Stopping second-generation TKIs in CML

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In this issue of Blood, Rea et al1 show that rigorously defined suboptimal response or resistance by European LeukemiaNet (ELN) criteria2 to first-line treatment with dasatinib or nilotinib (second-generation tyrosine kinase inhibitor [2G-TKIs]), or later in imatinib-intolerant patients, is a major negative predictor for the successful discontinuation of TKI therapy in chronic phase chronic myeloid leukemia (CML) patients who achieve deep sustained molecular responses. This result from an interim analysis of 60 patients in the observational STOP 2G-TKI study is an important contribution to the still evolving patient selection criteria for attempting to achieve a treatment-free remission (TFR) in clinical practice.3

This study included patients on TKI therapy for 3 or more years who had achieved a deep molecular response (BCR-ABL1 internationally standardized [IS] ≤ 0.0032%, or molecular response 4.5, MR4.5) with undetectable BCR-ABL1 with ≥40 000 ABL1 transcripts (uMR4.5), measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) for 2 or more years, before discontinuing TKI therapy. TKI therapy was resumed in patients with molecular relapse, defined by the loss of major molecular response (MMR) (BCR–ABL1 IS > 0.1%). After a minimum 1 year of follow-up, the overall rate of TFR was 63.33% at 12 months (the primary study endpoint), and 53.57% at 48 months. The probability of achieving a TFR at 48 months was markedly inferior in patients with prior suboptimal/resistant disease compared with those with optimal response or imatinib intolerance (18.18% vs 79.78%, respectively). A number of other variables, some noted to have an impact on the probability of achieving a TFR in other discontinuation trials,4 including age, sex, Sokal risk group, prior interferon-α, duration of TKI therapy, duration of uMR4.5, and type of 2G-TKI, had no significant impact in univariate analysis. In addition, a major difference in the rate of TFR at 48 months was observed by landmark analysis of patients who remained in MMR at 3 months between patients who were still in MR4.5 compared with those who lost their MR4.5 response (81.82% vs 17.59%, respectively).

Although this is a relatively small study, the key findings above raise the feasibility of using a probability of TFR-adapted approach to TKI discontinuation in routine practice, to minimize patient inconvenience and disappointment, and to reduce the excessive consumption of clinical and laboratory resources. The results suggest that TKI discontinuation in ELN-defined suboptimal response/resistant patients should not be considered routine until and if larger studies can identify patients within this subgroup that have a greater probability of achieving a TFR. Instead, the development of new trials using novel therapies to improve the chances of obtaining a TFR should be encouraged for this group of patients. Physicians may also consider reintroducing TKI therapy earlier on loss of MR4.5 response by 3 months after TKI discontinuation without waiting for the loss of MMR. This second group of patients could similarly be considered for new trials of novel TFR salvage therapy, given the low probability of achieving a second TFR on TKIs alone as reported in this and other studies.

The absence of disease transformation and the renewed response observed in all patients to the reintroduction of TKI therapy following molecular relapse in this study add to the safety record of TKI discontinuation in the ~2000 patients enrolled in various TFR trials to date. However, intermittently RT-qPCR–positive results in 13/33 (45.5%) of nonrelapsing patients highlight the importance of long-term monitoring. Similarly, in 13 relapsing patients in whom RT-qPCR was also measured at the time of treatment resumption, the number of patients who had BCR-ABL1 IS >1% increased from 2 (15.3%) to 7 (53.8%) over the 1.5-month median time interval spanning the loss of MMR and the reintroduction of TKI therapy, emphasizing the need for rapid turnaround of RT-qPCR test results and prompt resumption of treatment, in order to avoid the risk of cytogenetic and hematological relapses.

The results of this study suggest that 2G-TKIs may not be able to overcome the adverse disease biology reflected by prior ELN-defined suboptimal/resistant TKI responses to achieve a sustained TFR, even when a sustained deep molecular response (uMR4.5) is obtained. A reduced probability of achieving a TFR was similarly reported in the DADI trial of second-line dasatinib in resistant patients.5 Moreover, even though a greater number of patients may achieve deep molecular responses with the more potent 2G-TKIs compared with imatinib, there does not appear to be a large improvement, if any, in the rate of TFR in the
present and other 2G-TKI discontinuation trials compared with that reported for imatinib TFR trials, with all the caveats and limitations that apply to the nonrandomized comparison of trials of varying design and utilizing different criteria.

Perhaps the path to improving rates of TFR will be to tackle the relative or overt resistance of the CML clone with novel agents, as the results of this study might suggest. However, the stereotypical kinetics of early relapse vs stable TFR, and the persistence of low expression of BCR-ABL1 in some nonrelapsing patients, suggesting that residual CML stem cells may lose the ability to compete with Ph-negative cells to recapitulate the disease, indicates that additional mechanisms may be involved. Factors that could affect the relative fitness of competitive repopulation by posttreatment Ph-negative vs residual CML stem cells, changes in the stem cell niche microenvironment of CML patients, or differences in the immunological profiles of relapsing vs nonrelapsing patients have raised new hypothesis regarding the still mysterious process whereby a durable TFR can be achieved in some patients. The goalpost has clearly shifted to findings ways to achieve a TFR in the majority of patients, and the road ahead looks exciting and promising.

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REFERENCES
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Comment on Sbihi et al, page 855

iNKT cell defects in HHV-8–associated MCD

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In this issue of Blood, Sbihi et al provide the first evidence of invariant natural killer T (iNKT) cell abnormalities in patients with human herpesvirus 8 (HHV-8)–associated multicentric Castleman disease (MCD).

HHV-8, also known as Kaposi sarcoma (KS) herpesvirus (KSHV), is a γ-herpesvirus that can infect a variety of cells, including endothelial cells, B cells, and antigen-presenting cells. Like Epstein-Barr virus (EBV), the most closely related γ-herpesvirus, HHV-8 generally establishes latent infection in host cells. Important to the establishment of infection are HHV-8 codes for a variety of proteins that allow for immune evasion, including 2 ubiquitin E3 ligases, K3 and K5, that downregulate surface proteins that are important for immune surveillance such as MHC-I, ICAM, MICA, and CD1d. Although HHV-8 infection is generally asymptomatic in immunocompetent hosts, in

Model of HHV-8–associated MCD associated with diminished iNKT cells. (A) Controlled HHV-8 infection of B cells is associated with limited lytic activation of HHV-8 and effective immune surveillance by T cells and iNKT cells. Activated iNKT cells likely produce cytokines that further promote antiviral immunity in this setting. (B) HHV-8–associated MCD is associated with decreased iNKT cells. In addition, dysregulated lytic activation of HHV-8 leads to upregulation of the HHV-8–encoded E3 ubiquitin ligases K3 and K5, which downregulate CD1d and MHC-I and further promote immune evasion. Upregulation of human and viral IL-6 and other cytokines in this setting promotes proliferation of HHV-8–infected B cells. iTCR, invariant T-cell receptor; TCR, T-cell receptor; vIL-6, viral IL-6. Professional illustration by Patrick Lane, ScEYEnce Studios.
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