Tyrosine Kinase Inhibitors in the Clinical Setting: A Conundrum of Choices

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There is a comprehensive repertoire of tyrosine kinase inhibitor (TKI) molecules available today for treating chronic myeloid leukemia (CML), well supported by evidence from many multicenter, randomized clinical trials (RCTs). With greater choices though, comes the even greater responsibility of picking the drugs wisely and fitting them to the right patient population. In fact, even after 2 decades of experience with TKIs for CML, the debate on the best frontline molecule remains open, and is likely to continue into the future.

The oldest work horse, imatinib, has been used diligently since it was first approved in 2001 and has not shown any late complications on long-term follow-up studies [1]. Over the last decade, with the advent of more potent newer generation (NG) TKIs, a thrust has been to improve the “quality” of treatment responses, often equated with “faster and deeper” molecular remissions (MRs). This translates into a better progression-free survival but not overall survival, along with a higher likelihood of attempting discontinuation of TKIs in deep

MRs, eventually leading to the NCCN adopted end point of “treatment-free remission” (TFR) state. As the meta-analysis published in this issue of *Acta Haematologica* [2] shows, this is certainly achievable with NG-TKIs which show higher efficacy than imatinib in obtaining deeper and prolonged MRs.

There are certain caveats when it comes to generalization of these results to clinical settings outside of RCTs. First is the consideration for age, comorbidities, and cardiovascular events. Many clinical trials are selective with regard to their patient populations, excluding the elderly, frail, and/or patients with specific comorbidities. In the current meta-analysis, the median age of the patients was noted to be 41–58 years, which is lower than the epidemiological studies reporting the median age of CML diagnosis in the western world to be 65–67 years [3, 4], thus endorsing this argument. In the clinical practice, about 50% patients diagnosed with CML are elderly (>65 years), and population-based studies have reported that age at diagnosis does affect the overall survival in CML patients treated with TKIs [5]. Thus, caution is needed when extrapolating the results from controlled RCTs in a relatively young population to the elderly patients in clinical settings. Additionally, more

than 40% of CML patients, including younger ones, have comorbidities at diagnosis [2] that could preclude them from using one or the other NG-TKI due to the risk of organ-specific adverse events. The comorbidity burden has also been shown to predict poorer overall survival in CML treated with imatinib, as reported in the German CML IV study [6]. It is not known if the same will hold true for NG-TKIs which display an entirely different toxicity profile than imatinib. An important observation in this meta-analysis was that no difference in overall survival was noted beyond the first year of treatment despite a lesser incidence of “CML-related deaths” with NG-TKIs. This possibly implies that the NG-TKIs resulted in more “non-CML”-related deaths likely attributable to higher vascular adverse events [7], highlighting the importance of rigorous monitoring and treatment of cardiovascular risk factors while using NG-TKIs.

Secondly, the feasibility of TFRs has been demonstrated in several clinical trials, albeit under the purview of stringent eligibility and monitoring criteria. It is a significant challenge to duplicate the same concept outside of RCTs and will depend on factors related to individual health systems, often overlooked in the controlled settings. These include funding and the actual availability for stringent RQ-PCR testing to capture early relapses, patient participation, and willingness to travel to clinics or laboratories for this more rigorous monitoring, and lastly the immediate availability of salvage treatment options for patients who relapse in the TFR state. A large prospective study (SIMPLICITY) in a real-world setting has suggested that monitoring patterns are hardly as rigorous as recommended by NCCN or ELN, and many factors influence monitoring such as the type of practice (community vs. academic) and the age of the patient (<65 vs. >65 years), and whether the patient is receiving first- or second-line therapy. As an illustration, at our center, the largest for cancer treatment in Canada, many patients express their desire to come off the TKIs. However, as there is no approved funding for more frequent RQ-PCR monitoring (more frequent than every 3 months), the discontinuation of TKIs cannot be implemented with a reasonable degree of certainty that the molecular relapses will be captured at the earliest moment, and that the salvage treatment will be started immediately through the government’s special drug access programs.

Thirdly, quality of life as an outcome is not always reported in the clinical trials. Importantly, a more potent treatment may not always translate into a better

quality of life. This meta-analysis reports that the discontinuation rate was higher in the NG-TKIs as compared to imatinib, mainly due to a higher incidence of grade 3–4 thrombocytopenia, grade 3–4 diarrhea, nausea, and vomiting, and liver toxicity. Many of the clinical trials do not capture whether higher toxicities resulted in poor quality of life due to symptom burden and frequent visits to physicians or emergency rooms for their management. Interestingly, in the ENESTop trial, no difference in quality of life was noted following nilotinib discontinuation or treatment resumption, although pain/discomfort was notably more common after stopping treatment [8]. Thus, more information will be needed on the impact of TKI treatment with regard to treatment satisfaction, adherence, and quality of life, and this could play a role in patient preference for a TKI.

Finally, in tandem with the principle of equity, the results from this meta-analysis will inform and comfort the physicians in low- and middle-income countries (LMICs), which have most of the world’s cancer burden, about the comparability of the TKIs across the generations. In LMICs, even imatinib may be a luxury, let alone the NG-TKIs.

Thus, in our opinion, no TKI is superior over another in a real-world setting, where the choice of treatment is determined by age, frailty, specific comorbidities, risk for cardiovascular events, patient preference, and the availability of funding strategies for discontinuation of TKIs once persistent deep MR is achieved. Further studies in high-risk populations with high Sokal scores and comorbidity burden to compare the survival outcomes will inform decision making.

Disclosure Statement

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Author Contributions

Both authors contributed to the writing of this editorial.

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