Review

Long-term BCR-ABL1 Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia

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Abstract. *With the success of tyrosine kinase inhibitor (TKI) therapy for the treatment of patients with chronic myeloid leukemia (CML), CML is now treated as a chronic disease. As such, the community of oncologists may see patients with CML more often than the primary-care physician and must focus on long-term management of adverse events and adherence. BCR-ABL1 TKIs are effective therapies in CML but are associated with distinct safety profiles. Thus, selection of long-term treatment with any TKI requires assessment of patient comorbidities and regular monitoring to identify the potential emergence of adverse effects or new risk factors. With a focus on long-term safety, this review provides a holistic picture of the primary care needs of patients with CML, emphasizing on the importance of community oncologists who in many cases act as both oncologists and primary-care physicians.*

The BCR-ABL1 tyrosine kinase inhibitor (TKI) imatinib was first approved by the US Food and Drug Administration (FDA) as a therapy for patients with chronic myeloid leukemia (CML) in 2001 (1). In 2002, imatinib was approved as a first-line therapy for patients with CML in the chronic phase (CML-CP) based on the International Randomized Study of Interferon and STI571 (IRIS), that demonstrated significantly better efficacy and tolerability with imatinib than with interferon-alpha plus cytarabine (2, 3). Imatinib is currently indicated for adult and pediatric patients with newly-diagnosed CML-CP or patients with CML-CP, CML in accelerated phase (AP), or CML in blast phase (BP) after failure of interferon alpha therapy (1). Other BCR-ABL1 TKIs have been subsequently approved: dasatinib in patients with newly-diagnosed CML-CP or any-phase CML with resistance to or intolerance of prior therapy that included imatinib (4), nilotinib in patients with newly diagnosed CML-CP or adult patients with CML-CP or CML-AP with resistance to or intolerance of prior therapy that included imatinib (5), bosutinib in adult patients with any-phase CML with resistance to or intolerance of prior therapy (6), and ponatinib in patients with any-phase CML with the T315I mutation or for those in whom no other TKI therapy is indicated (7).

As a result of BCR-ABL1 TKI therapy, patients with CML are living longer than ever before. By one estimate, the prevalence of CML in the United States will increase from ≈70,000 patients in 2010 to ≈181,000 patients in 2050 (8). Therefore, oncologists may expect the number of patients with CML to increase dramatically over the next several decades, raising important implications for the future of patient care. Most patients with CML can be effectively treated with long-term TKI therapy (8). Community oncologists will likely care for their patients with CML for many years, possibly decades, during which patients are expected to remain on TKI therapy. Consequently, the management of TKI-related adverse events (AEs) will remain an important aspect of the long-term treatment of patients with CML, helping to ensure that patients stay on TKI therapy and maximize treatment effectiveness (9).

BCR-ABL1 TKIs are generally well-tolerated; nevertheless, long-term experience has revealed AEs of clinical significance. In addition, the longer survival of patients with CML on TKI therapy highlights the need to address concurrent medical conditions and to coordinate care between primary care physicians, oncologists, and other specialists to manage CML in the context of comorbid conditions. This review will focus on accumulating the long-term efficacy and safety data and

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Table I. *Summary of long-term clinical data of BCR-ABL1 TKI therapy in CML-CP.*

