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First line asciminib in chronic myeloid leukemia: a quest for the "Holy Grail" of tolerability

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First line asciminib in chronic myeloid leukemia: a quest for the "Holy Grail" of tolerability.

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At the dawn of the 21st century, the ATP-competitive inhibitor of BCR::ABL1 imatinib inaugurated the era of precision-targeted therapy in chronic myeloid leukemia (CML) and converted the naturally fatal course of the disease into a condition compatible with a near-to-normal life expectancy. However, the initial enthusiasm was rapidly tempered as the so called "magic bullet" had important limitations including resistance, intolerance and the need for a lifelong treatment. While next generations of ATP-competitive tyrosine kinase inhibitors (TKI) managed to overcome most resistance mechanisms, their use was accompanied by increased safety concerns and did not solve the challenge of curing CML. While research efforts for finding a cure continue, therapeutic goals following diagnosis have shifted towards finding a perfect balance between efficacy safety and tolerability.

ASC4FIRST is an international randomized clinical trial in which the allosteric drug asciminib is being compared to imatinib and 2nd generation (2G) ATP-competitive TKIs in newly diagnosed chronic phase-CML. The superior efficacy of asciminib over imatinib or imatinib and 2nd generation TKIs has been demonstrated by the higher major molecular response (MMR) rate obtained at 48 weeks (1). Moreover, discontinuation of therapy due to adverse events (AE) was markedly reduced with asciminib, providing proof of concept that greater selectivity of allosteric compounds resulted in improved safety (1,2).

Tolerability is a broad concept that encompasses more than safety alone, including detailed analyses of AE profile regardless of severity or seriousness together with patient-personal

factors (3). It may be defined as the degree to which drug-related AE affects adherence to the therapeutic program and impact on daily living.

So, what makes asciminib different from ATP-competitive TKIs in terms of tolerability?

In the work reported in this issue, Issa *et al,* provide results from a *post hoc* analysis of the 48 weeks safety database of the ASC4FIRST trial with the aim to compare asciminib tolerability with that of ATP-competitive inhibitors in newly diagnosed CML (4).

They found as expected that the overall risk of occurrence of any grade AE was lower with asciminib than with imatinib or with 2G ATP-competitive TKI. The incidence of usually low grade but clinically meaning full AE which commonly occur during imatinib treatment and may persist chronically, particularly nausea, diarrhea edema and muscle cramps were significantly reduced. Regarding the comparison with 2G TKIs, the signature toxicities associated with bosutinib, dasatinib or nilotinib such as hepatotoxicity, skin rash or pleural effusion were also much less frequent. As a result, fewer dose modifications and shorter duration of dose reduction were needed in asciminib-treated patients, which may have contributed to maintaining efficacy.

Issa *et al.* also attempted to identify specific tolerability warnings associated with asciminib. Lipase elevation, the mechanism of which is unknown, rarely led to clinical pancreatitis and was not asciminib-specific. Arterial hypertension was observed in some patients during asciminib or ATP-competitive TKI treatment, but causality assessments including ruling out alternative causes were missing, thus a class effect could not be established. Finally, although the cardiovascular risk profile of asciminib looks promising with only 1% of arterial occlusive events (AOE) against 2% with 2G ATP-competitive TKIs, a potential downside of drug selectivity may be the loss of the beneficial off-target effects of imatinib on the cardiovascular system, as no patient experienced AOE on imatinib (4,5).

Altogether, this work undoubtedly paves the way towards a better understanding of the tolerability of TKIs in CML and highlights the importance of selective approaches such as allosteric inhibition. The authors conclude that tolerability data support practice change in the frontline setting, bringing asciminib to the top of the podium. This type of conclusion should be nuanced as tolerability was not the main objective of ASC4FIRST and the follow-up is still

short. The omission of patient-reported outcomes (PROs) and quality-of-life (QoL) data from the report is unfortunate, as these outcomes provide important information about the patient experience and tolerability. In addition, treatment selection in clinical practice is a process that requires careful consideration of several factors besides tolerability including disease characteristics, probability of treatment success, therapeutic goals, drug availability and patient medical background and lifestyle.

In any case, future studies may incorporate multidimensional aspects of tolerability with not only type and duration of individual AE, dose modification, interruption, discontinuation of therapy, but also reversibility, permanence and chronicity, timing, clinical relevance, impact on daily living, QoL, and last but not least, relationship with efficacy (Figure 1) (6). Studying tolerability of TKIs in CML will require to develop direct and indirect assessment tools as well as a clear definition of what constitutes an acceptable level of TKI tolerability, with the final goal to optimize care and decision-making.

