



Lifelong TKI therapy: how to manage cardiovascular and other risks

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Beginning with imatinib and now spanning 6 oral, highly active, and mostly safe agents, the development of specific targeted therapy for patients with chronic myeloid leukemia (CML) has created a new world featuring chronic maintenance chemotherapy for all treated as such, treatment-free remission, and functional cure after prolonged deep remission in a subset. As a result comes a necessary shift in focus from acute to chronic toxicity, increasing attention to patient comorbidities, and critical thinking around specific adverse events such as metabolic, cardiovascular, and cardiopulmonary effects, which vary from agent to agent. This review aims to pull together the state of the art of managing the “C” in CML—a *chronic* myeloproliferative neoplasm treated at present over many years with oral *BCR-ABL*-targeted agents in a population whose overall health can be complex and potentially affected by disease and therapy—and determine how we can better manage a highly treatable and increasingly curable cancer.

LEARNING OBJECTIVES

- Understand the risks of a CML diagnosis and the importance of comorbidity assessment, especially cardiovascular
- Understand the specific risks of CML tyrosine kinase inhibitors (approved and forthcoming) and how to screen for and mitigate adverse events

Introduction

As has been stated often, the treatment of chronic myeloid leukemia (CML) was and remains revolutionized, with lower-risk small-molecule-specific targeted therapy with oral *ABL* tyrosine kinase inhibitors (TKIs) as the overwhelming mainstay approach. Palliative cytoreductive agents (hydroxyurea, busulfan) are rarely used except for initial temporization of blood counts; interferon-based therapy remains active in other myeloproliferative neoplasms but is only used rarely and in special circumstances in which TKI toxicity may be prohibitive (including pregnancy). Through advances in conditioning, graft-versus-host prevention, posttransplant TKI integration, and alternative donor sources, allogeneic stem cell transplant continues to be optimized, yet its use greatly diminished.¹ Allografting was previously viewed as the only “cure” for CML. Presently, patients treated with TKI therapy may avail themselves of the possibility of a “functional cure”—sufficient treatment with TKI therapy into a sustained deep remission followed by carefully observed TKI cessation—treatment-free remission (TFR). Long-term results from the earliest study of TFR demonstrate, importantly, that durable remission without TKI therapy can be sustained for many years, retreatment for failed TFR attempts is effective, and late

events are rare to absent.² The duration of treatment and duration of deep remission remain strong predictors of TFR success,³ while factors such as minimal residual disease stability,⁴ immune factors,⁵ and myeloid mutations beyond *BCR-ABL1* continue to be investigated as to their role.⁶

Increasingly, the number of patients potentially eligible or who have engaged in cessation of TKI therapy (TFR) grows. A number of unmet needs remain for the optimal treatment of CML, ranging from maximizing initial response while minimizing toxicity and progression risk, to safer and more efficient salvage approaches for heavily treated multi-TKI resistant or multi-TKI resistant/intolerant or even multi-TKI intolerant scenarios, to advanced phase or transformed disease; added to this list now is improving the outcomes of TFR—namely, by increasing the fraction of successful cessation. Many, or perhaps most, view the current goal of therapy to be successful treatment cessation subsequent to sustained deep remission—what has been termed as a functional cure. While this path is streamlined and being made possible for a higher fraction of patients, assuming the potential for lifelong TKI therapy remains a pragmatic approach and perhaps the best way to balance the risks and benefits of treatment strategies for those living with CML.

Survival in CML

The long-term follow-up of the pivotal trial in CML, the IRIS (International Randomized Study of Interferon and ST1571) trial, demonstrated the vastly improved outlook for patients treated with TKI therapy compared to the prior standard, interferon-based therapy,⁷ heralding the "TKI era." A comprehensive analysis of outcomes of current CML patients' survival relative to age-matched peers, irrespective of decade of age, concluded no significant difference—leading to the welcome conclusion of a "normal life span" in the TKI era.⁸ While the incidence of CML remains steady—European CML registry data cite an annual incidence rate of 0.7 to 1.0/100 000, a median age at diagnosis of 57 to 60 years, and a male/female ratio of 1.2 to 1.7—the prevalence of CML steadily increases worldwide due to markedly improved survival.⁹ Estimates in the US project increase from a pre-TKI era prevalence of roughly 25 000 individuals living with CML to 200 000 plus such individuals over the next 3 decades. Such remarkable success focuses attention on many fronts, including global disparity, addressed by groups such as the International CML Foundation, regarding education and treatment, and the Max Foundation, regarding patient advocacy and medication access; cost of therapy, given the multiplier effect of patient and patient-years on TKI therapy; and last and perhaps most importantly, increased attention to the quality of life and long-term outcome of CML "survivors."

