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Dr. Assouline`s research focuses on the development of new therapies for the treatment of hematological malignancies. She has conducted and participated in many phase I-III clinical trials of novel targeted agents, and has also performed epidemiological and translational research focusing on new approaches to treating these diseases. She is the director of the CML clinic at the Jewish General Hospital since 2006 and is a member of the Groupe Quebecois de Recherche en LMC/NMP (Quebec CML/MPN Research Group) with whom she has been involved in several clinical research projects pertaining to the management of patients with CML.

Chronic Myeloid Leukemia: Who Should Get a Treatment-Free Trial and How?

Introduction

Treatment with a BCR::ABL1 targeted tyrosine kinase inhibitor (TKI) has afforded a near-normal life expectancy for most patients with chronic myelogenous leukemia (CML).[1-3] Approximately half of CML patients achieve a deep molecular response with TKI therapy and can discontinue treatment. In these patients, the CML can remain in prolonged remission, and patients can experience an improvement in quality of life.[4]

The European Leukemia Network (ELN)[5] and the National Comprehensive Cancer Network (NCCN)[6] provide the most up-to-date frameworks for treatment-free trials (TFTs), reflecting best practices from over 13 clinical trials published since the concept first entered the CML vernacular around 2010.[7] Provincial guidelines also exist, such as those published in Quebec by the Groupe Québécois de Recherche en LMC-NMP (the Chronic Myeloid Leukemia and Myeloproliferative Neoplasms Quebec Research Group).

The discontinuation of therapy for patients with CML in deep remission marks a potential shift from the management of CML as a chronic illness to the potential for a curative approach to CML. However, for now, only 50% of eligible patients have undergone successful TFT; optimal patient selection and monitoring is required to ensure the best outcomes with such a management strategy.

Patient selection

In 2022, almost all patients with CML are candidates for one of several available TKIs, including the first generation TKI, imatinib; second generation TKIs, such as dasatinib, nilotinib, and bosutinib; and third generation TKIs, such as ponatinib and asciminib. These therapies are approved in Canada either in the first line or beyond and can all produce a molecular response level of at least MR4, (a BCR::ABL1 transcript level of <0.01% on the International Scale [IS]) the minimum value required for consideration of a TFT **(Figure 1)**.

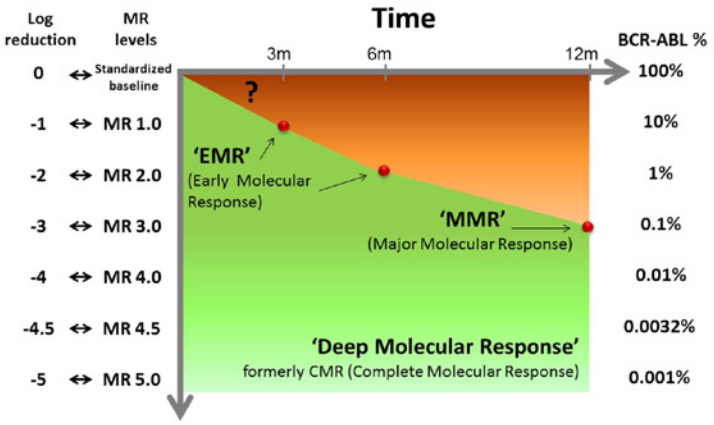

Figure 1. *The bar for molecular response in CML; adapted from Baccarani et al, 2014*

To be eligible for therapy discontinuation, patients must achieve sustained MR4 or better for at least 18 to 24 months (with measurements at least 6 months apart) and must have received TKI therapy for at least 3 years Based on EURO-SKI, the largest TKI discontinuation study in CML, the optimal duration of TKI therapy is about 5 years.[8] The duration and depth of molecular response may impact the success of a TFT.[8-11]

In addition, the patient's CML must have a measurable or typical transcript according to the results of the assay being used (98% of patients have a measurable transcript). The presence of an

atypical transcript can be assessed at the time of diagnosis if the real-time quantitative PCR (RT-qPCR) run along with cytogenetics shows a BCR::ABL1 transcript level of <MR2 (<1% IS) while the cytogenetics clearly demonstrate the presence of the Philadelphia chromosome. Being able to quantify the BCR::ABL1 ensures that the patient indeed has achieved deep remission and that a relapse can be identified early during the TFT.

Eligible patients must also be available and willing to undergo regular, frequent monitoring after stopping their TKI therapy. Since the depth of molecular response is strongly associated with compliance,[12] patients who are candidates for a TFT tend to have a history of good compliance with drug therapy and medical visits.

Choice of TKI prior to TFT

The possibility of a TFT should be discussed with all newly diagnosed patients as it may impact the choice of first-line therapy. Second generation TKIs given in the first-line setting are associated with a 10% to 20% higher deep MR4 rate than imatinib,[13-15] and thus potentially offer a greater chance at therapy discontinuation. However, the evidence shows that there is no noticeable difference in the overall success rate of TFTs based on the choice of initial TKI.[4,16,17] In selecting a first-line therapy, it is essential to first ensure that the chosen TKI will result in the best tolerability and long-term compliance, as the primary goal in treating CML remains a durable clinical response and the subsequent impact on survival.

