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TYROSINE KINASE INHIBITORS FOR THE FRONTLINE MANAGEMENT OF CML: AN OVERVIEW

Introduction

The introduction of Tyrosine Kinase Inhibitors (TKI) for the treatment of chronic myeloid leukemia (CML) has revolutionized CML therapy. These agents have increased the life expectancy of CML patients to 98% of those in the general population[1]. Since the first approval of imatinib for CML treatment (by the US FDA in 2001[2]), three additional TKIs have been approved for the indication of frontline therapy in CML during chronic phase (CP), including: dasatinib[3], nilotinib[4] and bosutinib[5]. This article will discuss the initial steps for newly diagnosed CML patients, its frontline therapy, and its management.

Goal of Frontline CML Treatment

The goal of CML treatment has evolved over last 2 decades in parallel with drug development. When imatinib was approved for CML therapy, the main goal was the reduction of transformation to blastic phase (BP) and the prolongation of survival[2]. As treatment evolved, this goal changed to achieving complete cytogenetic response (CCyR) or major molecular response (MMR) within a certain timeframe[3-5]. With successful replication in multiple TKI discontinuation studies for the treatment-free remission (TFR) attempt[6-8], the achievement of deep molecular response (DMR), which is required for qualification of TFR attempt, is also considered an ultimate goal of CML therapy[9]. In addition, quality of life (QoL) during CML therapy has been underscored over last 10 years as another important goal of treatment given that several TKIs can induce significant and critical toxicities.

The determination of frontline CML treatment goal(s) should be individualized for patients given the heterogenous nature of the illness and will require careful consideration of multiple factors including demographic characteristics, medical, and the physical or social condition of the patient as well as the patient's lifestyle. Careful discussion with the patients and their families prior to frontline TKI drug selection is critical.

Disease Risk Assessment

For the initial risk assessment of CML, three risk stratification systems have been frequently utilized[9]:

1) Sokal risk score, 2) Hasford risk score, 3) EUTOS long term survival (ELTS) score[9]. While the Sokal and Hasford risk scores had been traditionally used for initial risk assessment over the last 4 decades, the ELTS score has been shown to predict the probability of long-term antileukemic efficacy of TKI therapy and CML-related death following frontline imatinib therapy[10]. The following formula can be used to calculate the ELTS score. Additionally, an online calculator can be found at https://www.leukemia-net.org/leukemias/cml/eutos_score/

ELTS score =

$0.0025 \times (\text{age in completed years}/10)^3$

$+ 0.0615 \times$ spleen size below costal margin

$+ 0.1052 \times$ blasts in peripheral blood

$+ 0.4104 \times (\text{platelet count}/1000)^{-0.5}$

An ELTS score value ≤ 1.5680 defines the low-risk group

An ELTS score value > 1.5680 but ≤ 2.2185 defines the intermediate-risk group

An ELTS score value > 2.2185 defines the high-risk group

The detection of additional chromosomal abnormalities (ACA) is also extremely helpful when identifying high-risk patients[9]. High-risk ACA need to be closely monitored, which include trisomy 8, a second Ph chromosome (+Ph), isochromosome 17[(i(17)], +19, -7/7q-, 11q23 or 3q26.2 aberration, and complex aberrant karyotypes[9].

In the last version of the European LeukemiaNET (ELN) 2020 recommendations for CML, patients with a high-risk ELTS score or high-risk ACA were classified in a "warning" category at baseline due to their higher risk of progression and poorer response to TKI therapy, thus necessitating careful monitoring of the disease during administration of TKI therapy[9].

Comorbidities and Other Medical Condition Assessments

Based on the ELN recommendation in 2020[9], the initial diagnostic workup and investigation should include physical examination (especially for spleen size), CBC with differential, bone marrow aspirate and biopsy with chromosome banding analysis for cytogenetics, RT-PCR for BCR-ABL with biochemical profile, and hepatitis B-serology. In our center, lipid profile, HbA1C, urinalysis, ECG, and a chest X-ray are also included as part of the routine investigation for newly diagnosed CML patients.

Recently, it has been increasingly recognized that there is an elevated risk of cardiovascular toxicities associated with the use of 2nd generation TKIs including nilotinib and ponatinib, such as arterial occlusive events[11]. Accordingly, it can be onerous to assess a CML patient's cardiovascular risk profile and underlying comorbidities during their clinical visits. The Framingham cardiovascular risk score can be calculated based on age, sex, smoking history, total and HDL cholesterol level, systolic blood pressure, as well as the use of antihypertensive treatment[12].

However, higher risk groups for cardiovascular comorbidities should be referred to a cardiologist for further evaluation, in addition to a 2D echocardiography.

Consideration of Drug-Drug Interactions

Another factor that should be kept in mind during the process of frontline TKI drug selection is the potential for drug-drug interactions. A careful review of the patient's whole list of medications is required[13]. Drug-drug interactions can result in CML patients suffering from toxicities from the use of TKI itself or from concomitant medications beyond TKI therapy.