New frontier: CML survivorship

A natural extension of highly effective therapy, the high fraction of patients ushered into deep and stable remissions, and the promise of a growing potential fraction of patients deemed functionally cured begs the question of "CML survivorship." Distinct from the past in which CML survivors would be a mix of those followed after allografting in the prototypical posttransplant survivorship clinic and a rare long-term responder to interferon-based therapy, the present era calls for the organized care of those successfully treated with TKIs, whether in TFR or not. Organized care of the leukemia itself, of course, remains high priority; for those remaining on TKI therapy, regular blood-based monitoring with highly sensitive quantitative polymerase chain reaction for the *BCR-ABL1* fusion continues indefinitely per current recommendations.¹⁰ For those patients who have undergone successful TFR, guidance regarding optimal initial monitoring continues to be scrutinized; subsequent questions will include the more difficult question of tapering of long-term monitoring after successful TFR.¹¹ Patients with CML thus continue to have long-standing relationships with their CML physicians, and the development of a tailored approach to the "lifelong" TKI algorithm, to tackle the "end" of CML treatment for those in TFR, and to delineate what comes next from the perspective of relevant follow-up and risk management is a next step ripe for development.

CLINICAL CASE

A 55-year-old woman is referred in (via telehealth) for a recent diagnosis of CML. Records indicate lower-risk disease by the Sokal and EUTOS Long Term Survival score, as her white blood cell count is 32 000 with normal hemoglobin and platelets, no circulating blasts, and a modest left-shifted differential with 3% each basophils and eosinophils. She has no splenomegaly,

and bone marrow studies support chronic-phase disease morphologically, with cytogenetics revealing 100% sole Philadelphia chromosome translocation in 20 metaphases and baseline *BCR-ABL* transcripts of the e14a2 variant of p210 fusion measuring 90% on the International Scale. She wishes to hear from you on risks of disease and medication choices and understands that treatment "may not need to be forever."

Risks at presentation with a diagnosis of CML

The diagnosis of CML encompasses a number of signs and symptoms, including fatigue, weight loss, loss of energy, decreased exercise tolerance, low-grade fevers, sweats resulting from hypermetabolism, bone pain, and early satiety resulting from encroachment by an enlarged spleen on the stomach, as well as left upper quadrant fullness and pain. Infarction of the spleen can be observed, especially with marked enlargement. Blood count changes include leukocytosis and variable platelet count elevation or, with advancing-phase disease, reduction; anemia is generally proportional to disease burden. Bleeding, petechiae, and ecchymoses are more likely with advanced disease and thrombocytopenia.

The presentation of CML with marked thrombocytosis (platelets >1 million) may occur, and vascular injury and thrombotic events appear more common in such cases, as well as a female predominance and younger age.¹² In children, thrombosis may be less likely, but as is seen in other myeloproliferative neoplasms, acquired von Willebrand syndrome and mild clinical bleeding may develop due to the binding of von Willebrand factor multimers, especially large multimers, to platelets.¹³ Not surprisingly, a growing number of case reports are emerging identifying the coexistence of myeloproliferative "driver" mutations, such as *JAK2* v617F and calreticulin along with *BCR-ABL* fusion, as deep sequencing becomes more utilized, suggesting that better characterization of myeloid mutations in CML may be of clinical use.

Often isolated to settings where presentation and diagnosis may be delayed, complications related to leukostasis in target organs at risk for vascular injury include priapism and retinopathy. Leukapheresis can be used for clinical signs of injury due to leukostasis and remains a therapeutic "bridging" strategy during CML and pregnancy, when cytoreductive therapy and definitive therapy with TKIs may pose excessive fetal risk.¹⁴

Risks associated with the first-line TKIs imatinib, nilotinib, dasatinib, and bosutinib

The initial treatment of CML increasingly is the direct use of TKI therapy in order to promptly induce hematologic control/complete hematologic response; cytoreduction with hydroxyurea prior to TKI start, if used, may augment the myelosuppression observed with subsequent TKI therapy. Myelosuppression remains a ubiquitous initial effect commensurate with TKI start and is somewhat variable among the available ABL kinase inhibitors; in comparative trials of first-line therapy with imatinib, nilotinib, dasatinib, and bosutinib, dasatinib was associated with the greatest rates of grade 3 or 4 neutropenia and thrombocytopenia. Myelosuppression may be best viewed as a mix of disease and therapy-related effects given its (early) kinetics and propensity to resolve; a subset of patients, often with higher-risk features, may face severe and persistent myelosuppression precluding TKI delivery and response to therapy, posing a specific intolerance and challenge.

