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Review Article

How to manage CML patients with comorbidities

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Patients with chronic myeloid leukemia (CML) often have comorbidities, at an incidence that might be higher than in the general population. Because of the favorable outcome of most patients with CML treated with tyrosine kinase inhibitors (TKIs), a greater number of comorbidities might be the most significant adverse feature for long-term survival. The presence of comorbidities may also affect the risk of developing adverse events with TKIs. This effect is perhaps best exemplified by the risk of developing arterio-occlusive events, which is greatest for patients who have other risk factors for such events, with the risk increasing with higher numbers of comorbidities. The coexistence of comorbidities in patients with CML not only may affect TKI selection but also demands close monitoring of the overall health condition of the patient to optimize safety and provide the opportunity for an optimal outcome to such patients. With optimal, holistic management of leukemia and all other conditions afflicting them, patients with CML and comorbidities may aim for a near-normal life expectancy, just as the more select patients enrolled in clinical trials now enjoy. (*Blood*. 2020;136(22):2507-2512)

The clinical benefits of treatment with tyrosine kinase inhibitors (TKIs) for patients with chronic myeloid leukemia (CML) are unquestionable. The ability for some patients to achieve deep molecular responses, to prevent transformation, to return to near-normal life expectancy, and more recently to discontinue therapy successfully are well documented. There are currently 5 TKIs approved for CML, although approval and availability vary widely worldwide. TKIs are generally considered safe, albeit with some variability in their association with the most commonly observed adverse events (AEs). Still, most patients experience some AEs, most frequently mild and often transient, but serious AEs may occasionally be observed.

Our understanding of the general benefit of TKIs comes largely from clinical trials. A common feature of clinical trials is the patient selection, with multiple inclusion and exclusion criteria. This is done for safety purposes, particularly important in the early stages of the development of a drug. But exclusions can often be extensive. For example, the clinical trials for frontline therapy with dasatinib (DASISION)[1] or nilotinib (ENESTnd)[2] compared with imatinib had 18 and 21 exclusion criteria, respectively (some of them listing several subcategories within 1 main category). Because they are excluded from clinical trials, information about how to manage patients with some comorbidities or recent events (eg, cardiovascular or cancer), or whose who are receiving many of the concomitant medications used to manage such conditions, is scant and available only from small series or anecdotal reports.

Patients with CML often have comorbidities, many of which have made them ineligible for clinical trials. One report of patients with CML showed that, at baseline, cardiovascular risk factors included obesity and hypertension in ~30% of patients, diabetes in 11%, and dyslipidemias in 18%. This finding led to a Framingham score of 12.8% (compared with 8.7% average for the US population), and 17% had a history of coronary heart disease.[3] Others have reported similar data,[4,5] with the incidence of comorbidities and number of concomitant medications increasing with age.[6] For example, hypertension was reported for 62% of patients age >75 years. Comorbidities not only increase the risk of developing AEs such as arterio-occlusive events (AOEs)[7] but are now the main cause of death for patients with CML treated with TKIs.[8] In a study of 1,519 patients participating in CML Study IV, 40% had comorbidities, with 61% having a Charlson Comorbidity Index (CCI) of ≥3 (22% had a score of ≥5). The 8-year survival for patients with a CCI ≥5 was 48%, compared with 91% for those with a CCI of 2.[8] Thus, the presence of comorbidities is an important element of the management of patients with CML.

The patient

Our patient is a 59-year-old construction worker with an 8.5 pack-year smoking history, obesity, and hypertension treated with lisinopril but still poorly controlled. He has been found to have hyperglycemia on several visits to his primary doctor but has never been told he has diabetes or started on specific therapy. His total cholesterol level is 232 mg/dL (5.99 mmol/L). He is now diagnosed with chronic phase CML with a high Sokal risk score. This is not an uncommon scenario, a patient with various comorbidities, often undiagnosed, uncontrolled, or unmanaged. First, we need to discuss thoroughly with the patient the diagnosis, the treatment options, the goals of therapy, and the risks and benefits of each treatment option.