BCR-ABL1 TKI	Study	N[a]	Follow-up	CCyR, %[b]	MMR, %[b]	OS, %	EFS, FFP, or PFS, %	Discontinuation for AEs/Safety, %
First-line clinical studies								
Imatinib	IRIS (79, 80)	553	7 years	82	NR	86	EFS: 81 FFP: 93	5
			8 years	NR	NR	85	EFS: 81 FFP: 92	6
	ENESTnd (10)	283	3 years	NR	53	94	EFS: 93 PFS: 95	11
	DASISION (11)	260	2 years	82	46	95	PFS: 92	5
	BELA (12)	252	2 years	80	49	95	EFS: 88	9
	EPIC (13)	134[c]	3 months	NR	0[d]	NR	NR	<1
Nilotinib	GIMEMA (81)	73	5 years	99	97	97	EFS: 83 PFS: 97	NR
	ENESTnd (10)	300 mg: 282 400 mg: 281	3 years	NR	300 mg: 73 400 mg: 70	300 mg: 95 400 mg: 97	300 mg EFS: 95 PFS: 97 400 mg EFS: 97 PFS: 98	300 mg: 10 400 mg: 14
Dasatinib	DASISION (11)	259	2 years	86	64	95	PFS: 94	9
Bosutinib	BELA (12)	250	2 years	79	59	97	EFS: 92	25
Ponatinib	EPIC (13)	133[c]	3 months	NR	29[d]	NR	NR	7
Second- or later-line clinical studies								
Dasatinib	CA180-034 (14)	Total: 670 100 mg: 167 R/I: 124/43	5 years	NR	100 mg (R/I): 42/53	100 mg (R/I): 77/82	100 mg (R/I): PFS: 56/63	NR
Nilotinib	2101 (15)	321	4 years	45	NR	78	PFS: 57	21
Bosutinib	NCT00261846 (16)	288	2 years	43	35	91	PFS: 81	23
Ponatinib[e]	PACE (17)	Total: 449 CP: 267	2 years	53	38	86	PFS: 67	NR

[a]Number of patients in the intent-to-treat population. [b]Cumulative rates of response. [c]Only those patients with evaluable data were considered imatinib treatment arm of the study. [d]Response rate at 3 months of treatment. [e]Efficacy data are provided for patients with CML-CP only. AE, Adverse event, AP, accelerated phase; BP, blast phase; CCyR, complete cytogenetic response; EFS, event-free survival; FFP, freedom from progression to AP or BP; MMR, major molecular response; NR, not reported; OS, overall survival; PFS, progression-free survival; R/I, resistant to/intolerant of imatinib.

provide a clinical perspective on how the success of TKI therapy in CML has led to the evolution of the role of the community oncologist in the overall care of patients.

Long-term Efficacy and Safety of TKI Therapy

Long-term Efficacy: First- and second-line settings. Head-to head comparative clinical studies of TKI therapy in patients with CML-CP have consistently shown that faster, deeper, and higher rates of cytogenetic and molecular responses are achievable with second- and third-generation TKIs *vs*. imatinib in the first-line setting (10-13) and second-line setting following imatinib intolerance or resistance (Table I) (14-17). In the 6-year follow-up of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials–Newly Diagnosed Patients (ENESTnd) study, 54%, 55%, and 45% of patients receiving nilotinib 300 mg twice daily, 400 mg twice daily, and imatinib, respectively, remained on core treatment (18). Patients treated with nilotinib 300 mg twice daily had significantly higher 6-year rate of major molecular response (MMR; 77%) *vs*. imatinib (61%; nominal $p<0.0001$) and $MR^{4.5}$ (*BCR-ABL1*≤0.0032% on the International Scale; 56%) *vs* imatinib (33%; nominal $p<0.0001$) (18). With 5 years of follow-up, final results of the DASatinib *versus* Imatinib Study in treatment-naive CML patients (DASISION) study showed that 61% and 63% of patients randomized to receive dasatinib 100 mg once daily and imatinib 400 mg once daily, respectively, remained on treatment (19). MMR rates by 5 years were 76% with dasatinib *vs*. 64% with imatinib ($p=0.002$), and rates of $MR^{4.5}$ were 42% and 33% with dasatinib and imatinib,

respectively (p=0.025) (19). ENESTnd and DASISION each showed improved response rates with nilotinib and dasatinib, respectively, over imatinib. In ENESTnd, the rate of 5-year freedom from progression to AP/BP was higher with nilotinib 300 mg than with imatinib (96% *vs* 92%; p=0.0403) (20). With 6 years' follow-up in ENESTnd, similar rates of overall survival (OS) were observed in the nilotinib 300-mg and imatinib arms (92% and 91%, respectively; p=0.709); however, the 6-year OS rate in the nilotinib 400-mg arm was higher than in the imatinib arm (96% *vs*. 91%; p=0.0314) (18). In DASISION, 5-year rates of progression-free survival (PFS) were 85% with dasatinib *vs*. 86% with imatinib (19). Similar rates of OS at 5 years were also observed with dasatinib (91%) *vs*. imatinib (90%) (19). Follow-up of ENESTnd is ongoing and updates to survival end-points (PFS and OS) are awaited.