Other adverse events common to the entire class of ABL inhibitors used at diagnosis are generally reversible and pose little known long-term risk. Examples of such laboratory findings include transaminase elevation, lipase elevation (more often biochemical and lower with pancreas inflammation or pancreatitis), hyperbilirubinemia (observed more with nilotinib and often unmasking Gilbert's syndrome), and others.¹⁵ Adverse events more closely linked to imatinib include edema (periorbital and peripheral), muscle cramps, musculoskeletal pain, and diarrhea; those more closely linked to nilotinib include rash, pruritus, headache, nasopharyngitis, constipation, abdominal pain, vomiting, pyrexia, upper urinary tract infection, back pain, cough, and asthenia; those more closely related to dasatinib include, as previously mentioned, myelosuppression as well as fluid retention, including pleural and pericardial effusions and headache; and those more closely related to bosutinib include diarrhea and increases in alanine and aspartate aminotransferase. Common, more frequent adverse events across TKIs include fatigue myalgias and gastrointestinal symptoms such as nausea and vomiting. Given a broad investigation into the optimal therapeutic dose, imatinib plasma trough levels were noted to correlate with efficacy and the correction of suboptimal response¹⁶; however, drug levels did not correlate with adverse events. Longer follow-up of imatinib-treated patients in the landmark IRIS trial concluded that adverse events were not typically observed after the first year of therapy.⁷

Particular awareness and preparedness are warranted for adverse events of specific interest (associated with greater morbidity and potential long-term impact) for TKIs used at diagnosis. Imatinib is associated with hypophosphatemia; further investigation demonstrated a potential link to altered bone mineralization.¹⁷ Renal injury, manifesting as a decline of the glomerular filtration rate, was noted with imatinib therapy, with reductions steadily over 4 years' time before plateau and isolated to those with no chronic kidney disease prior¹⁸; in a separate study, nearly identical changes were observed for bosutinib therapy.¹⁹ Interestingly, TKI dose did not correlate with injury and reversibility was apparent. Nilotinib is associated with impaired fasting glucose levels,²⁰ whereas imatinib has been suggested to improve them²¹; this effect with nilotinib is reported to be reversible, to be linked to increased body mass index, and not to trigger type 2 diabetes.²² Lipid profiles may show similar changes, with imatinib improving levels and nilotinib, as early as 3 months into treatment, triggering increases in cholesterol (both low-density and high-density lipoproteins and in turn total cholesterol); any effect of dasatinib appears more modest.²³⁻²⁵

In contrast to imatinib, vascular adverse events have been associated with newer-generation TKIs, most prominently with the later-line therapy agent ponatinib as well as with the second-generation TKIs dasatinib and nilotinib,^{26,27} while minimal association has been observed with bosutinib.²⁸ Long-term follow-up of the ENESTnd trial compared nilotinib at varied doses vs imatinib for newly diagnosed CML. At the 10-year median follow-up, rates were 16.5% for nilotinib at 300mg twice daily and 23.5% for 400mg twice daily vs 3.6% for imatinib, including in Framingham cardiovascular-assessed low-risk patients.²⁹ Mechanisms remain under investigation; postulated causes include endothelial cell effects,³⁰ proinflammatory and pro-oxidative stress factors,³¹ and lipid, coagulation, and platelet effects (some paradoxical),³² among others. Sequencing studies have suggested differential expression patterns in target tissues (such as endothelial cells),³³

and the specter of clonal hematopoiesis has been rightly raised as a potential contributing factor in thrombotic events in CML.³⁴ Of note, the presence and potential impact of other myeloid mutations aside from *BCR-ABL1* fusion on several fronts, including primary response, the ability to achieve successful TFR in otherwise "eligible" cases, and adverse events, especially vascular, are just beginning to be unveiled as broader, deeper sequencing is performed in CML.⁶