In most discontinuation trials, results have shown that patients were not refractory to any prior TKI (defined as a loss of response or failure to achieve at least a complete cytogenetic response [MR2, or 1% IS]). Non-TKI refractory patients who switch due to intolerance or to achieve deeper response have a similar TFT success rate as those stopping after a first-line therapy.[18-20] However, among first line imatinib-resistant patients who switched to dasatinib or nilotinib to achieve a deeper molecular response, the rates of TFT success have been shown to be lower.[19-21] Accordingly, the ELN and NCCN favour non-refractory patients for TFTs.

Ultimately, approximately 50% to 60% of patients will be eligible for a TFT when the criteria for discontinuation are met **(Figure 2)**.

Molecular monitoring

The assay used to measure molecular response prior to the TFT must have a sensitivity of at least 1/10,000, and the copy number of the control gene should be provided for each molecular response assessment to ensure that an adequate quantity of RNA was evaluated in generating the result. Ideally, the molecular assay should use the International Scale (IS) to ensure validity against an international standard and consistency across different laboratories. In addition, the turnaround time for molecular results should be no longer than 4 weeks to allow for a timely assessment n in case of a rising PCR value.

Once a patient starts the TFT, they must undergo molecular monitoring every 4-8 weeks during the first year. Thereafter,

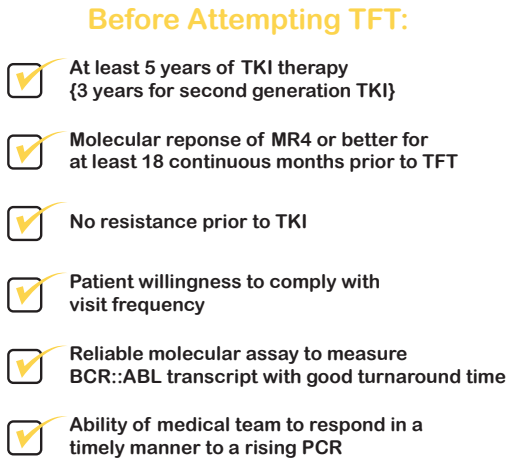

Figure 2. *Criteria for TFT eligibility; courtesy of Sarit Assouline, MD*

monitoring can be done every 12 weeks. The goal is to maintain a minimum major molecular response (MR3, <0.1% IS). Most losses of molecular response during TFTs typically occur within the first 6 to 12 months of the discontinuation of TKI therapy, but there can be late losses, which reinforces the need for long-term monitoring. The molecular patterns following the initiation of a TFT can vary, as shown in **Figure 3**.

There is rarely loss of cytogenetic or hematological remission during TFTs. The risk of such outcomes is mitigated by close patient follow-up during the TFT period. Most patients (95%) who lose MR3 regain at least MR3 when either the original or a new TKI is re-initiated. Episodes of blast crisis, the transformation of CML from the chronic phase to the blast phase, during TFTs have been reported, raising some concerns, but more research is needed to determine the rate of transformation and the surrounding circumstances.

While frequent molecular monitoring is essential, clinic visits need not be as frequent if the treating team is able to follow and communicate molecular results in a timely manner.

Clinical Scenarios for TFT consideration

When criteria for discontinuation are met, a patient should be offered a TFT because of the potential long-term adverse effects associated with chronic TKI treatment. Interestingly, many patients do not choose a TFT, citing the security of taking a medication to control their disease, the absence of bothersome adverse effects, and the risk of relapse associated with discontinuation. Patients who choose to discontinue therapy have reported doing so because of persistent or recurrent side effects, concerns about long-term toxicity, the impact on quality of life of taking medication, and the cost of their therapy.[22]

While men who wish to conceive need not discontinue therapy, TKI therapy is unsafe for the developing fetus. For women wishing to become pregnant, a TFT appears to be the best option but given that only 50% of patients qualify for a TFT and that only 50% have a successful TFT outcome, this option may be unachievable for many. For patients planning to become pregnant, the safest option is surrogacy, but pregnancy following TKI therapy can be safe once MR3 levels or better have been

