How I Manage Patients with Chronic Myeloid Leukemia (CML): Perspectives from Clinical Practice

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Abstract: The management of chronic myeloid leukemia (CML) has remarkably changed in the last 20 years with the availability of tyrosine kinase inhibitors (TKI). Most patients with chronic phase CML now have a life expectancy like that of age matched controls. Understanding the practical aspects of choosing the appropriate TKI, monitoring response and side-effects are key to long term success. Currently, treatment cessation is also an option in patients achieving sustained deep molecular response. Novel agents are needed in patients with lack of response to TKI and in those with advanced disease.

Keywords: leukemia, myeloid, chronic, treatment

Introduction
Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of t (9, 22) leading to BCR-ABL1 gene rearrangement. In United States, it is diagnosed at a median age of 67 years with about 8450 new cases in 2020.1 Although CML was considered as a deadly disease in the past, the availability of BCR-ABL tyrosine kinase inhibitors (TKI) have remarkably changed the outlook of this disease. Currently, CML is considered as a disease that is well manageable with oral TKI giving excellent long-term results and the option for stopping treatment in some patients. In this review, we will discuss about the practical aspects of managing CML and the common considerations given at various levels of management.

Considerations for Diagnosis
Most patients with CML present with leukocytosis and left shifted granulocytes, and/or thrombocytosis. Symptoms at presentation are variable and could include fever, night sweats, fatigue, and some patients are asymptomatic. To diagnose CML, the demonstration of the Philadelphia chromosome abnormality or the BCR-ABL gene rearrangement is important. At the cytogenetic level, CML is characterized by a reciprocal translocation in chromosomes 9 and 22.2 This leads to the fusion of BCR and ABL1 genes. The breakpoint typically occurs in introns 13 or 14 of the BCR gene in chromosome 22 and exons 1 or 2 of ABL1 in chromosome 9. This results in the typical transcripts (e13a2 or e14a2) and major fusion protein (p210). In some patients, the break points can occur at other exon location (e1a2 with p190, e19a2 with p230, e13a3, e14a3) and should be considered if the classical major BCR is not present. Confirmation of t (9, 22) can be done using conventional karyotyping or Fluorescence-in-situ-hybridization studies and the identification and quantitation of the BCR-ABL1 fusion transcripts can be done using polymerase chain reaction (PCR). Testing can be done either from the peripheral blood or bone marrow specimens, although, obtaining a bone marrow biopsy at baseline would also assist in confirming the disease phase and provide an opportunity to assess for additional chromosomal abnormalities.

Once a diagnosis established, it is important to know the disease phase and the risk status to determine the optimal first line therapy. CML has 3 phases - chronic, accelerated and blast phase. While most of the patients diagnosed with CML are in chronic phase, some patients have higher disease risk with presentations such as accelerated or blast phase. Knowing the disease phase is important as the management and prognosis differs significantly based on this aspect. Patients with chronic phase CML now have a survival that is similar to age matched controls without CML, but patients
with blast phase CML have a median survival of 7–11 months.\textsuperscript{3,4} Chronic phase CML can be risk stratified using Sokal risk score (used more commonly in US) based on age, spleen size by clinical exam, platelet counts and peripheral blast percentage.\textsuperscript{5} This stratification helps in understanding the prognosis and choosing the first line therapy.

Considerations for Initial Management with First Line TKI

Currently, imatinib, dasatinib, nilotinib and bosutinib are available as first line options for management of CML. Imatinib is a first generation TKI that was compared against interferon and cytarabine for newly diagnosed CML and showed significantly higher response rates (major cytogenetic response 87.1% vs 34.1%) and lower risk of transformation to accelerated or blast phase (freedom from progression 96.7% vs 91.5%).\textsuperscript{6} Subsequently, second generation TKI such as dasatinib, nilotinib, and bosutinib were compared against imatinib in prospective clinical studies and showed encouraging efficacy\textsuperscript{7–12} (Table 1). In general, starting treatment with second generation TKI would lead to quicker achievement of cytogenetic and molecular responses, minimizes the risk of transformation to accelerated phase or blast crisis and allows for patients to be eligible for stopping therapy after achievement of a sustained deep molecular response. However, the overall survival is not significantly different between first generation and second generation TKI and patients treated with imatinib therapy can still be candidates for treatment cessation as long as they achieve the goals (see Considerations for Stopping TKI).