As expected, in the second-line setting, response rates and survival rates with TKIs were generally lower and discontinuation rates generally higher than in the first-line setting (14-17). In the Study 2101, in which patients were treated with nilotinib after imatinib resistance or intolerance, 31% of patients remained on second-line nilotinib at the 4-year analysis, and rates of OS and PFS were 78% and 57%, respectively (15). Among patients in the CA180-034 study receiving second-line dasatinib 100 mg once daily after imatinib resistance or intolerance, 35% remained on treatment at 5 years, and 5-year OS and PFS rates were 78% and 58%, respectively (14). In the Study 200, a study of bosutinib after imatinib resistance or intolerance, 2-year OS and PFS rates were 91% and 81%, respectively (16); however, 55% of patients had discontinued from the study at the 2-year analysis (16).

Long-term Safety: First- and second-line settings. The high discontinuation rates due to intolerance observed with early available therapies for CML (up to 18% in a literature analysis of interferon-alpha (21)) are generally not observed with currently available TKIs (Table I). Although the possibility of stopping TKI treatment in patients with sustained deep molecular response to TKI therapy is under investigation in clinical trials of treatment-free remission (22-25), at present, the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet recommend indefinite treatment with BCR-ABL1 TKIs in optimally-responding patients (9, 26). Thus, clinicians must remain vigilant and proactively manage AEs over the long term, and the potential effects of persistent low-grade AEs on patient quality of life and treatment adherence should not be overlooked (27, 28). Notably, the definitions of TKI intolerance used in clinical studies (based on the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) were developed to describe acute AEs in patients undergoing finite chemotherapy treatments and as a result may be inadequate for clinical assessments in patients with CML on long-term therapy. In addition, AEs considered to be minor under NCI-CTCAE definitions could significantly affect quality of life if they persist over time (28). For instance, fatigue is a major factor negatively impacting quality of life in patients with CML on TKI therapy (29), with significantly higher rates and severity of fatigue reported in patients with CML relative to age- and sex-matched controls (30). This is particularly important in light of patient survey data showing a relationship between health-related quality of life and intentional non-adherence (31). Therefore, oncologists should regularly query patients about their quality of life (28). To this end, disease- and symptom-specific assessment tools, including the Functional Assessment of Cancer Therapy-Leukemia scale (32), the MD Anderson Symptom Inventory Chronic Myeloid Leukemia Module (33), and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire CML24 (34), are available or under development. As a general rule, intolerance of BCR-ABL1 TKI therapy should be managed with symptom-directed supportive care or dose adjustments or interruptions before considering a switch to another approved BCR-ABL1 TKI (28).

System-specific Safety Issues

Pulmonary AEs: Pleural effusion. Pleural effusion is more commonly associated with dasatinib than with other approved TKIs (35). Pleural effusion with dasatinib has been observed in both the first- and second-line settings, and the risk does not appear to decrease with time (11, 19, 36). In DASISION, any-grade pleural effusion was reported in 10%, 14%, and 29% of dasatinib-treated patients with 1, 2, and 5 years of follow-up, respectively (11, 19, 37). In a separate single-center study, 35% of patients had pleural effusion after a median of 42 weeks of dasatinib treatment (35). In the study CA180-034, 24% of patients on second-line dasatinib experienced pleural effusion by 5 years (36). Pleural effusion has also been reported in 7% of patients with CML-CP on second-line ponatinib in the Ponatinib Ph+ ALL and CML Evaluation (PACE) study after a median follow-up of 10 months (7) and in 4% of patients on second-line bosutinib in Study 200 after a median follow-up of 24.2 months (38).