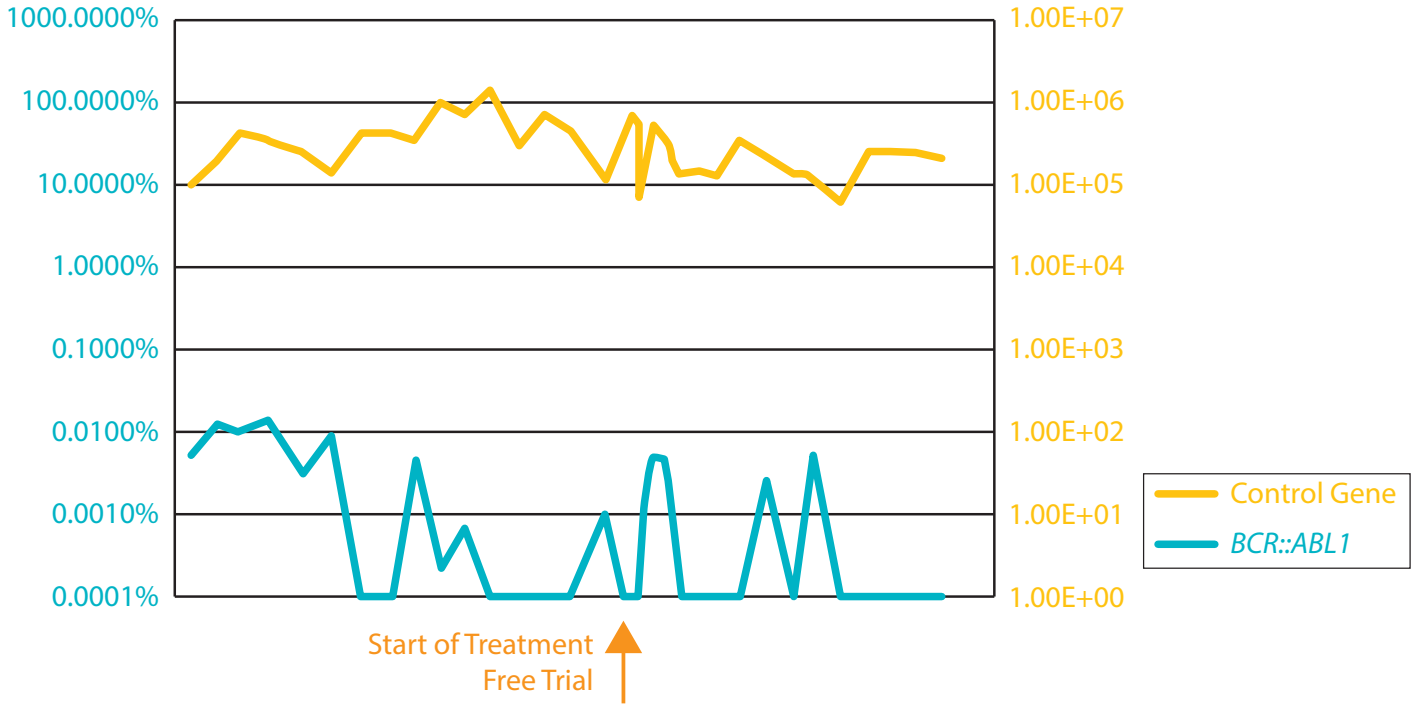

Figure 3. *Sample molecular patterns following initiation of TFT; courtesy of Sarit Assouline, MD*

achieved and the pregnancy is planned at least after 2 years of TKI therapy, when the risk of disease transformation to blast crisis is significantly reduced.[23] Furthermore, there are anecdotal reports that nilotinib and imatinib can be administered safely during the later stages of pregnancy, but this is not recommended in the respective product monographs.[23]

Some patients may discontinue TKI therapy without consulting their treating physician, often based on information gleaned from sources outside the clinic. It is therefore important to counsel patients that the best outcomes are achieved in close collaboration with their healthcare team.

TKI withdrawal syndrome

Among patients who attempt a TFT, 20% to 30% may experience withdrawal syndrome which typically manifests as musculoskeletal and peri-articular pain. TKI withdrawal syndrome usually appears within weeks to months after discontinuing therapy and may take months to resolve. Symptoms can be managed with acetaminophen, non-steroidal anti-inflammatories and glucocorticosteroids, if needed.[24] Patients should be reassured that the withdrawal symptoms will eventually resolve or improve. There are reports of patients resuming TKI therapy due to the symptoms of withdrawal. Notwithstanding those affected by TKI withdrawal syndrome, most patients report an improvement in pain when stopping TKI therapy.[4]

Second TFTs

Second TKI discontinuation attempts are less successful, measured at about a 20% success rate, with even lower rates among patients who have a rapid loss of MR3 levels during a first TFT attempt[25]. As such, a second TFT is not yet recommended by the ELN and NCCN. If considering a second TFT for the sake of diminishing TKI toxicity, better options may include switching TKIs or dose reductions to optimize tolerance.

Improving the TFT success rate

Ongoing studies are currently underway to examine of the combination of imatinib and asciminib, a third generation TKI targeting the myristoyl pocket of ABL. These studies are promising, and early results suggest that the combination of ATP binding TKI and asciminib is more effective than either agent alone[26].

Conclusion

TFTs have become part of routine practice in the treatment of CML in the last several years, owing to robust data and revised management guidelines. For Canadian patients with CML, a TFT should be considered from the time of diagnosis and throughout the course of treatment. When performed correctly, a TFT can be a very positive experience for both the patient and medical team alike.

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