NCCN Guidelines Updates: Discontinuing TKI Therapy in the Treatment of Chronic Myeloid Leukemia

Presented by Neil P. Shah, MD, PhD

ABSTRACT

The NCCN Guidelines for Chronic Myeloid Leukemia (CML) criteria for discontinuation of tyrosine kinase inhibitor (TKI) therapy have not seen significant updates in the past year, but the current guidelines reinforce the safety of treatment discontinuation in appropriate and consenting patients with CML in the chronic phase who have achieved and maintained a deep molecular response. According to Dr. Neil Shah, who presented the current data, some clinicians are still unaware that treatment discontinuation is an option. Patients who wish to stop TKI therapy should consult with a CML specialty center to confirm that discontinuation is safe and appropriate; they also should be counseled on all potential benefits and risks of stopping therapy, including TKI withdrawal syndrome. In patients with CML who experience relapse after discontinuing TKI therapy, a second TKI discontinuation can be successful among those who regained a deep molecular response after TKI rechallenge, although experience to date with second discontinuation attempts is very limited. Second-generation TKIs have also demonstrated improvement in rates of deep molecular remission, making treatment discontinuation possible for a larger proportion of patients.

Discontinuation of tyrosine kinase inhibitor (TKI) therapy appears to be safe among adult patients with chronic myeloid leukemia (CML) in the chronic phase who have achieved and maintained a deep molecular response (DMR), according to the updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML. According to Neil P. Shah, MD, PhD, Professor of Medicine, Division of Hematology and Oncology, UCSF Helen Diller Family Comprehensive Cancer Center, who discussed the updated NCCN Guidelines for CML at the NCCN 2019 Annual Conference, no major updates were introduced this year in regard to discontinuing TKI therapy in CML. However, when combined with careful molecular monitoring, the current guidelines reinforce the safety of discontinuation in appropriate patients. “Based on data presented a couple years ago, [the NCCN panel] decided to modify the guidelines to incorporate TKI discontinuation as a reasonable option in select patients,” said Dr. Shah. “These recommendations in the guidelines have only been around for about 2.5 years, so in the last year nothing has really changed. But some clinicians, still to this day, are not aware that stopping is an option.”

According to the guidelines, achievement and maintenance of a DMR characterized by ≥4 log reduction in BCR-ABL1 transcripts (MR4.0) for ≥2 years is required before considering TKI discontinuation outside the context of a clinical trial. Loss of MMR (MR3.0; BCR-ABL1 >0.1%) should trigger immediate resumption of TKIs, with monthly monitoring, until MMR is regained. Approximately 50% of patients who attempt to discontinue TKI therapy after achieving a stable deep molecular remission remain in a treatment-free remission (TFR) after 5 years.

Who Should Be Considered for Discontinuation?

According to Dr. Shah, patients who wish to discontinue TKI therapy commonly express a desire to improve their quality of life, minimize potential late-emerging toxicities, minimize drug–drug interactions, and reduce “financial toxicity.” Patients who do not wish to discontinue may have none of these concerns and may fear the repercussions of stopping a well-tolerated therapy that has made their disease essentially undetectable.

Discontinuation should be considered in women of childbearing potential who are interested in having children, he advised. “Men [on TKI therapy] seem to be able to father healthy children, and there seem to be no significant issues with fertility or birth defects from what we’ve seen,” said Dr. Shah. “In women, it’s another story. There is a concern for birth defects in children who have been exposed in utero to any TKI.”

Discontinuation can also be considered in “younger” patients to minimize possible late toxicities and to reduce their financial burden. “We still don’t know much
about longer-term toxicities—“longer” being >15 to 20 years on TKI therapy—and that’s something we have to keep an eye out for,” he added.

**Importance of DMR**

According to Dr. Shah, the STIM1 study is responsible for transforming the collective way of thinking about TKI discontinuation in CML. Patients eligible for discontinuation had to achieve and maintain for 2 years a very deep molecular remission of MR5.0 in *BCR-ABL1* transcripts, as measured by real-time quantitative RT-PCR. In the trial, 38% of patients remained in TFR at 60 months without molecular recurrence.

“This was rather a brave study. What [the investigators] actually had the guts to do in their analysis was to stop imatinib in consenting patients who had achieved a DMR,” said Dr. Shah. “And what [they saw] was survival without molecular recurrence in a substantial proportion of patients.” This has been replicated in numerous subsequent analyses, but the definition of DMR has become more relaxed. In the STIM1 study, the definition was stringent (MR5.0), but further research confirmed that lowering the threshold to a molecular response of 4.5 or 4.0 did not significantly affect rates of molecular relapse (Figure 1).

Relaxing the threshold, as well as the duration of DMR, has made TKI discontinuation available to a larger number of patients. For example, the phase III EURO-SKI trial of 755 patients required only a 4-log reduction for at least 1 year and saw a TFR rate of 50% at 12 months. When liberalizing the threshold for stopping treatment with TKIs, the threshold at which to resume therapy must also be relaxed, Dr. Shah noted, to loss of a 3.0-log reduction, as stated in the current NCCN Guidelines.

**Second TKI Discontinuation**

In patients with CML who experience relapse after discontinuing TKI therapy, a second TKI discontinuation can be successful among those who regain DMR after TKI rechallenge.