Pulmonary complications of TKI therapy are also of specific interest, warranting awareness, early intervention, and consideration of specific surveillance. Most notably, pleural and pericardial fluid accumulation as well as pulmonary arterial hypertension have been observed, most often with dasatinib therapy. Initial analysis suggested that cardiac disease and systemic arterial hypertension were predisposing factors to develop pleural effusions on dasatinib³⁵; a larger meta-analysis with longer follow-up suggested, in multivariate analysis, that age was an independent predictor.³⁶ Distinct from many other effects associated with TKIs, the risk of developing pleural effusions may be spread over many years' time or the entirety of treatment; a 7-year follow-up of second-line dasatinib noted a cumulative incidence of 28% to 35% (depending on TKI dose) and a 5% incidence of new events in year 7.³⁷ The DASISION study of frontline dasatinib noted a steady 8% per year incidence and a cumulative incidence of 38% at 5 years and also cited age as a predictor.³⁸ Both dose and schedule influenced the likelihood of pleural effusions in second-line studies, contributing to the change to optimized once-daily reduced dosing of dasatinib in CML. Continued inquiry into optimizing the risk/benefit balance with dasatinib is evidenced by a compelling single-center, single-arm study of 50mg dosing for newly diagnosed chronic-phase CML in which pleural effusions were observed in only 6% of patients after a median follow-up of 24 months.³⁹

Specific management recommendations in the case of dasatinib pleural effusions have been developed⁴⁰; however, the exact mechanisms of action and the best mitigation strategy remain elusive. Given its profile beyond ABL kinase inhibition, as an inhibitor of the SRC family of kinases and lymphocyte-specific protein kinase, a related phenomenon observed with dasatinib therapy includes peripheral blood lymphocytosis,⁴¹ with a large granular lymphocyte morphology that is directly correlative to dasatinib dosing.⁴² While potentially associated with other inflammatory phenomena, including colitis and follicular hyperplasia/lymph node enlargement,⁴³ peripheral blood lymphocytosis is observed in approximately one-third of treated patients and is associated with higher response rates, longer response durations, and increased overall survival, supporting a potential immunomodulatory role.⁴⁴ Additionally, pulmonary arterial hypertension has been observed, thankfully rarely (<1%).⁴⁵ It is most often associated with dasatinib (and occurs less often but has been noted with bosutinib and ponatinib) yet confounded by how infrequently right heart catheterization is performed to investigate symptoms properly. Carefully vetted cases (diagnosed with right heart catheterization) warranted TKI discontinuation, and while the majority were reversible, approximately one-third of cases demonstrated persistence,⁴⁶ validating the need for closer attention to this TKI risk.

Risks associated with ponatinib

Considered independently given its more distinct risk profile, ponatinib offers an excellent ability to salvage poor response in

chronic-phase CML, shows efficacy in the face of select resistance (ABL kinase domain mutation threonine for isoleucine at position 315-T315I), and has a probably often misunderstood adverse event profile. Ponatinib experience in a phase 1 study noted prominent adverse effects, including rash and acneiform dermatitis, arthralgias/fatigue, and a clear risk of pancreas inflammation greater than other TKIs with lipase elevation, hypertriglyceridemia, and pancreatitis at equally elevated rates⁴⁷; a signal of vascular toxicity had not yet emerged. Commensurate with publication of the PACE trial in late 2013,⁴⁸ the US Food and Drug Administration (FDA) requested and the manufacturer (at that time, Ariad Pharmaceuticals) agreed to suspend the marketing of ponatinib. Data from PACE showed "significant antileukemic activity across categories of disease stage and mutation status" but reported that serious arterial thrombotic events (including cerebrovascular, cardiovascular, and peripheral vascular events) were rising, initially numbering 8.9% (2.9% treatment related) during the study and then going up to 11.8%. The incidence of all arterial thrombotic events, serious or not, was 17.1%. While the rate was not increasing over time, the accumulation with additional follow-up (>24 mo) led to the marketing suspension and halting of ponatinib frontline studies. As mentioned relative to the second-generation TKIs nilotinib and bosutinib, the mechanisms and basis for such events remain unclear, with several hypotheses. A focus on ponatinib in particular is ongoing and includes such concepts as a thrombotic thrombocytopenic purpura-like microangiopathic mechanism.⁴⁹