Cardiovascular risk and comorbidities

There are 2 elements to treating a patient with several comorbidities: Deciding what the best TKI option is (Table 1) and managing

Table 1. Suggestions for TKI selection for frontline therapy based on selected comorbidities

Comorbidity	Preferred	Less preferred
Diabetes	Imatinib, dasatinib, bosutinib	Nilotinib
Pulmonary disease/pulmonary arterial hypertension	Imatinib, bosutinib, nilotinib	Dasatinib
Gastrointestinal issues	Nilotinib, dasatinib	Imatinib, bosutinib
Cardiovascular	Imatinib, bosutinib	Nilotinib, dasatinib
Peripheral arterial	Imatinib, bosutinib (dasatinib?)	Nilotinib
Liver	Imatinib, dasatinib (nilotinib?)	Bosutinib
Renal	Nilotinib, dasatinib	Imatinib, bosutinib

the comorbidities. Perhaps the greatest risk for this patient is the development of AOEs. Since the first reports of AOEs with ponatinib, it has become evident that this is a risk shared by most TKIs, although at different levels of risk. It is difficult to precisely quantitate the AOE risk with each TKI because the available descriptions from different TKIs report AOEs in various forms, some with a precise inclusion of only specific events, and others with a wider search for various Medical Dictionary for Regulatory Activities (MedDRA) terms that could possibly reflect an AOE. The latter approach documents more events but may include false positives. There is no direct comparison between the second-generation tyrosine kinase inhibitors (2GTKIs), but the randomized trials of dasatinib, nilotinib, and bosutinib versus imatinib allow us to analyze the relative incidence using imatinib as a "control." The risk of cardiovascular events is significantly higher with 2GTKIs (at least dasatinib and nilotinib) than with imatinib, with a 5-year risk of cardiovascular ischemic events 2 times higher with dasatinib and nilotinib (both reporting 4%) than with imatinib (2% in both studies)[9,10] (Table 2). One analysis that adjusted for the variability in reporting by using the same method to identify these events in separate trials with various TKIs suggests a similar trend (risk 1.5–2 times higher with nilotinib or dasatinib than with imatinib),[7] and a meta-analysis of published literature also suggests a higher risk with all TKIs than with imatinib (statistically significant for all except bosutinib, albeit with smaller sample size and shorter follow-up).[11] In the Swedish registry the incidence of myocardial infarction for patients treated with nilotinib or dasatinib is 3.6 and 2.4 times higher than for those treated with imatinib.[12] Thus, imatinib seems to confer the lowest risk, although patients with CML overall have a risk of arterial or vascular events 1.7 times higher than in the general population.[12] Patients with high-risk features for AOEs could be treated preferentially with imatinib. However, this suggestion should be weighted with the patient's risk and goals. Patients with higher Sokal risk scores have a poor response to imatinib, and patients interested in eventually considering treatment discontinuation have a higher probability of achieving that goal with a 2GTKI. In this case, a 2GTKI, possibly bosutinib, might be preferable.

It is important to underscore the role comorbidities play in the risk of AOEs. With ponatinib, the risk of developing AOEs was 27% for patients with history of hypertension (53% of all patients) and 12% for those without hypertension (ie, relative risk 2.1 for patients with hypertension). Similarly, patients with history of heart disease, diabetes, hypercholesterolemia, or obesity had a higher risk of developing such events.[13] The more risk factors a patient has, the greater the risk.[7,13] Among patients receiving frontline therapy with a TKI, patients with 1 risk factor had an incidence rate ratio for AOEs of 1.7 compared with those without known risk factors. This ratio increased to 2.31 with 2 risk factors and to 3.08 with ≥3.[7] In ENESTnd, the risk of developing any AOE correlated strongly with the Framingham risk category, with AOEs reported in 1.7%, 12.2%, and 17.5% of patients treated with nilotinib in the low-, intermediate-, and high-risk Framingham categories.[10] The Systematic Coronary Risk Evaluation was predictive of the risk of AOEs for patients treated with ponatinib.[14] Therefore, in a patient like ours it is important to aggressively control all risk factors. This includes properly managing underlying conditions such as hypertension and making the lifestyle changes necessary to decrease risk (eg, stop smoking, lose weight, exercise). Aspirin is sometimes recommended in this setting, but its benefit has not been studied prospectively, and it could be questioned considering that ponatinib,[15] like dasatinib,[16] may inhibit platelet aggregation. An intriguing mechanism by which ponatinib may contribute to these events is through vascular toxicity mediated by von Willebrand factor–mediated platelet adhesion. This effect would not be expected to respond to antiplatelet therapies, but it opens the even more intriguing prospect of interventions such as use of N-acetyl cysteine to help ameliorate this effect (as it did in preclinical models).[17] This prospect remains hypothetical and awaits clinical testing. Guidelines have been proposed for the management of these cases.[18,19] However, these guidelines are often unbalanced in their recommendations with assessments such as blood pressure checks, fasting glucose, and lipid levels recommended for patients on nilotinib but not those on ponatinib.[19] These should be standard assessments for all patients based on the aforementioned similar risk of AOEs and certainly for all patients at higher risk, such as our patient. The ABCDE approach,[20] recommended for the general population, can be considered for patients receiving TKIs, particularly those with comorbidities, and those with the highest-risk disease (eg, by Sokal) for whom control of the disease is better served by a 2GTKI despite the higher risk of AOEs. (Table 3).