“When we think about mechanisms that may explain what is going on here, I think the most straightforward one would be that we’ve gotten rid of the disease,” said Dr. Shah. He maintains that the most straightforward explanation for successful TFR is leukemic stem cell erosion or exhaustion due to the fact that *BCR-ABL1* transcript levels tend to decline rapidly initially, then more gradually until a DMR is achieved.

“Eventually, the level of disease in many patients becomes undetectable. Beyond that, of course, we don’t know what’s happening, but it’s reasonable to surmise that perhaps there’s a continual, gradual decline until eventually all the diseased stem cells are gone,” he added. “The fact that a second attempt at treatment discontinuation is successful in some patients is somewhat supportive of the concept of disease eradication; it’s not conclusive, but it is supportive.”

**Predictors of Molecular Relapse**

According to multivariable analysis of the STIM1 trial, a high-risk Sokal score at diagnosis—which may be a surrogate measure of increased disease burden—was another factor found to be predictive of molecular relapse after stopping treatment (hazard ratio [HR], 2.22; 95% CI, 1.11–4.42; *P*=.024). Duration of TKI therapy prior to stopping was also a factor predictive of molecular response; imatinib duration of ≥58.8 months before discontinuation was associated with a lower likelihood of relapse (HR, 0.54; 95% CI, 0.32–0.92; *P*=.024). According to Dr. Shah, these findings support the concept of stem cell erosion in a subset of patients.

Data from EURO-SKI confirmed that a cutoff of approximately 6 years for TKI duration was associated with greater likelihood of maintaining MMR when stopping treatment. Patients who discontinued at <6 years had a greater chance of relapse. In the trial, MMR loss if discontinued at ≤5.8 years was 57% (95% CI, 48%–64%), whereas MMR loss if discontinued at >5.8 years was 34% (95% CI, 29%–39%).

In some patients, there remains evidence of a stable low level of disease following treatment discontinuation. It is hypothesized that immune surveillance is playing a role in controlling the disease in these cases. A high number of NK cells and enhanced Th1-type responses have been associated with successful TFR.

**Increasing the Proportion Eligible for Treatment Discontinuation**

“We estimate that maybe no more than 50% of patients on TKIs will ultimately have the opportunity to stop treatment. The others will not achieve the sufficiently
deep molecular response to enable them to even try this,” said Dr. Shah.

However, second-generation TKIs have been shown to improve the rate of DMR, making treatment discontinuation possible for a larger proportion of patients than those treated with imatinib.6,7 Although 3 of the second-generation TKIs—nilotinib, dasatinib, and bosutinib—have demonstrated improvement in DMR rates over time compared with imatinib, none are associated with significantly improved overall survival or transformation-free survival compared with imatinib. “So, when we think about using these agents, the decision sometimes has to be informed by how important it is to get a patient to where we can potentially stop treatment,” he said.

Combining imatinib with other agents, particularly interferon, has shown promise in helping patients achieve and maintain DMRs.8 This also seems to be applicable when interferon is combined with second-generation TKIs like dasatinib.9 “This certainly is encouraging and suggests that we can get more patients to a point where they may be able to try stopping therapy,” he said.

Rather surprisingly, according to Dr. Shah, a TKI withdrawal syndrome has been reported, and is characterized by newly occurring adverse events seemingly related to stopping the drug in patients who have already undergone TKI discontinuation. TKI withdrawal syndrome was first reported in a cohort of 50 patients, in which approximately 30% developed musculoskeletal symptoms.10 “In some instances, these patients actually elected to go back on a TKI, not for treatment of CML, but to treat the musculoskeletal discomfort that arose,” he said. “It can happen with any of the drugs, so it’s something patients need to be aware of so that they’re not blindsided if they stop treatment and all of a sudden have pain in their shoulders, spine, or hips.”

**Criteria for Discontinuation**

Patients should only be considered for discontinuation if all of the criteria outlined in the NCCN Guidelines have been met (see the NCCN Guidelines at NCCN.org [CML-E]). Patients who wish to discontinue TKI treatment after achieving and maintaining a DMR should have access to frequent molecular monitoring and should be counseled on the potential benefits and risks of stopping, including the possibility of TKI withdrawal syndrome. In addition to maintaining a stable DMR for at least 2 years, monthly molecular monitoring is recommended during the first year after discontinuation (when the risk of molecular relapse is highest), every 6 weeks during the second year, and every 12 weeks beyond that. Loss of MMR should prompt immediate resumption of TKI therapy.

Patients should have no history of accelerated- or blast-phase CML (nothing beyond chronic-phase), maintained a 4.0-log reduction for at least 2 years, and been on approved TKI therapy for at least 3 years. “[The CML Guidelines Panel] decided to be relatively conservative,” Dr. Shah noted.

Patients should be referred to a CML Specialty Center for at least 1 consultation to ensure that all of these criteria are met and to confirm that TKI discontinuation is safe and appropriate. “It is strongly encouraged to notify the NCCN panel of any potential new toxicity that may occur, or any bad disease-related outcome that may occur in patients who have stopped therapy,” Dr. Shah concluded.

**References**