Based on additional data from the phase 1 study and the aforementioned emerging data, the label for ponatinib then included a vascular adverse event (arterial and venous) rate of 27% and a fairly narrow indication (*T315I* mutation-bearing patients and those in whom "no other TKI is indicated"), and a risk evaluation and mitigation strategy was requested. In contrast, ponatinib retained European Medicines Agency marketing authorization as well as its indication for patients carrying the *T315I* mutation and those resistant or intolerant to dasatinib or nilotinib and for whom imatinib was not clinically appropriate and concluded a somewhat lower vascular event rate. Data and further guidance for the optimal use of ponatinib have continued to evolve; as such the 2020 updated guidelines issued by the European LeukemiaNet recommend ponatinib in patients with resistance to a second-generation TKI (dasatinib, nilotinib, and bosutinib), even without specific mutations, unless its use is precluded by the presence of cardiovascular risk factors.⁵⁰ Very recent data from the dose-finding OPTIC study,⁵¹ enrolling patients with CML resistant/intolerant to ≥ 2 TKIs or carrying the *T315I* mutation to receive 45, 30, or 15mg initially followed by 15mg maintenance upon achieving $\leq 1\%$ BCR-ABL levels, suggest an optimal benefit/risk profile for the 45mg starting dose.

What lies at the heart of the matter—no pun intended—regarding the true risk of vascular adverse events is perhaps how they are quantified and attributed. A recent study deployed an independent end point adjudication committee (EAC) including cardiology, hematology, and neurology input to reexamine the vascular adverse events from the PACE study of ponatinib. It noted that while AOE identified by the *Medical Dictionary for Regulatory Activities* preferred terms numbered 25%, the blinded EAC, using American College of Cardiology/American Heart Association definitions, noted 17%.⁵² Serious AOE by the *Medical Dictionary for Regulatory Activities* terms numbered

20%, while the EAC verified 16%. With these data and a supplemental new drug application, the FDA approved an updated indication for ponatinib in the US—namely, patients with resistance or intolerance to at least 2 prior kinase inhibitors.

On the horizon: asciminib

Asciminib is a novel ABL kinase inhibitor, a so-called STAMP (specifically targeting the ABL myristoyl pocket) inhibitor. Functioning as an allosteric inhibitor of the deregulated BCR-ABL kinase by targeting the myristoyl pocket in contrast to the active site (adenosine triphosphate-binding) mechanism of all other licensed ABL kinase inhibitors, asciminib holds the promise of distinct single-agent activity in Philadelphia-positive leukemias as well as the potential for rational combination therapy (adenosine triphosphate-binding + myristoyl-binding ABL inhibitor therapy). Initial phase 1 study reports in mainly chronic-phase patients with multi-TKI resistance/intolerance indicated convincing efficacy and minimal resistance via novel mutations.⁵³ A subsequent randomized study of asciminib in comparison to bosutinib for chronic-phase CML patients with 2 prior therapies and no resistance mutations to bosutinib or *T315I* mutation confirmed asciminib's superiority regarding major molecular response at 6 months, the primary end point of the study, as well as other end points, including complete cytogenetic response.⁵⁴ Given its novelty as a STAMP inhibitor, its potency and specificity for the myristoyl pocket of *ABL1*, and its broad inactivity against other kinases, including SRC kinase,⁵⁵ the toxicity profile of asciminib to date has also been promising. The phase 1 study limiting toxicity was limited to lipase elevation with a single case of pancreatitis, arthralgia/myalgia, abdominal pain, and bronchospasm and a single case of acute coronary syndrome; lipase elevation/pancreatitis remains a class effect prominent with nilotinib and ponatinib and now associated with asciminib. In the phase 3 ASCSEMBL study comparing asciminib to bosutinib, markedly lower-gastrointestinal adverse events were observed with asciminib compared to bosutinib, as one might expect; however, as with all TKIs, closer attention is often paid to vascular adverse events, and 2 deaths occurred in the asciminib arm falling into this category (ischemic stroke and arterial embolism per the report). Dissecting out any association and risk will take more time, and recognition of the heavily pretreated nature of the patient population in the ASCSEMBL trial is warranted. At the present time, asciminib appears to have a narrow spectrum of toxicity, and no conclusive evidence of a vascular/cardiovascular signal exists as of yet, notably after a very long-lasting (>7 years) phase 1 study. It offers great promise in resistant/intolerant patients, will inspire ongoing exploration into combination approaches, and represents a significant advancement in the field.

CLINICAL CASE (Continued)

After thorough discussion about risk stratification and the relative merits and risks of available TKI therapies specific to her case, you find yourself noting the safety and likely success of imatinib-based therapy contrasted with the potential for improved early and deep response with any of the second-generation TKI options and presenting either option as reasonable.

You proceed to take a more detailed background medical history and find her to be free of any active cardiovascular or metabolic disorders such as heart disease, hypertension, diabetes, renal disease, hyperlipidemia, or other chronic conditions. Her weight is near ideal, and she does not smoke; however, she cannot offer a family history as she was adopted as an infant. When asked about recent screening for the above conditions, she cannot recall her last primary care appointment as she is "very healthy and has not needed to go to the doctor, especially during the pandemic" and has never seen a cardiologist or had any cardiovascular studies.