Glucose and lipids

Other considerations also play a role in the treatment selections for our patient. The patient has hyperglycemia and hypercholesterolemia. These are risk features for AOEs, and TKIs may have an effect on them. Nilotinib is associated with hyperglycemia and hyperlipidemia. In ENESTnd, 7% of patients treated with nilotinib experienced grade 3–4 hyperglycemia, compared with 0.4% of those treated with imatinib.[10] Despite these frequent abnormalities, development of diabetes, impaired fasting glucose, or metabolic syndrome, according to the criteria of the American Diabetes Association, do not seem to be more common with nilotinib than with dasatinib or imatinib.[21] Still, patients receiving nilotinib should have glucose levels and lipid profile monitored before, during, and after treatment.[22] For diabetic patients, self-monitoring and regular assessment of hemoglobin A1c are recommended.[22]

Table 2. AOEs reported in frontline randomized trials with ≥4 y follow-up

	DASISION[9]*				ENESTnd[10]†				BELA[40]‡			
	Dasatinib		Imatinib		Nilotinib		Imatinib		Bosutinib		Imatinib	
	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5	Any grade	Grade 3–5
Any ischemic event	4.65	3.49	2.32	1.55	7.8	4.6	2.1	1.8	4.84	1.21	3.59	1.59
Cardiovascular	3.88	2.71	1.55	1.16	3.9	2.2	1.8	1.4	2.42	0.81	1.99	0.40
Cerebrovascular	0.78	0.78	0	0	1.4	1.1	0.4	0.4	0.81	0.40	0.80	0.80
Peripheral arterial disease	0	0	0.77	0.39	2.5	1.4	0	0	1.61	0	0.80	0.40

*5-y follow-up report. Cardiovascular events include myocardial infarction, angina pectoris, coronary artery disease, and acute coronary syndrome; cerebrovascular events included only transient ischemic attack; peripheral arterial disease not specified.

†Minimum 5-y follow-up. Nilotinib dosage was 300 mg twice daily. Ischemic heart disease was defined as any AE reported under any preferred term (PT) in the standardized MedDRA queries (SMQ) narrow terms for *ischemic heart disease*. Ischemic cerebrovascular event was defined as any AE reported under any PT in the SMQ narrow terms for *ischemic cerebrovascular conditions*. An SMQ for peripheral artery disease (PAD) does not currently exist; therefore, PAD events were identified by the following PTs: *arterial occlusive disease*, *arterial stenosis*, *femoral artery occlusion*, *intermittent claudication*, *ischemic limb pain*, *peripheral arterial occlusive disease*, *peripheral artery angioplasty*, *peripheral artery bypass*, *peripheral artery restenosis*, *peripheral artery stenosis*, *peripheral artery stent insertion*, *peripheral artery thrombosis*, *peripheral coldness*, *peripheral ischemia*, *peripheral revascularization*, *peripheral vascular disorder*, *poor peripheral circulation*, and *Raynaud's phenomenon*.

‡Bosutinib 500 mg once daily was used in this study. Follow-up was ≥48 mo. Analysis was based on MedDRA PTs "likely indicating vascular or cardiac toxicities"; cerebrovascular treatment-emergent adverse events (TEAEs) (related high-level terms under the high-level group terms *central nervous system* [CNS] *vascular disorders*, including *CNS hemorrhages and cerebrovascular accidents*, *CNS vascular disorders not elsewhere classified* [NEC], and *transient cerebrovascular events*), cardiovascular TEAEs (all PTs under the high-level terms *ischemic coronary artery disorders* and *coronary artery disorders NEC*), and peripheral vascular TEAEs (related terms under the high-level group terms *arteriosclerosis*, *stenosis*, *vascular insufficiency and necrosis*, *embolism and thrombosis*, *vascular disorders NEC*, *cardiac and vascular investigations excluding enzyme tests*, and *vascular therapeutic procedures*).