In practice, the choice of TKI is guided by disease risk status, side-effect profile and financial affordability and reimbursement for patients. Given the higher risk of transformation to advanced stage disease in patients with intermediate-high risk chronic phase CML, starting treatment with second generation TKI would reduce this risk and is commonly preferred. In patients with low-risk disease, either first generation (imatinib) or second generation TKI are suitable options for frontline therapy. A careful assessment of concomitant medications is essential while administering TKI as medications such as proton pump inhibitors and H2-receptor blockers decreases the drug exposure whileazole antifungals, certain antidepressants, supplements such as curcumin, green tea extract, and \textit{Ginkgo biloba} increases the drug exposure. The side-effect profile between the TKI also play an important role in the therapy selection. Imatinib is associated with rash, fluid overload, muscle cramps and liver abnormalities. Dasatinib is associated with pleural effusions and pulmonary hypertension. Nilotinib could cause QTc prolongation, pancreatitis, hyperglycemia and peripheral arterial occlusive disease. Bosutinib could lead to diarrhea and hepatotoxicity. Hence, choosing them based on patient’s comorbid conditions and preference would be reasonable. For example, imatinib, dasatinib, and bosutinib could be options for patients with arrhythmia, heart disease, pancreatitis, or hyperglycemia while imatinib, nilotinib, or bosutinib could be selected for patients with lung disease.

Dose holding and adjustments are considered in the event of toxicities from therapy. Cytopenia such as neutropenia (ANC <1.0x10\textsuperscript{9}/L) and thrombocytopenia (platelets <50x10\textsuperscript{9}/L) would require dose holding, growth factor support as indicated and resumption of therapy upon improvement. Similarly, grade 3–4 non-hematological toxicities such as diarrhea, transaminitis (with or without hyperbilirubinemia), QTc prolongation are addressed by dose interruption till resolution and restarting at the same or reduced dose based on the severity and time taken for recovery. Gastrointestinal upset is manageable by taking the medication with meal (if appropriate) and large glass of water. Pleural effusion associated with dasatinib can be addressed with additional measures such as diuretics, steroids, and pleural tap. In patients who develop recurrent pleural effusion or pulmonary arterial hypertension, dasatinib would be switched to another appropriate TKI.

| TKI Choice        | Early Molecular Response | Complete Cytogenetic Response at 12 Months | Major Molecular Response at 12 Months | Accelerated/ Blast Phase Transformation | Overall Survival at 5-Years |
|-------------------|--------------------------|------------------------------------------|-------------------------------------|----------------------------------------|-----------------------------|
| Dasatinib vs Imatinib | 84% vs 64%              | 83% vs 72%                                | 46% vs 28%                         | 4.6% vs 7.3% by 5 years                | 91% vs 90%                  |
| Nilotinib vs Imatinib | 91% vs 67%              | 80% vs 65%                                | 44% vs 22%                         | 0.7% vs 4.2%                          | 93.7% vs 91.7%              |
| Bosutinib vs Imatinib | 75% vs 57%              | 77% vs 66%                                | 47% vs 37%                         | 2.2% vs 2.6%                          | 94.5% vs 94.6%              |
Monitoring of Response

After initiation of first line therapy, patients are periodically monitored for molecular response using PCR for BCR-ABL transcript every 3 months. Achievement of BCR-ABL1 (IS) ≤10% by 3–6 months after starting therapy is known as early molecular response and is associated with improved outcomes. Major molecular response (MMR) is defined by BCR-ABL1 (IS) ≤0.1% and would be typically expected to happen within 1 year after starting therapy. Deep molecular responses with BCR-ABL1 (IS) ≤0.01—0.0032% (MR4-MR4.5) are also seen in patients responding to treatment. In patients not achieving molecular milestones at appropriate timepoints or in patients with loss of response, measures such as ensuring compliance to therapy, reviewing concomitant medications, testing for cytogenetics to look for additional cytogenetic abnormalities, performing bone marrow biopsy to reassess disease phase, and checking BCR-ABL kinase domain mutations are considered based on true lack of response versus inadequate drug delivery.

