

Chronic Myeloid Leukemia TKIs: Long-term Side Effects and Co- morbidity

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Multiple Treatment Options for Chronic Phase CML Patients in 2014

In many parts of the world, frontline TKI options consist of imatinib, nilotinib and dasatinib; second-line/beyond TKIs include bosutinib and ponatinib.

With the overall favorable outcomes in the TKI era, it is increasingly important to maximize quality of life and minimize side effects, particularly serious and irreversible toxicity.

Long-term toxicities: Imatinib

- Approved in 2001; longest long-term follow-up
- Most side effects are experienced within the first two years.
 - Fatigue, musculoskeletal pain, diarrhea are among the side effects that can be problematic in some patients.
 - Serious/ potentially irreversible toxicities include rare cases of fatal hepatotoxicity

Long-term toxicities: Dasatinib

- First approved in 2006.
- Most side effects are experienced within the first two years. The risk of pleural effusion appears to be constant over time
 - Acne, headache, gastrointestinal discomfort and pleural effusion are among the side effects that can be problematic in some patients. Pleural effusions may be associated with drug trough level, increased age, pulmonary disease, cardiovascular disease and hypertension
 - Serious/irreversible toxicities include rare cases of pulmonary arterial hypertension (estimated <1%; largely reversible)

Long-term toxicities: Nilotinib

- First approved in 2007.
- Most side effects are experienced within the first two years.
 - Rash, headache, gastrointestinal discomfort are among the side effects that can be problematic in some patients. Pancreatitis and hyperglycemia occur in a small proportion of patients.
 - Serious/irreversible toxicities include arterial occlusive events (~7% in ENESTnd; primarily in patients with one or more risk factor) and sudden death (rare),

Long-term toxicities: Bosutinib

- First approved in 2012.
 - Diarrhea, gastrointestinal discomfort, and liver function test abnormalities are among the side effects that can be problematic in some patients.
 - Serious/irreversible toxicities are not well-described, but experience to date with bosutinib is very limited

Long-term toxicities: Ponatinib

- First approved in 2012.
 - Rash, musculoskeletal discomfort, and hypertension are among the side effects that can be problematic in some patients.
 - Serious/irreversible toxicities include vaso-occlusive events in a proportion of patients (~15% after two years). Whether this risk will be limited to the first few years following treatment initiation is not clear.

TKI Toxicities: Some Remaining Questions

- Are “older” individuals, who have shorter life expectancies, better-served by imatinib than some or all of the other TKIs?
- Should drugs with thrombotic risks (ponatinib, nilotinib) or pulmonary effusion risk (dasatinib) be avoided in the elderly, who are more likely to have associated risk factors for these events (hypertension, hypercholesterolemia, history of prior cardiovascular event)?
- Should these drugs be avoided in younger patients because the long-term risks are less clear?
- *Can dose reductions of these drugs modify the risk of serious, potentially irreversible toxicities without compromising activity?*

Risk Factors

- *Risk factors are imperfect at predicting for toxicity.*
 - Example: while various cardiovascular risk factors, such as age, hypertension, diabetes, prior history of thrombosis may be associated with an increased likelihood of suffering a thrombotic event, many patients with risk factors do not experience such events, and some without risk factors do have such events
 - *In a disease with a prognosis as good as chronic phase CML, is it acceptable to use a drug that may cause a stroke in a 25-year old with no risk factors?*
- ECG and echocardiographic monitoring have *not* been shown to identify early changes associated with thrombosis. Ankle-brachial indices (ultrasound) may detect pathological changes in patients treated with certain TKIs, but it is not known how predictive these changes are for eventual cardiovascular toxicity
- Whether lower TKI doses preserve efficacy and mitigate the risk of serious and potentially irreversible toxicity is not known.

Serious/Irreversible Toxicities and Treatment Choice

- While imatinib appears to be the safest BCR-ABL TKI, it is inferior to nilotinib and dasatinib with respect to achievement of cytogenetic/ molecular response rates and associated with an increased likelihood of disease progression/transformation
- All patients should be counseled regarding serious toxicities associated with TKIs. Comorbidities may be incorporated into the treatment decision, but there are very few absolute contraindications for TKIs (e.g. none for ponatinib).
- While bosutinib does not appear to be associated with serious/irreversible toxicities, experience is limited
- Ponatinib, while clearly a very active TKI, appears to be associated with the highest risk of serious/irreversible toxicity, and should therefore be reserved for patients without other meaningful TKI options