; for those with significant cardiac or vascular history, avoiding nilotinib or ponatinib may reduce the risk of cardiovascular AEs if treatment with other TKIs is feasible. Furthermore, when selecting a TKI, it is important to consider the patient as a whole and take into account prior therapies and AEs, lifestyle and adherence to therapy, cognitive function, familial support, and insurance coverage. Patient education plays a key role in this aspect, allowing patients to understand their disease and recognize potential AEs, which may facilitate their detection and lead to improved monitoring and reporting. The ability of patients to monitor key milestones in their treatment journey against standard guidelines may also increase compliance and strengthen the relationship between patient and health-care practitioner.

Health-care practitioners should also be aware of when it may be appropriate to continue or interrupt TKI therapy or lower the dose in the event of an AE. This decision depends on several factors, including type and severity of AE and the patient's molecular response to the TKI, given the therapeutic goal of remission from CML-CP. However, in general, consistent with the ELN recommendations, grade 1 AEs typically do not warrant a change in TKI therapy or dose. For grade 2 AEs, withholding the TKI until the AE improves to grade 1 or better is preferred, but continuing treatment for a week can be considered; recurring grade 2 AEs may warrant a dose reduction. For grade 3 events, withholding the TKI until the AE improves to better than grade 3 and resuming TKI treatment at a dose reduction is preferred; alternatively, withholding the TKI until the AE is better than grade 2 and resuming treatment at the same dose level is an option. Switching TKIs may be required if

a grade 3 AE does not resolve within 4 weeks or in the case of recurrent grade 3 AEs. If grade 4 events occur, therapy should be discontinued and treatment with another TKI should start when appropriate. Although switching TKIs is recommended for grade 3 AEs that persist and grade 4 AEs, practical limitations such as TKI availability and cost may preclude the switch, such that dose reductions with the same TKI may suffice until disease progression. In addition to dose reduction and temporary interruption of TKI therapy in response to AEs, lower starting doses and a modified dosing schedule are potential strategies for reducing toxicity while sustaining efficacy.

Results from a single-center, single-arm, phase II study support a lower dose of dasatinib (50 mg once daily) as an effective and well-tolerated therapy for patients with first-line CML-CP, most (66%) of whom had a low Sokal risk score (Naqvi et al., 2020). In a retrospective study, intermittent dosing with dasatinib (3–5 days on treatment, followed by 2–4 days off treatment) demonstrated reduced pleural effusions and hematologic toxicity, and maintained disease control in 58% of patients (La Rosee et al., 2013). The randomized phase III DasaHIT study, assessing daily dasatinib dosing vs. 5 days on treatment followed by 2 days off, will provide more insight into the efficacy and safety of intermittent dosing (ClinicalTrials.gov, 2020).

Long-term dose reduction for patients with sustained MMR is also being considered. In the phase II DESTINY trial, patients with stable MMR or better received half the standard dose of imatinib, dasatinib, or nilotinib for 12 months; 7% of patients lost MMR while on the half dose (but regained MMR within 4 months of restarting the full dose), and there was an improvement in AEs during the first 3 months of dose reduction, but not thereafter (Clark et al., 2017). This study also applied the strategy of dose reduction as a prelude to treatment-free remission (Clark et al., 2019), which may be feasible for patients who achieve sustained deep response to therapy (Saussele et al., 2016). Stopping TKI therapy for an indefinite or prolonged period of time may substantially reduce AEs, although musculoskeletal events related to imatinib, dasatinib, and nilotinib discontinuation have been reported during treatment-free remission (Park et al., 2016; Richter et al., 2014; Ross et al., 2018; Shah et al., 2019).

The majority of patients will experience AEs while receiving TKIs; however, appropriate management can minimize their effect on TKI dosing, patient health, and quality of life. We have discussed pleural effusion, cardiovascular events, and hematologic toxicities as events of particular interest due to their frequency with first-line TKIs, but it is important to note that other AEs associated with TKI use have not been addressed. Nonetheless, the underlying goals of selecting the appropriate TKI to minimize AEs, resolving AEs when they arise, and preventing further occurrences while maintaining the efficacy of TKI therapy remain the same. Guidelines developed by a panel of experts from established organizations such as ELN and NCCN are valuable resources for health-care practitioners and should be consulted. Appropriate management, monitoring, and intervention strategies based on treatment guidelines but adjusted on a case-by-case basis could enable health-care practitioners to optimize TKI therapy for each patient and achieve this goal.

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