The dasatinib prescribing information recommends that patients with symptoms suggestive of pleural effusion on dasatinib should have a chest x-ray (4). Patients with pleural effusion on dasatinib were typically treated with supportive care measures, including diuretics or short-course steroids (4); however, thoracentesis and oxygen may be required for severe cases (4).

Pulmonary AEs: Pulmonary arterial hypertension (PAH). PAH is another AE observed primarily with dasatinib, most commonly in the second-line setting and in patients who

previously experienced pleural effusion, suggesting a common etiology for these conditions (35, 39-46). Pulmonary hypertension was diagnosed in 3 patients (1.2%; grade 1/2) in DASISION after 2 years of follow-up; of these patients, 1 had no evidence of PAH and 2 were not evaluated for PAH (11). Additional cases of pulmonary hypertension, but no confirmed cases of PAH, were reported in DASISION with 5 years of follow-up (19). Of note, PAH can develop after years of stable treatment with dasatinib (40, 42-46).

Prior to initiating dasatinib, patients should be evaluated for PAH risk and for signs and symptoms of PAH during treatment (4). In high-risk individuals or those with a history of physical examination findings suggestive of pulmonary hypertension, such as dyspnea, chest pain, jugular venous distension, or abdominal swelling, a screening echocardiogram should be obtained (47). Dasatinib should be permanently discontinued if PAH develops on treatment (4).

Cardiovascular AEs: Vascular events. Peripheral arterial occlusive disease (PAOD; defined as atherosclerotic and thrombotic events, excluding functional [vasoreactive], embolic, or aneurysmal disorders, in the arteries of extremities) has been described in case reports and clinical studies of nilotinib (10, 48-55). A retrospective analysis of PAOD risk in patients enrolled in IRIS, ENESTnd, and Tyrosine Kinase Dose Optimization Study (TOPS) demonstrated that the exposure-adjusted relative risk for patients on first-line nilotinib vs. imatinib was 0.9 (95% CI=0.2-3.3) vs. 0.1 (95% CI=0.0-0.5); the relative risk for patients not treated with BCR-ABL1 TKIs was set to 1 (55). Nilotinib did not confer an increased risk compared to no BCR-ABL1 TKI therapy; however, imatinib demonstrated decreased risk compared with no BCR-ABL1 TKI therapy (55). This same analysis showed that the time to onset of PAOD ranged from 1-3 years after initiation of first-line nilotinib (55). The 6-year follow-up of ENESTnd indicated that PAOD/ischemic heart disease/ischemic cerebrovascular events occurred in 4.3%/5.0%/1.4% of patients on nilotinib 300 mg, 3.2%/10.1%/3.2% of patients on nilotinib 400 mg, and 0%/2.1%/0.4% of patients on imatinib, respectively (18).

PAOD has also been reported with other BCR-ABL1 TKIs. In a pooled analysis of 11 clinical studies of first- or second-line dasatinib (N=2,705), 6 patients (0.2%) with median dasatinib treatment duration of 39.1 months (range=9.9-74.4 months) were identified as having experienced PAOD or a related event on dasatinib (56). Among 570 patients on second- or later-line bosutinib treatment for a median of 11.1 months (range=0.03-83.4 months), cardiovascular events occurred in 4.2%, cerebrovascular events in 2.3%, and peripheral vascular events in 8.2% of patients (57). With a median of 33.1 months of follow-up in the Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) study, cardiovascular/cerebrovascular/peripheral vascular events occurred in 1.6%/0.8%/8.1% of 248 patients receiving first-line bosutinib and 1.2%/0.4%/4.8% of 251 patients receiving first-line imatinib, respectively (57).

