Chronic myeloid leukemia - Section 3

Treatment-free remission: A new goal for all chronic phase (CP)-CML patients

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Take Home Messages

- TKI discontinuation can be envisaged in CP-CML patients with deep and durable molecular responses despite the persistence of a reservoir of leukemic cells.
- Deep molecular responses are more frequently obtained with frontline 2nd generation TKIs than with imatinib, but the pros and cons of using a particular TKI in a given patient must be discussed.
- Assessment of residual disease by means of sensitive RT-qPCR plays a key role in detecting CML relapse after TKI discontinuation and the loss of a major molecular response is an indication to restart TKI therapy promptly.

Introduction

Chronic myeloid leukemia (CML) arises from hematopoietic stem cell transformation by BCR-ABL1, a hybrid gene generated by the acquired reciprocal t(9;22)(q34;q11) translocation. The chimeric BCR-ABL1 oncprotein, a constitutively activated tyrosine kinase whose biological properties include impairment of multiple intracellular signaling pathways and induction of genomic instability, is directly responsible for leukemogenesis. ATP-competitive ABL1 tyrosine kinase inhibitors (TKIs) revolutionized the prognosis of patients with CML by preventing disease progression to a very large extent thus dramatically increasing overall survival. TKIs currently approved to treat CML include the 1st generation drug imatinib, the 2nd generation TKIs dasatinib, nilotinib and bosutinib and the 3rd generation compound ponatinib. Among prognostic factors of outcome, molecular responses play a key role and RT-qPCR tests have become major tools to monitor TKI efficacy. Provided the achievement of an optimal response currently defined as a major molecular response (MMR: BCR-ABL1 ≤0.1% IS), life expectancy of adult patients diagnosed in the chronic phase (CP) of the disease is very close to that of the general population. The persistence in most if not all TKI-treated CML patients of a reservoir of quiescent leukemic cells whose survival does not depend on BCR-ABL1 activity represents one important limitation of currently existing TKIs, as a lifelong treatment is required in the majority of patients in order to prevent the otherwise ineluctable relapse and progression. In this regard, efforts have to be made towards fine tuning of TKIs use to mitigate iatrogenic effects, promotion of long-term adherence to treatment and alleviation of the financial burden of TKIs borne by individuals or health care systems. Nevertheless, a major lesson learnt from clinical research conducted during the last 10 years reside in the consistent observation that a subset of CP-CML patients with long-lasting deep molecular responses are able for unclear reasons to maintain an optimal response after TKI discontinuation in the absence of any further medical intervention, a situation named treatment-free remission (TFR). In all clinical trials performed to date, CP-CML patients with deep and sustained molecular responses were able to remain treatment-free without facing a molecular relapse in approximately 50% of the cases. While achievement and maintenance of MMR on-therapy remains an essential step during CML patient management, obtaining a deep molecular response in the view of TFR emerges as a novel treatment goal (Figure 1). Recommendations for CP-CML management in clinical practice are on the way to adjust to this new reality.

Deep molecular responses during TKI treatment

During first line TKI treatment, deep molecular responses such as MR4 (0.0032% IS ≤BCR-ABL1 ≤0.01% IS or undetectable BCR-ABL1 with at least 10000 copies of ABL1 or 24000 copies of GUSB) or MR4.5 (.0.0032% IS ≤BCR-ABL1 ≤0.0032% IS or undetectable BCR-ABL1 with at least 32000 copies of ABL1 or 77000 copies of GUSB) are increasingly reached over time. Clinical trials provided reliable evidence that the probability to achieve a deep molecular response to 1st line treatment was not evenly distributed among patients but was influenced by several factors including CML prognostic scores at diagnosis, type of molecular responses obtained early after treatment introduction and initial TKI choices. In this regard, deep molecular responses are more frequently obtained with 1st line 2nd generation TKIs than with imatinib and the time to achieve such responses is shorter. These data argue in favor of the use of the most potent TKIs upfront in the view of TFR as a treatment goal in CP-CML patients. Alternatively, one could opt for imatinib and treatment intensification based on failure to achieve time-specific target responses either during the first 12 months of therapy or at later time points. There is also an increasing interest in strategies
combining TKIs with other anti-leukemic drugs. Imatinib administered upfront together with interferon has already shown enhanced capacity to induce deep molecular responses compared to imatinib alone and other randomized trials are underway.²

Hurdles against a systematic use of 2nd generation TKIs upfront in all patients include lack of a worldwide access to these drugs, economic considerations and the toxicity profile of these compounds especially in comorbid or elderly patients.⁸ As to the issue of combination therapies, access to clinical trials is warranted as none has received approval by health authorities. Some research efforts are made in order to find specific and clinically applicable targeting strategies of residual leukemic cells.

**TKI discontinuation: State-of-the-art**

The achievement of deep molecular responses such as MR4 or MR4.5 is an indisputable prerequisite to consider TKI discontinuation and these deep responses need to be sustained. Among factors contributing to the risk of relapse after treatment cessation, the prognostic relevance of TKI treatment duration and probably more importantly that of the deep molecular response has been demonstrated.⁹ Other factors are also likely to play a role such as a history of resistance during the course of therapy.¹⁰ The impact of varying deep molecular response levels on the relapse risk is difficult to address with current RT-qPCR techniques and the use of more precise and innovative techniques such as digital PCR may help address this issue.

In TKI discontinuation studies, molecular response monitoring played a key role in detecting relapse but thresholds of BCR-ABL transcripts over which patients were instructed to resume therapy varied, ranging from loss of a deep molecular response to MMR loss. Despite this inconsistency, studies unanimously showed that frequent molecular monitoring was required at least during the first year following TKI discontinuation as the majority of molecular relapses occurred early after TKI discontinuation, before 6 to 12 months, and with rapid kinetics.⁴ An agreement is now emerging on how to define molecular relapse and MMR loss appears as a robust operational criterion. Importantly, patients facing molecular relapses remain highly sensitive to TKIs. Of note, a “TKI withdrawal syndrome” was described in about one third of patients stopping therapy, consisting in newly occurring or worsening osteoarticular pain but this syndrome is usually benign and transient.

**Conclusion and perspectives**

MMR remains an important endpoint for patients with CML but the new standard for a maximum clinical benefit of TKI therapy is evolving towards TFR. Recommendations for TKI discontinuation in clinical practice are emerging (Figure 1). However, this new goal is still reserved for a minority of CP-CML patients. Increasing the frequency of deep and sustained molecular responses as well as TFR rates through innovative therapeutic approaches without jeopardizing safety represents a clinical challenge for the future as well as understanding reasons underlying divergent outcome after TKI discontinuation.

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