Management Prior to Frontline TKI Treatment

Prior to initiation of frontline TKI drug treatment, a short course of hydroxyurea can be administered with allopurinol to prevent tumor lysis syndrome, which can occur with TKI therapy[9]. During this phase, vigorous hydration is also strongly encouraged.

While white blood cell (WBC) and/or platelet counts can be controlled with hydroxyurea, consideration can be given for which TKI drug should be used as frontline TKI therapy in an individual patient. In some provinces, this choice is restricted by reimbursement criteria.

Frontline TKI Drug Selection

Currently, 4 TKI agents are commercially available: imatinib, nilotinib, dasatinib and bosutinib. Their efficacy, toxicity profiles, and long-term toxicity are summarized in **Table 1**.

Three Potential Scenarios for Individualized Frontline TKI Drug Selection

To help clinicians appreciate the approach to individualized TKI drug selection, three scenarios are presented below.

1. 2nd generation TKI in a 55-year-old patient with diabetes; aiming for TFR

A 55-year-old man has a diagnosis of CML-CP with a history of diabetes. With approximately 30+ years of life expectancy, the ultimate treatment goal should be treatment-free remission. The disease risk classification is intermediate, and the cardiovascular risk profile is low. The patient prefers a once-daily agent due to his work environment. Accordingly, the decision was made to proceed with dasatinib frontline therapy to increase the chance of achieving DMR while nilotinib is contraindicated due to diabetes.

2. Imatinib in a 82-year-old patient with multiple cardiopulmonary comorbidities

An 82-year-old lady has a diagnosis of CML. She has multiple comorbidities of coronary artery disease, chronic obstructive pulmonary disease, inflammatory bowel disease with diabetes. A practical treatment goal is disease

References: 1. ADCETRIS (brentuximab vedotin) Product Monograph. Seagen, Inc. June 11, 2021.

	Imatinib	Dasatinib	Nilotinib	Bosutinib
Class	1st generation-TKI	2nd generation-TKI	2nd generation -TKI	2nd generation-TKI
Dose	400 mg once daily, with meal	100 mg once daily	300 mg twice daily dosing with dietary restriction	400 mg once daily
Key data for efficacy	higher CCyR and MMR & better PFS and OS than Interferon/AraC therapy	Higher MMR and MR4 than imatinib; Similar PFS/OS to imatinib	Higher MMR and MR4 than imatinib; Similar OS to imatinib	Higher MMR than imatinib
MMR	60-80% at 5 yrs	76% by 5 yrs	77% at 5 yrs	73.9% at 5 yrs
MR4	35-68% at 5 yrs	42% by 5 yrs	66% at 5 yrs	58% at 5 yrs
TFR data	50-60%	50-60%	50-60%	Not reported but expected to be similar
Toxicity profile	Fluid retention, GI symptoms, muscle cramps, fatigue	Pleural effusion (in up to 37% of patients), pulmonary hypertension	Pancreatitis, QTc prolongation, metabolic side effects	Transient diarrhea (in up to 30% of patients); elevation of transaminase
Long-term toxicity	No life-threatening toxicity, but rarely low GFR	Rare cases of pulmonary hypertension and nephropathy	Cardiovascular toxicity of arterial occlusive event	Not known
Reference	IRIS study[2]	DASISION study[3]	ENESTnd study[4]	BFORE study[5,14]

Table 1. *Summary of efficacy and toxicity profile with front line TKI therapy*[9]

control to prevent progression and to improve survival. The patient's disease risk is classified as intermediate, but the cardiovascular risk profile is very high. In this case, the decision was made to proceed with imatinib therapy as upfront treatment. Nilotinib, dasatinib and bosutinib were contraindicated due to the patient's underlying comorbidities.

3. 2nd generation TKI in a 33-year-old patient with high risk CML

A 33-year-old patient has a diagnosis of CML-CP with a 20 cm sized spleen palpable on examination. The Sokal and ELTS risk score is classified as 'high'. Chromosome band analysis shows +8 in addition to t(9;22). The patient's disease risk is high, and the cardiovascular risk profile is low. The decision was made to go ahead with nilotinib front line therapy.

Side Effect and Toxicity Management

In most cases, supportive management of side effects and toxicities with the use of TKIs is required. For example, imatinib- and dasatinib-related supportive management includes the use of diuretics for fluid retention, calcium/electrolyte replacement for muscle cramps, and diuretics/short term steroid therapy for pleural effusions[9]. However, temporary therapy interruption is the first step in managing dasatinib-associated pleural effusion or TKI-induced pancreatic enzyme elevation. Complete cessation of therapy is warranted in cases involving pulmonary hypertension with dasatinib, cardiovascular events, including arterial occlusive disease, with nilotinib, irreversible liver enzyme elevation with bosutinib[15] and gastric antral vascular ectasia with imatinib[16].

Cross disciplinary recommendations from cardiology and endocrinology include the management of cardiovascular and metabolic risk and potential toxicities, by adopting risk assessment and life style modification such as blood pressure/cholesterol/diet/weight management, diabetes prevention, exercise, and smoking cessation[11].