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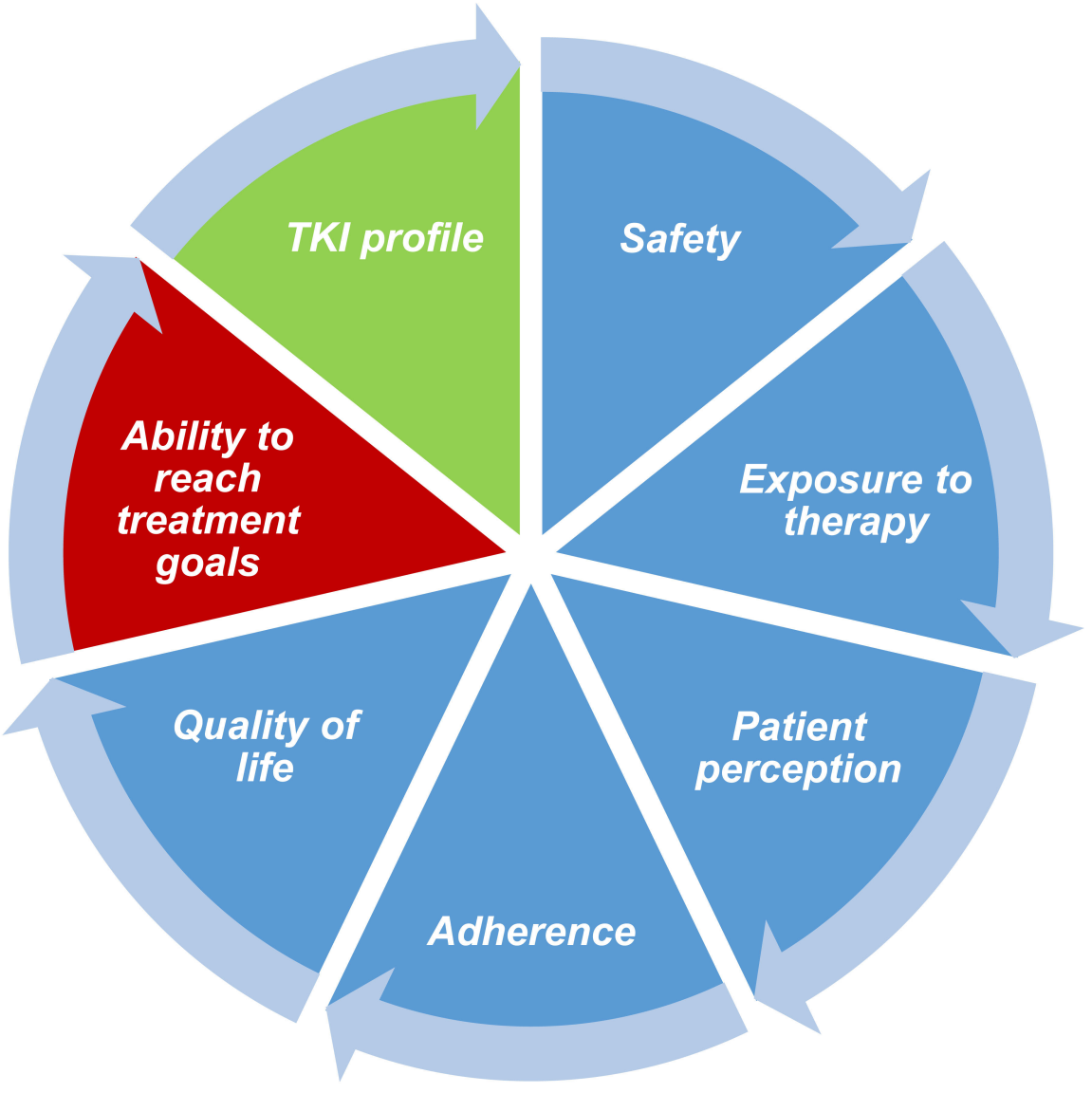
Figure 1:

Different aspects of tolerability and their impact on efficacy


TKI profile
Safety
Exposure to therapy
Patient perception
Adherence
Quality of life
Ability to reach treatment goals