Ponatinib carries a black box warning for vascular occlusion, heart failure, and hepatotoxicity (7). In October 2013, the US FDA issued a statement requesting suspension of ponatinib marketing and sales based on reports of vascular occlusion events occurring in ponatinib clinical studies (58). In PACE (N=449), serious cardiovascular, cerebrovascular, and peripheral vascular events occurred in 7%, 5%, and 4% of patients, respectively (59). Overall, the most common arterial thrombosis event was myocardial infarction or worsening coronary artery disease (60). On the basis of occurrence of vascular events in PACE, the phase 3 Evaluation of Ponatinib *vs*. Imatinib in CML (EPIC) study of first-line treatment for CML-CP was terminated prematurely (13). With a median of 3 months of follow-up in EPIC, 7% of patients on ponatinib and 4% of patients on imatinib had experienced vascular occlusive events (13). Clinical practice guidelines and the ponatinib prescribing information advise that treatment should be interrupted (with consideration of discontinuation) if patients develop arterial thrombotic events, and dose modification or discontinuation should be considered in patients who experience serious venous thromboembolism (7, 9).

Patients experiencing vascular events on TKI therapy often had ≥1 risk factor (*e.g.*, history of smoking, cardiovascular disorders, diabetes, or obesity) at baseline (39, 48-54, 56, 57, 60, 61). Consequently, it is highly advisable to evaluate the cardiovascular status of patients before starting therapy (61, 62). All patients with or without CML should be screened for cardiovascular risk using the 2013 American College of Cardiology/American Heart Association Guidelines, which include assessment of lipids, diabetes status, and blood pressure (63). Patients with CML and known atherosclerotic cardiovascular disease should be treated based on secondary prevention guidelines, and such comorbidities should be considered when choosing a first-line TKI (62, 64). Patients without known atherosclerotic cardiovascular disease between the ages of 40 and 79 with >7.5% 10-year risk of an atherosclerotic cardiovascular disease event should be started on a moderate-dose statin regardless of their lipid panel (63, 65). Additional risk factor modification including glucose and blood pressure control as well as smoking cessation should be aggressively pursued (66). It is also reasonable to consider a referral to a cardio-oncologist if available (or general cardiologist) to manage cardiovascular risk. If acute signs or symptoms of cardiovascular events occur, TKI therapy should be discontinued and medical attention should be sought immediate.

Cardiovascular AEs: Corrected QT interval (QTc) Prolongation. The QT interval is an electrocardiographic measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with an increased risk of the life-threatening rhythm torsades de pointes and sudden cardiac death. Although the QT interval is a relatively poor predictor for the development of torsades de pointes, it remains an important part of oncology drug development and surveillance (67).

QTc prolongation (QTc ≥500 ms) is rare with BCR-ABL1 TKI therapy in either the first- or second-line settings, even after years of treatment (10, 15, 37, 38, 68, 69). The 3-year follow-up of the ENESTnd study showed that no patients treated with nilotinib had QTc ≥500 ms, 1 patient (0.2%) had QTc ≥480 ms, and 4 patients (0.7%) had ≥60 ms change in QTc from baseline (10). In the 2-year follow-up of Study 2101, 4 patients (1.2%) on second-line nilotinib had QTc ≥500 ms and 8 patients (2.5%) had ≥60 ms change in QTc from baseline (69). In clinical studies of first- and second-line dasatinib, 16 of 2440 patients (<1%) had QTc prolongation; 22 (<1%) had QTc >500 ms by the Fridericia formula (4).

Nilotinib carries a black box warning related to the risk of QTc prolongation and sudden death. In multiple clinical trials with 5,661 nilotinib-treated patients with CML, 0.3% of patients experienced sudden death, potentially due to ventricular repolarization abnormalities (5). As indicated in the nilotinib and dasatinib prescribing information (4, 5), use of BCR-ABL1 TKI therapy in patients with known risk factors for QT prolongation, including those with genetic long QT syndromes or those concomitantly taking medication known to prolong QT interval, is not recommended due to potential synergistic effects. Magnesium and potassium abnormalities can also prolong the QT interval, and electrolyte imbalances should be corrected prior to administration. Electrolytes should also be monitored periodically during TKI therapy.