Considerations for Second Line TKI

Patients with CML may require a second line TKI either due to lack of response or intolerance to first line TKI. In case of intolerance to a first line TKI, switching to a second line TKI with non-overlapping toxicity profile is reasonable. Similarly, intolerance to a second generation TKI is mostly addressable by switching to a different TKI with non-overlapping toxicity profile. Lack of response to standard dose first line imatinib is addressed best by switching to a second generation TKI as shown in prospective clinical trials. Achievement of major cytogenetic response was the primary endpoint in most of these trials and dasatinib (major cytogenetic response 59%, complete cytogenetic response 44%), nilotinib (major cytogenetic response 56%, complete cytogenetic response 41%) and bosutinib (major cytogenetic response 57%, complete cytogenetic response 44%) yielded similar results. The choice between these second generation TKI can be guided further through kinase domain mutation analysis as certain mutations such as T315I are sensitive to ponatinib (Table 2).

The choice of a subsequent TKI in patients with lack of response or progression after initial second generation TKI is challenging. Mutation profiling is helpful in identifying resistance mutations to various TKI in this setting and further therapy selection. Both bosutinib and ponatinib have prospective data in this patient population and could be considered. In patients with T315I gatekeeper mutation, ponatinib is an active agent although there is risk of arterial occlusive events with higher dose (45mg). However, the OPTIC study explored the efficacy and safety of three different doses of ponatinib (15mg, 30mg, and 45mg) and demonstrated that starting treatment with 45mg dose followed by dose reduction to 15mg upon achievement of BCR-ABL1 ≤1% yielded the optimal risk/benefit ratio. This strategy is currently recommended while using ponatinib. An additional newer option for managing patients with resistance to TKIs is described later (Newer agents).

For patients treated with first line imatinib who do not achieve optimal response at 3, 6 or 12 months, switching to a second generation TKI such as dasatinib or nilotinib could improve the responses. However, this would be a consideration only after certain important steps such as close monitoring and repeat testing to confirm suboptimal response, ensuring treatment adherence, and discussion with the patient about this option.

Considerations for Stopping TKI

Given the excellent deep responses with long term TKI therapy, studies have demonstrated the feasibility of stopping TKI therapy in patients who achieve sustained deep molecular remission. In United States, a prospective longitudinal study (LAST study) with 173 patients showed a treatment free remission rate of 60.8% and similar results have been shown in other studies (Table 3). The current NCCN guidelines describes the eligibility for TKI cessation as patients with age ≥ 18 years, chronic phase CML, no prior history of accelerated phase/blast phase, presence of a quantifiable BCR-ABL transcript,

| Mutation         | Drug to be Avoided |
|------------------|--------------------|
| V299L, G250E, F317L, T315I | Bosutinib         |
| F317L/V/I/C, V299L, T315I     | Dasatinib         |
| Y253H, E255K/V, F359V/C/I, T315I | Nilotinib     |
treatment with TKI for at least 3 years with minimum 2 years of stable molecular response of MR4 (BCR-ABL1 ≤0.01), and access to reliable PCR monitoring during follow-up.28 During the period after stopping TKI, close monthly monitoring with q-PCR for the first 6 months, bimonthly monitoring during months 7–12, followed by quarterly thereafter indefinitely is recommended as long as they maintain major molecular response (BCR-ABL1 ≤0.1%). In patients who lose MMR, prompt resolution of TKI can get most of them back to MMR. For example, in the ENESTfreedom study, 98.9% of patients who need to restart nilotinib regained MMR and 92.3% regained MR4.5.27 Additional attempts of TKI cessation can be considered under clinical trials and referral to academic centers is recommended.