Assessing comorbidity in the CML patient population

Simply stated, to manage the cardiovascular and other risks in patients with CML, one must embrace the "whole patient"—the full health history, active and quiescent comorbid conditions, vulnerabilities as best one can judge—placing general medical considerations in clear focus in anticipation of leukemia care. The average age at CML diagnosis varies widely across the globe,⁵⁶ ranging from medians in the 40s in Asia and Africa, to the 60s in North America, and to >70 in the Oceanic region (Australia, etc). The local/regional specifics of potential clinical challenges vary and may not be well characterized—eg, in a large tertiary referral center in Soweto, Johannesburg, South Africa, 7% of all CML patients carry a diagnosis of both HIV and CML.⁵⁷ Access to therapy is not equitable globally; organizations such as the nonprofit MAX Foundation (www.themaxfoundation.org) have partnered with key sponsors to facilitate low- or no-cost TKI therapy for CML and other diseases, accounting for >10 million doses of therapy over a recent span of 3 years. Underserved regions may have limited access to providers and risk assessment, adding to the challenge.

In more economically favorable settings, data suggest that comorbidities are common in patients with CML and may influence treatment choice and outcome. A large US series of >2000 CML patients and data from the EUTOS (European Treatment and Outcome Study for CML) study with nearly 3000 cases found that comorbidities were present in >50% of CML cases, and cardiovascular-related comorbidities such as hypertension and diabetes were present in approximately 40% of cases.^{58,59} The large observational SIMPLICITY study reported that the primary basis for TKI choice (US/EU data set) was for "perceived efficacy" in >50%, while only approximately 9% primarily regarded comorbidities.⁶⁰ Widely used treatment guidelines such as the European LeukemiaNet have begun to incorporate a broader consideration of comorbidities into the initial screening (inclusion of lipid profile, diabetes screening, etc) and comment on patient selection based on comorbid risks and adverse event profiles of the various TKIs.⁵⁰ The US National Comprehensive Cancer Network,¹⁰ while clearly stating TKI toxicities and management, has yet to significantly incorporate comorbidity assessment or related risk stratification.

Several studies have clearly driven home the centrality of comorbidities in CML outcomes. The Charlson Comorbidity Index, which incorporates age along with key conditions—including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, cancer (blood and solid

tumor), and AIDS—was examined in the setting of imatinib-based therapy in the German CML IV study and in the broader setting of imatinib, nilotinib, and dasatinib.^{61,62} Both studies found that the Charlson Comorbidity Index was consistently the strongest predictor of survival in CML, including age-independent analysis, and in fact did not affect TKI treatment success, leading to the conclusion that survival of patients with CML is determined more by comorbidities than by CML itself.

The who, what, and when of risk assessment and mitigation for the patient with CML

One of my most memorable quotes from medical school, from a cherished leukemia attending, was simple and powerful: "You can't be a good hematologist/oncologist unless you are a good internist first." A leukemia diagnosis, even one with such hope, multiplicity of effective options, and guidance based on response milestones as CML has, often leaves other health issues and follow-up in a blur as leukemia care comes into focus. Leukemia care engulfs the present, with frequent blood work and checkups; given the intensity and nuances of care, others feel it best to step aside and stay at a distance for fear of negatively affecting cancer treatment success. Rather than a point of separation, in CML, the time of diagnosis and thereafter need to be the opposite—a point of alliance between leukemia specialists, primary care/internal medicine, and others as needed, particularly in cardiovascular medicine. Continued follow-up with primary care/internal medicine is essential for patients with CML. With high rates of remission and data supporting a normal life expectancy, *everything stays on the table*. Age-appropriate "other" cancer screenings should proceed, as well as management of the frequently observed and potentially exacerbated comorbidities of hyperglycemia/diabetes, hyperlipidemia, and hypertension and first and foremost, screening for and management of cardiovascular disease. Open dialogue, division of labor, and free communication regarding treatment plans and interventions must be established early after diagnosis to prevent missed opportunity. Seemingly minor things, such as prescription of acid suppression medication such as proton pump inhibitors, may severely impair TKI exposure and response.⁶³

