Failing a second-generation TKI: when the guidelines don't always help

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The majority of patients with chronic myeloid leukemia (CML) respond well to tyrosine kinase inhibition (TKI) and will have a life expectancy similar to unaffected age-matched individuals. National and international recommendations for patient management are widely available and regularly updated. These guidelines are, as far as possible, evidence based and understandably utilise the results emanating from well-designed and executed clinical trials. Advice regarding diagnostic investigations, molecular monitoring, response criteria and first and second line treatments is robust and easy to follow. Management becomes more difficult when patients require several changes in TKI because of intolerance and/or resistance, or where co-morbidities limit the choice of subsequent TKI. In these patients, in whom the goal at diagnosis of treatment free remission now seems unrealistic, our overall aim must remain the prevention of disease progression. The challenge becomes the balance of efficacy versus tolerability. For patients with multiple intolerance to TKI, strategies such as dose reduction with increased frequency of molecular monitoring become a pragmatic 'real-world' choice. Those with true resistance pose a different challenge. Worldwide most patients still receive imatinib as their first-line treatment and some 30% will demonstrate resistance, defined as failure to achieve pre-defined levels of response at certain timepoints or loss of a previous response despite good compliance. After an obligatory investigation for a kinase domain mutation these patients will move onto a second generation TKI (2GTKI), the precise choice dictated by local drug availability, previous adverse events, pre-existing co-morbidities and patient preference, and some 50% will respond durably. Increasingly, newly diagnosed patients begin treatment with a 2GTKI and approximately 15% will have resistance, In these individuals, second-line management is equivalent to third-line treatment in those who started with imatinib, and here the guidelines are less prescriptive and less supported by published studies. Choosing an alternative 2GTKI for patients who are resistant to the first 2GTKI is largely futile in terms of achieving durable molecular remissions, but moving to a third generation TKI (3GTKI) is often a difficult choice given the more serious side effects associated with more potent agents. The recently published OPTIC study investigated the efficacy and safety of three different doses of ponatinib, the most widely available 3GTKI: rather surprisingly there was little difference in the toxicity of the varying doses and less surprisingly, the higher dose was more effective. Further analyses within this study have identified the need to start with the higher dose (45mg daily) in patients with kinase domain mutations and in those whose response to the most recent TKI was at best complete haematological remission. The explanation for the lower incidence of arterial thrombotic events compared to the original Phase 2 study is less clear, but may reflect physician awareness, patient selection and better management of underlying co-morbidities. Asciminib has now been licensed and is available as a third line option in some countries. The recent ASCEMBL randomized study of asciminib versus bosutinib in third or subsequent line treatment has shown improved efficacy of asciminib compared to bosutinib, and to date, the adverse event profile of asciminib seems acceptable. These recent data provide a better understanding of the use of 3GTKI in patients at risk of disease progression and should increase patient and physician confidence in earlier instigation when necessary.