Gastrointestinal (GI)-related AEs. GI-related AEs have been reported with all approved BCR-ABL1 TKIs. In the first-line setting, GI-related AEs were more frequent with imatinib than with either nilotinib (70) or dasatinib (37) and were more frequent with bosutinib than with imatinib (71). Most GI-related AEs associated with first-line bosutinib were low grade. Diarrhea was the most frequent GI-related AE, and tended to occur early in the treatment course and be of short duration and manageable (68). The bosutinib prescribing information recommends withholding treatment in the event of grade 3/4 diarrhea until recovery to grade 1, then resuming bosutinib at 400 mg once daily (6). GI-related AEs (*e.g.*, diarrhea, nausea, and vomiting) were reported in 84% of patients treated with bosutinib in the second-line setting (38). Across all lines of therapy, bosutinib-related all-grade abdominal pain has been reported in 14%-23% of patients (16, 71). Among heavily pre-treated patients with CML-CP on ponatinib, all-grade abdominal pain was reported in 27% of patients (72).

Laboratory Abnormalities. Abnormalities in metabolic parameters have also been reported with all BCR-ABL1 TKIs. The incidence of grade 3/4 elevated glucose was 12.2% with second-line nilotinib and 5.8% with first-line nilotinib (both doses) (10, 69). A study of the effect of nilotinib in patients with type-2 diabetes at entry to ENESTnd showed minimal changes in glucose parameters, body weight, and glycated hemoglobin in any arm at 12 months' follow-up (73). In a single-center study of patients treated with nilotinib (first and second lines), nilotinib-induced hyperglycemia was manageable and likely related to increased body mass index (74). In the package insert, both elevated glucose (58%) and decreased glucose (24%) are reported with ponatinib among patients with CML or acute lymphoblastic leukemia that is TKI resistant (7). The long-term consequences of glucose metabolism and implications for the increase of cardiovascular complications by these drugs remain unclear.

Grade 3/4 hypophosphatemia occurred more frequently in the first-line setting with imatinib than with dasatinib (24% *vs*. 7%; 2-year minimum follow-up in DASISION) or with imatinib than with bosutinib (20% *vs* 6%; 2-year minimum follow-up in the BELA study) (11, 12). In the second-line setting, grade 3/4 hypophosphatemia was reported in 17% of patients on second-line nilotinib with 2 years' minimum follow-up in Study 2101 (69) and in 9% of patients on second-line bosutinib with 2 years' minimum follow-up in Study 200 (16). In addition, chronic hypophosphatemia during TKI therapy may lead to disorders of bone mineralization, as observed in some patients with long-term imatinib treatment (75, 76).

Grade 3/4 elevated lipase has been reported in clinical studies with nilotinib (10, 69), bosutinib (38, 68), and ponatinib (7); however, the implications are unclear due to low incidence of pancreatitis observed with nilotinib and bosutinib (10, 12, 59, 77). With 3 years' minimum follow-up in ENESTnd, 1.8% of patients on nilotinib 300 mg twice daily had any-grade pancreatitis (10). In a study of 37 patients with CML receiving second-line nilotinib following imatinib intolerance or resistance, no pancreatitis was reported after 26 months' median follow-up (77). No pancreatitis was reported with bosutinib after 2 years' minimum follow-up in BELA (12). In PACE (18 months' minimum follow-up), pancreatitis was the most common drug-related serious AE on ponatinib, occurring in 5% of patients (59); however, it generally occurred early and was manageable with dose modification, resulting in 1 discontinuation (59).

The nilotinib prescribing information recommends monthly monitoring of serum lipase levels (or as clinically indicated) and withholding therapy and adjusting dosage in cases of grade 3/4 elevated lipase or amylase (5). Nilotinib may be resumed at 400 mg once daily if serum lipase or amylase returns to grade ≤1 (5). The ponatinib label recommends checking serum lipase levels every 2 weeks for the first 2 months of therapy, with ongoing monthly checks thereafter or as clinically indicated (7). In particular, more frequent monitoring may be warranted in patients with a history of alcohol abuse or pancreatitis, which is another example of how the responsibilities of oncologists and primary-care physicians may overlap. Increased serum lipase may be managed with dose reduction or interruption of ponatinib (7). If lipase elevation occurs with abdominal symptoms on nilotinib or ponatinib, treatment should be interrupted and patients should undergo evaluation for pancreatitis (5, 7). Ponatinib should not be re-started until patients have a resolution of symptoms and lipase levels return to grade ≤1 (7).