The subspecialty field of "cardio-oncology"—cardiologists who focus on cancer disease and therapy complications—has been a boon to hematology/oncology providers managing CML as the trifecta of (1) remarkably longer survival/normal life span expectations with the development of TKIs, (2) the breadth of TKI choices, including more potent *BCR-ABL1* inhibitors, and, unfortunately, (3) the recognition that vascular/cardiovascular AEs may be among the most impactful risks hindering the overall success of CML therapy. Having cardiology present as part of the CML education session at the 2017 American Society of Hematology meeting demonstrated the need for closer alliance, collaboration, and comanagement.⁶⁴ Provisional guidelines have been published in reviews over the last several years focused on managing cardiovascular adverse events in CML,⁶⁵⁻⁶⁷ focused specifically on ponatinib and nilotinib,⁶⁸⁻⁷⁰ as well as position papers suggesting CML clinical trial adverse event reporting should align with cardiovascular medicine definitions.⁷¹

So, who? Practically speaking, inventory of comorbid conditions and vetting of necessary interventions, and specific inventory of cardiovascular risk, is prudent for *all patients*. How? Several validated tools are readily available to assess cardiovascular risk and subsequent event (for example, 10 year) risk,

including the Framingham “hard” (nondiabetic, no prior claudication/coronary heart disease) risk score stemming from the long-running Framingham heart study.^{72,73} The European Society of Cardiology developed and validated the SCORE (Systematic Coronary Risk Evaluation) Risk Charts for use as a cardiovascular disease risk assessment model for patients in Europe. It is divided into higher- and lower-risk countries and can be calibrated for specific countries’ mortality data.⁷⁴ The SCORE charts were examined in the setting of nilotinib therapy by several CML groups, including France and Italy,^{75,76} demonstrating that baseline assessment via SCORE could be a valid tool to identify patients at high risk of atherosclerotic events during nilotinib treatment. Long-term data emerging from the ENESTnd study of frontline nilotinib, using Framingham risk assessment, cautioned that in addition to higher cumulative rates of cardiovascular events reported with nilotinib (300mg twice daily, 16.5%; 400mg twice daily, 23.5%) vs imatinib (3.6%), said events were possible in Framingham low-risk patients.²⁹ Other region-specific risk assessment tools can and should be incorporated into practice with CML patients; in the United Kingdom, the QRISK score also calculates the 10-year risk of cardiovascular or cerebrovascular events specific to the UK population and incorporates postal codes in addition to an increasing number of clinical predictors.⁷⁷

The “when” of cardiovascular risk assessment—frequency or periodicity of key interventions at a general level at least and ideally patient or patient/TKI risk level—and likely the more precise details of which diagnostic tools, potential biomarkers, etc, are most informative continue to be investigated. A unique prospective study in the US of cardiovascular and metabolic parameters at diagnosis of CML and subsequently through treatment, agnostic to TKI choice, has reported high rates of baseline risk and continues to gather data on changes with time on treatment.⁷⁸ At present, the use of provisional cardio-oncology-derived guidelines and leukemia consortium-based guidelines,^{64,79,80,81} driven by patient comorbidity and TKI choice, adds simple and lower cost empiric monitoring based on known risks and the best-available diagnostics/predictors of preexisting or accelerating vascular disease. At the most basic level, broad use of a simple ABCDE approach—(a)wareness, (a)nkle-brachial index testing, (a)spirin therapy, (b)lood pressure control, (c)igarette cessation, and (c)holesterol lowering—will raise awareness and at a minimum facilitate standard of care intervention for comorbid findings in CML patients.

CLINICAL CASE (Continued)

While finalizing the last hematologic assessments and confirming her genetic results and pathology, you offer the patient a consultation in your center’s primary care clinic, which she eagerly pursues as she is worried about her general health given the CML diagnosis. The result of your TKI choice discussion led you to recommend a second-generation TKI, and in discussion with the primary care team, a screening evaluation with the center’s cardiology group is scheduled. She undergoes basic metabolic and functional imaging and is found to have a low risk of events in the next 10 years. Cardiovascular monitoring is prescribed by the cardiologist to continue in the

primary care and hematology clinics with basic blood pressure and metabolic disease screening, with a return to cardiology if symptoms or evidence of vascular disease develops.

Cardiovascular risk management and prevention: too much, too little?