**Role of Allogeneic Hematopoietic Stem Cell Transplantation (HCT)**

In the current era, patients with chronic phase CML patients are not routinely considered for allogeneic HCT given excellent long-term outcomes with TKI. However, in patients with resistance to all available TKI, progression to accelerated phase or blast phase while on TKI and in those who present with accelerated or blast phase CML, early referral to allogeneic HCT is important. A recent analysis by the center for international blood and marrow transplant research (CIBMTR) showed a 5-year overall survival of 53% after allogeneic HCT with either myeloablative or reduced intensity conditioning.29

**Role of Omacetaxine Mepesuccinate**

Omacetaxine mepesuccinate is a protein synthesis inhibitor that blocks protein translocation in ribosomes and induces apoptosis of oncoproteins such as BCR-ABL1, Mcl-1, cMyc, cyclin D1 and is unaffected by BCR-ABL1 mutations. It is approved for treatment of CML patients in chronic or accelerated phase with resistance or intolerance to 2 or more TKI. Major cytogenetic response of 18–20% in chronic phase and a major hematological response of 14–27% in accelerated phase has been seen in clinical studies.30–32 This is an option for management of progressive or TKI intolerant CML although newer agents are actively being investigated in this setting.

**Newer Agents**

Asciminib is an allosteric inhibitor that binds to the myristoyl pocket of the BCR-ABL1 kinase and acts independent of the ATP binding site (which is the mechanism of action for most TKI). In a Phase I study, single agent asciminib resulted in 92% hematological response, 54% complete cytogenetic response, 48% major molecular response by 12 months.

### Table 3 TKI Cessation Studies

| Study     | Characteristics                                      | Treatment Free Remission/Molecular Relapse Free Survival | Trigger to Restart TKI |
|-----------|------------------------------------------------------|----------------------------------------------------------|-------------------------|
| LAST      | N= 173 TKI – imatinib, dasatinib, nilotinib, bosutinib | 60% at 12 months                                        | Loss of MMR             |
| ENESTfreedom | N=215 TKI – nilotinib                             | 51.6% (48 weeks)                                        | Loss of MMR             |
| DasFree   | N=84 Dasatinib                                       | 46% (2 years)                                           | Loss of MMR             |
| Euro-SKI  | N=821 TKI - Imatinib, nilotinib or dasatinib        | 50% (12 months)                                         | Loss of MMR             |
| Twister   | N=40 TKI - imatinib                                 | 47.1% (24 months)                                       | Loss of MMR or two consecutive positive samples at any value |
| STIMI     | N=100 TKI- Imatinib                                 | 38% (60 months)                                         | Loss of MMR or atleast 2 positive PCR with 1 log increase |

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including those in patients with T315I mutation (28%) or resistance/intolerance to ponatinib (57%). 33 In a Phase III open label randomized study, asciminib was compared against bosutinib in CML patients after 2 or more prior TKI and showed superior MMR at 24 weeks (25.5% vs 13.2%) with a difference of 12.2% after adjusting for baseline major cytogenetic response. 34 The drug was FDA approved in October 2021 for the management of chronic phase CML with 2 or more prior TKI and those with T315I mutation. This is an exciting option given the unmet need for patients with resistance/intolerance to current available TKI and those with T315I mutations. The dose is 80 mg once daily or 40 mg twice daily. In patients with T315I mutation, the dose is 200 mg twice daily. Rare complications such as asymptomatic lipase elevation and clinical pancreatitis needs to be monitored.

**Conclusions**

CML is a prototype disease where molecular discoveries and targeted therapies have revolutionized the clinical management and outcomes. Both continuous management with TKI as well as cessation of therapy after achievement of deep sustained molecular response are available as options for managing these patients. While the outcomes of chronic phase CML remain excellent, careful monitoring of response, management of side-effects and considering the financial burden of therapy are key aspects of management. Novel therapies are needed to address patients with disease progression after TKI and those with blast crisis.

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