Response Monitoring

Following the initiation of front line TKI therapy, molecular response should be monitored on a regular basis (every 3 months) using the *BCR::ABL1* qPCR test[9]. Many of the treatment guidelines suggest determining early molecular milestones based on the *BCR::ABL1* qPCR test results at 3, 6 and 12 months (**Table 2**). If the patient achieves molecular response below 10%^{IS} at 3 months, 1%^{IS} (i.e. MR2) at 6 months, and 0.1%^{IS} (i.e. major molecular response [MMR]) at 12 months, they are classified as having achieved optimal response which precludes the need for treatment switches to other TKIs. If the patient fails to achieve 10%^{IS} at 6 months, 1%^{IS} at 12 months, loses 1% of response at any time after 12 months, develops *ABL1* kinase domain mutations or if any additional chromosomal abnormalities arise, the patient will be classified as "failure", implying that switching to a new TKI may provide better long-term outcomes. For cases that fall between the optimal response and failure, the patient is classified as "warning", which implies that very careful monitoring of response is required, otherwise there is risk of failure.

In cases of treatment failure, activation of the ABL1 kinase domain mutation (KDM) test is the first step in the ongoing monitoring of response[9,17]. Clinicians should note that the analytical sensitivity detection limit with Sanger sequencing-based KDM tests is about 10-20%, meaning that the KDM test fails to capture some ABL1 KDMs due to this detection limit, particularly in patients with PCR levels below 1%^{IS}.

Once a patient achieves 1-0.1%^{IS} or a deeper response, besides *BCR::ABL1* qPCR, it is recommended to repeat the chromosome banding analysis test from the marrow sample. About 10% of CML patients achieve responses that could develop a clonal evolution in Philadelphia chromosome negative clone[18]. Some of those cases, particularly with monosomy 5/7 or del(5) or del(7), can develop MDS/AML, although its occurrence is rare.

Ongoing and Upcoming Clinical Trials for Frontline Therapy in CML

A novel agent, asciminib, is a first-in-class Specifically Targeting the ABL1 Myristoyl Pocket (STAMP) inhibitor[19], and is currently being investigated in newly diagnosed CML patients in CP. Results from these pivotal trials are expected to be available in next 1-2 years.

Conclusion

Individualized determination of frontline TKI drug selection is required after careful discussion with newly diagnosed CML patients. This determination process includes detailed discussion involving the goals of CML therapy, disease risk, as well as better understanding underlying comorbidities and concurrent medical conditions before making a final selection of the preferred frontline TKI agent.

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	Optimal*	Warning	Failure
Baseline	-	High risk ACA, high risk ELTS score	-
3 months	≤10%IS	>10%^{IS}	>10%^{IS} if confirmed
6 months	≤1%IS	>1-10%^{IS}	>10%^{IS}
12 months	≤0.1%IS	>0.1-1%^{IS}	>1%^{IS}
Any time	≤0.1%IS	>0.1-1%^{IS} Loss of ≤0.1%^{IS}	>1%^{IS} Resistance mutation, high risk ACA
*For patients aiming for TFR, the optimal response (at any time) is *BCR::ABL1* ≤0.01%^{IS} (i.e. MR4)			

Table 2. *Molecular milestone for front line CML therapy based on the BCR::ABL1 transcript levels*[9]

References:

1. *Bower H, Bjorkholm M, Dickman PW, Hoglund M, Lambert PC, Andersson TM. Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. J Clin Oncol. 2016;34(24):2851-2857.*
2. *O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003;348(11):994-1004.*
3. *Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362(24):2260-2270.*
4. *Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251-2259.*
5. *Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018;36(3):231-237.*
6. *Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018;19(6):747-757.*
7. *Laneuville P. When to Stop Tyrosine Kinase Inhibitors for the Treatment of Chronic Myeloid Leukemia. Curr Treat Options Oncol. 2018;19(3):15.*
8. *Kim DDH, Novitzky-Basso I, Kim TS, et al. Optimal duration of imatinib treatment/deep molecular response for treatment-free remission after imatinib discontinuation from a Canadian tyrosine kinase inhibitor discontinuation trial. Br J Haematol. 2021;193(4):779-791.*
9. *Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34(4):966-984.*
10. *Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. Leukemia. 2020;34(8):2138-2149.*
11. *Cortes J. How to manage CML patients with comorbidities. Blood. 2020;136(22):2507-2512.*
12. *Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35(2):440-453.*
13. *Haouala A, Widmer N, Duchosal MA, Montemurro M, Buclin T, Decosterd LA. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood. 2011;117(8):e75-87.*
14. *Brummendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia. 2022;36(7):1825-1833.*
15. *Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol. 2018;11(1):143.*
16. *Ong J, Yeung D, Filshie R, Hughes TP, Nandurkar H. Imatinib-induced gastric antral vascular ectasia in three patients with chronic myeloid leukaemia. Int J Hematol. 2015;102(5):639-642.*
17. *Soverini S, Hochhaus A, Nicolini FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011;118(5):1208-1215.*
18. *Issa GC, Kantarjian HM, Gonzalez GN, et al. Clonal chromosomal abnormalities appearing in Philadelphia chromosome-negative metaphases during CML treatment. Blood. 2017;130(19):2084-2091.*
19. *Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019;381(24):2315-2326.*