Liver enzyme elevation is also observed with BCR-ABL1 TKIs and may be a class effect, although the mechanism remains to be elucidated (78). Grade 3/4 elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported with bosutinib in the phase 3 BELA trial (12% AST and 23% ALT; minimum follow-up, 2 years) (12) and among ponatinib-treated patients with CML-CP in PACE (2% AST and 3% ALT; median follow-up, 15 months) (72) and with nilotinib 300 mg twice daily in ENESTnd (4% ALT and 1% AST; minimum follow-up, 3 years) (10). Ponatinib carries a black box warning for hepatotoxicity following 3 cases of fatal liver failure in PACE; the prescribing information recommends monitoring of liver function at baseline and then monthly or as clinically indicated thereafter, with dose reductions or discontinuation based on clinical need (7).

Evolving Role of the Community of Oncologists in Treating CML

As the patient population ages, age-related comorbidities such as hypertension, diabetes, or hypercholesterolemia are more likely to occur; however, management of comorbidities should not be over-shadowed by the treatment of the cancer, and *vice versa*. The NCCN guidelines for CML recommend that treatment response be monitored at 3-month intervals (9); thus, patients with CML typically see their oncologist more often than their primary care physician. Given comorbidities and the need to monitor CML treatment response and treatment-related AEs, community oncologists in practice should monitor cardiac health, liver function, blood glucose levels, serum lipids, pancreatic enzymes, and electrolyte levels and manage any irregularities. To facilitate this, community oncologists may find it beneficial to establish partnerships with their patients' primary-care physicians and specialists to coordinate care to ensure that treatment plans for comorbid conditions do not interfere with CML management.

Discussion and Conclusion

The success of BCR-ABL1 TKIs in the treatment of CML has changed the natural history of the disease, allowing patients with CML to be treated with oral therapy. Long-term follow-up data on the newer TKIs suggest that these TKIs may be a better option than imatinib in certain cases, although further investigation will determine the comparative effect of TKIs on OS. Investigations of TKI discontinuation in patients with prolonged deep response to TKI therapy are also ongoing in clinical trials of treatment-free remission (22-25).

The efficacy of TKIs, coupled with our ability to manage most AEs, has allowed patients to stay on therapy for longer periods and benefit more from improved outcomes. Many AEs associated with TKI therapy can be managed by careful monitoring and by withholding treatment or adjusting doses, as necessary. In some cases, permanent discontinuation of TKI therapy may be necessary. Given the TKI options available, patients can often continue with another TKI that may be more tolerable. Late onset of certain adverse effects underscores the need for community oncologists to remain vigilant throughout treatment.

Consequently, community oncologists who treat patients with CML must help ensure that patients remain adherent to TKI therapy by improving adverse effect management and focusing on quality-of-life issues. Oncologists will benefit from working closely with primary care physicians to ensure that BCR-ABL1 TKI–related AEs are adequately managed, while also taking on greater responsibility for the management of comorbid chronic conditions that may be affected by TKI therapy.

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Conflicts of Interest

Javier Pinilla-Ibarz is a consultant for Ariad Pharmaceuticals, Bristol-Myers Squibb, Novartis Pharmaceuticals, Pfizer Corporation, and Teva Pharmaceutical Industries, serves on the speaker bureaus of Bristol-Myers Squibb, Pfizer, and Teva, and receives research support from Ariad and Novartis. Kendra Sweet is a consultant for Ariad Pharmaceuticals and Pfizer, serves on the speaker bureaus of Novartis, Ariad, and Pfizer. Josephine Emole and Michael Fradley have nothing to disclose.

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