Hyperlipidemia is another risk factor for AOEs, and our patient has an elevated cholesterol level. Imatinib may improve the lipid profile of patients, and nilotinib may worsen it, usually soon after treatment starts.[23] In a report of nilotinib-treated patients, by 3 months the proportion of patients with "nonoptimal" low-density lipoprotein cholesterol increased from 48% to 89%. A similar effect was observed for high-density lipoprotein cholesterol.[23] The risk with dasatinib appears lower than with nilotinib.[24] Patients should have a lipid profile assessment before the start of therapy and at regular intervals (eg, every 3–6 months for patients at higher risk) during therapy with TKIs. Management should be instituted with attention to the possible drug–drug interaction with some statins. Coadministration of TKIs induces increased exposure to atorvastatin and simvastatin; there is less interaction with pravastatin and rosuvastatin.[25] Guidelines for management of glycemia and lipids have been proposed by a panel of expert endocrinologists that can be used for patients at highest risk. Although reasonable, prospective validation of such recommendations is not currently available (Table 3).

Pleural effusion

This patient may also have an increased risk of developing pleural effusion with dasatinib. Hypertension may increase the risk of developing pleural effusion,[26] although in a multivariate analysis age was the dominant risk factor.[26,27] From DASISION, the median age for patients who developed pleural effusion was 56 years, compared with 41 years for those who did not.[27] Dosage and schedule are important factors in the risk of developing pleural effusion, with 100 mg once daily associated with lower risk than the originally approved dosage of 70 mg twice daily.[28] Although lower dosages of dasatinib have not been directly compared with the standard 100 mg daily, a recent report of dasatinib starting at 50 mg once daily for patients with newly diagnosed chronic phase CML reported an incidence of pleural effusion of only 6% after a median follow-up of 24 months.[29] Longer follow-up is needed to determine the actual incidence because the first pleural effusion event may occur some years after the start of therapy, but it suggests that lower dosages may decrease the incidence and could be considered for patients at higher risk for this AE. Recommendations for the treatment of patients with pleural effusion have been recently published.[30]

Renal dysfunction

Patients like ours will probably have some borderline or decreased renal function. A decrease in glomerular filtration rate has been reported for patients treated with imatinib and bosutinib.[31] The decline is modest and similar with both agents, but it must be monitored. Dasatinib and nilotinib do not seem to be associated with such declines.[32] Changes in glomerular filtration rate with imatinib have been linked to the development of cardiovascular events.[33] For patients with modest levels of kidney dysfunction (or liver dysfunction) at baseline, imatinib, dasatinib, and nilotinib have been shown to be safe when administered at the standard dosages.[34,35] Efficacy is maintained, and although some patients may experience further decline in kidney function, it seems to be transient and manageable with treatment interruptions and hydration. Dosage reductions are needed more frequently for such patients.[34,35] Therefore, these patients can be treated with a TKI that is considered most appropriate and closely monitored, and dose adjustments can be used when needed. For patients with chronic kidney failure undergoing dialysis, there is only limited, anecdotal evidence. There are few instances of safe administration and plasma levels within the levels in the general population with imatinib,[36] and there is 1 report of a patient with increased trough plasma levels of dasatinib.[37] Thus, patients undergoing dialysis may perhaps be

Table 3. Suggested follow-up of patients with comorbidities for selected health conditions based on recommendations from an expert panel of cardiology[20] and endocrinology[22] experts