It is inarguable that intervention for comorbidities, such as aspirin or lipid-lowering therapy as primary or secondary prevention in patients with identified indications based on cardiovascular guidelines, is essential. Intervention based on risk of complications during TKI therapy, based solely on the TKI risk, is much less clear of a benefit/risk and ideally should be studied in controlled trials. Given the size needed for such trials done in the non-CML setting, firm evidence-based data for preemptive intervention may be elusive. Smaller directed studies have looked at preventative interventions; an Italian study examining ponatinib-treated patients (n=85), stratified based on the European Society of Cardiology SCORE charts as was done for nilotinib, included a primary prevention strategy using 100mg of aspirin daily in a subset (n=19); no significant differences were noted, but trends toward decreased AOE and improved survival were reported.⁸² Drug-drug interactions and other adverse event risks from adding preventative therapy are not to be overlooked. While we may feel compelled to intervene with prevention for all patients treated with higher-risk TKIs, risk stratification may help justify intervention in larger numbers of cases, but an “only where indicated” approach may be more prudent.

Is TKI therapy lifelong, and could better therapy help mitigate risk?

We are at a crossroads in the treatment of CML, having first revolutionized the principal approach with the development of TKIs and now moving away from a “transplant when possible” approach and expectations of diminished survival in others to a paradigm of “transplant only when absolutely needed” and near-normal or normal life expectancy for most. Targeted therapy in CML has fostered a new modus operandi of *chronic maintenance chemotherapy*—new in cancer for the most part—thus raising reasonable fears of morbidity from continual, potentially lifelong chemotherapy. Twenty years after imatinib’s record-breaking fast approval by the FDA, we take solace in the relative safety of TKIs, led by imatinib, followed by more hesitant confidence in the long-term safety of our more potent and subsequently developed agents. The advent of TFR as an option for CML has brought the next crossroad: Can we make CML therapy as limited as possible, and functionally cure the cancer, in more/many/all patients?

TFR studies have expanded greatly, and data from trials performed after primary or secondary treatment with second-generation TKIs are available. Trials with nilotinib and dasatinib as second-line therapy after imatinib resistance or intolerance, or as a means to optimize deep remission, have proven that TFR is both feasible and similarly successful to a more uncomplicated TFR after primary imatinib or second-generation TKIs.^{83,84} While overall rates of TFR success may not be higher in studies with second-generation TKIs used as frontline therapy,^{84,85} the rapidity of deep remission may afford more rapid eligibility to

consider TFR and thus reduce treatment duration/exposure and the potential likelihood of toxicities. If TFR were more pervasive and successful and achievable on a more global level, this would change the perspective on toxicity for certain as short-term and lifelong risk are strikingly different. The next steps in long-term toxicity assessment should incorporate critical thinking into the relative benefits of more potent therapies and strategies coupled with the benefits of limiting duration of treatment for patients with CML.

CLINICAL CASE (Continued)

Your patient proceeded to therapy with a second-generation TKI and achieved rapid and deep response. Major molecular response occurred within 6 months, and deep remission (>MR 4, <0.01% IS *BCR-ABL*) was present from 9 months through a total 3 years of treatment. She continued with her new primary physician and did not develop any major complications. She was delighted with her response and eager to pursue TFR shortly after her 3 years in remission and 2 ¼ years in deep molecular remission. She remains off treatment in successful TFR and is eternally grateful for you managing her CML so well and ensuring she had excellent primary care and an introduction to cardiology care.

Key points

- At diagnosis/initial presentation of CML, appraisal of the patient's full comorbidity profile is vitally important and affects survival more than the CML.
- CML risk stratification (Sokal, EUTOS Long Term Survival, etc) affects TKI response and the success of potential TFR outcome and may assist with TKI choice.
- Cardiovascular risk assessment (Framingham, SCORE, others) at diagnosis can also assist with TKI choice and can clarify the need and merits of any preventative interventions.
- TKI choice dictates general (class) and drug-specific baseline and longitudinal monitoring for adverse events; TKIs with more significant cardiovascular risk warrant regular cardiovascular monitoring.
- Partnership and coordination with primary care/general internal medicine and subspecialty medicine, especially cardiology/cardio-oncology, serves CML patients best to identify and manage adverse events and continue age-appropriate health and other cancer screenings.
- TFR as a goal of therapy, by limiting TKI duration, may significantly modify TKI therapy risk, but lifelong therapy remains a necessary paradigm and mindset in managing the increasing number of patients surviving CML.

Conflict-of-interest disclosure

Michael J. Mauro: research funding: Novartis, Bristol Myers Squibb, Sun Pharma/Spac, Takeda; consultancy: Novartis, Bristol Myers Squibb, Takeda, Pfizer.

Off-label drug use

Michael J. Mauro: nothing to disclose.

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DOI 10.1182/hematology.2021000239