Monitoring and management of cardiovascular risk[19,20]		Comment
A	Assessment of risk	At baseline and throughout TKI therapy.
	Antiplatelet therapy	No available data in context of TKIs; consider risk of bleeding (eg, with dasatinib).
B	Blood pressure	Monitor and manage optimally; ponatinib is associated with high blood pressure (VEGFR inhibition)[13] but has been reported with other TKIs.[7]
C	Cholesterol	Reported more frequently elevated with nilotinib.
	Cigarette or tobacco cessation	
D	Diet and weight management	Rule out (and manage if appropriate) weight gain from fluid retention.
	Diabetes prevention and management	Hyperglycemia more common with nilotinib; lower glucose levels with imatinib.
E	Exercise	May help manage fatigue.
Monitoring and management of glycemia[22]		**Comment**
TKI treatment may lead to hyperglycemia or hypoglycemia.		Hyperglycemia more common with nilotinib; hypoglycemia rare (case reports with imatinib).
In case of diabetes under TKI, metformin should be used.		
Hemoglobin A1c target for TKI-induced diabetes <8%; should be personalized.		
Diagnosis of diabetes under TKI does not contraindicate continuation.		
In hypoglycemia under TKI in patients with prior therapy for diabetes, treatment may need to be adapted or interrupted.		
Assess glucose before initiation of TKI.		
If preexisting diabetes, achieve good glucose balance before initiation of TKI.		
Nondiabetic patients, glucose assessed every 2 wk during 1st month, then monthly.		Most important while on nilotinib.
If moderate hyperglycemia or diabetes before TKI, close glucose self-monitoring and education; hemoglobin A1c every 3 mo.		
Upon TKI termination, 4-wk glucose monitoring to adapt antidiabetic therapy.		
Monitoring and management of dyslipidemia[22]		**Comment**
Adapt lipid targets to general health status and prognosis.		Consider drug–drug interactions if therapy is needed.
Assess together with thyroid assessment; hypothyroidism should be treated before start of TKI.		
Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides before start of TKI.		
Lipid assessment every 6 mo.		
Upon TKI discontinuation, stop lipid reduction therapy and re-assess at 2 mo if no prior therapy or reassess optimal dosage if prior therapy.		

These recommendations may be valuable particularly for the highest-risk patients. Prospective validation of these recommendations is not available at the time of this writing.

treated as clinically indicated based on their disease risk score, with imatinib possibly being safest, with close monitoring for AEs.

Salvage therapy

Let us assume our patient received imatinib with no complete cytogenetic response after 12 months, and then bosutinib with a transient major molecular response but now lost complete cytogenetic response. He has no mutations. We face again the dilemma of what TKI to use next. In my view, this patient should be treated with what we think gives him the best opportunity for a durable response. For third-line treatment, the best data available among TKIs approved at the time of this writing are for ponatinib, with major cytogenetic response reported for 60% of such patients. The risk of AOEs is an issue for our patient because of his comorbidities. However, after 2 prior TKIs failed, the risk of progression and death from CML is greater (expected 5-year survival 80% after failure of 2 prior TKIs[38]) than the risk of dying of an AOE with ponatinib (1% of patients died of AOEs after 5 years[13]). The exposure-adjusted incidence of AOEs, based on a very broad definition of these events, was 14.1 per 100 patient-years.[13] Our patient should be carefully monitored and the comorbidities controlled, with particular attention to hypertension, which is more common with ponatinib and may necessitate treatment adjustments. The starting dosage is an important consideration. The standard dosage is 45 mg daily. A recent randomized study suggests there is a correlation of dosage with efficacy and safety. The probability of achieving BCR-ABL1/ABL1 $\leq$1% is greater with 45 mg daily (39%) than with 30 mg (27%) or 15 mg (27%), with AOEs reported in 5%, 4% and 1%, respectively.[39] Thus, I would probably use 45 mg and reduce to 15 mg once transcript levels of $\leq$1% are achieved, with adequate monitoring and management of comorbidities.

Conclusion

In summary, patients with comorbidities have a higher risk of developing AEs with TKIs. Still, with adequate patient education and proper attention to their overall health, these risks can be managed, and patients should receive the TKI that best suits their needs depending on the stage, prior therapies, and patient goals. Throughout therapy, monitoring should include not only polymerase chain reaction but also review of other health conditions, whether they were present at the start of therapy or developed during therapy, to provide optimal management. Management may include referral to other specialists (eg, onco-cardiologists, endocrinologists) when appropriate to optimize care. This co-management should be considered for patients at the highest risk of cardiovascular or other complications and those with more risk factors and comorbidities. If we do this, patients with comorbidities may have a reasonable opportunity to have a good overall treatment outcome.

Authorship

Contribution: J.C. reviewed the literature, analyzed and summarized the information, and wrote, reviewed, and approved the manuscript.

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Footnotes

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