WHO 2016 DEFINITION OF CHRONIC MYELOID LEUKEMIA AND TYROSINE KINASE INHIBITORS

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ABSTRACT

Philadelphia (Ph+) / BCR-ABL1 positive-chronic myeloid leukemia (CML) shall be considered as a chronic life-long disease, which could be manageable with Tyrosine Kinase Inhibitor (TKI) drugs. The target of TKI drug treatment is to provide age- and sex-matched duration of life in a given patient with CML. Personalized CML treatment with TKI drugs is the key strategy regarding the harmonization of CML disease characteristics, clinical experience and best clinical evidence. Specific CML disease characteristics in a given patient include CML disease risk, comorbidities, molecular profile, compliance, life style, and drug off-target risk profile. CML research evidence includes randomized clinical trials indicating the data on the safety, efficacy, tolerability, toxicity, possible long-term adverse events and cost of TKI. Clinics and physician experience include TKI availability, TKI reimbursability, drug experience, adherence, and BCR-ABL1 monitorization facility. Key decision choosing of TKI for CML should be made via the consideration of those variables. The aim of this paper is to outline WHO-2016 defined CML and its proper management with TKI drugs.
KEY WORDS
Chronic myeloid leukemia, CML, Tyrosine Kinase Inhibitor, TKI

INTRODUCTION
Philadelphia (Ph*)/ BCR-ABL1 positive-chronic myeloid leukemia (CML) is a chronic neoplastic disease, which can be functionally curable via the administration of Tyrosine Kinase Inhibitor (TKI) drugs (1). The overall aim of TKI therapy in CML is to provide normal life duration and quality to the given patient. The harmonization of CML disease characteristics, physician/clinic facilities and best clinical evidence is vital to reach this ultimate aim (2, 3). The disease characteristics in a given patient include CML disease risk, comorbidities, molecular profile, compliance, life style, and drug off-target risk profile. CML research evidence includes randomized clinical trials (RCT) indicating the data on the safety, efficacy, tolerability, toxicity, possible long-term adverse events and pharmacoeconomy of TKI. Clinical experience involves TKI availability, TKI reimbursability, drug experience, adherence, and monitorization facility. Critical decision making of TKI for CML should be reached via the optimization of those variables in every single CML patient (Figure 1) (3). The aim of this paper is to outline proper TKI treatment for the management of CML, which had been described in the WHO 2016 classification (3).

WHO 2016 DEFINITION OF CHRONIC MYELOID LEUKEMIA (CML)
The essential clinicopathological characteristics of the Ph*(+) CML in the latest WHO 2016 classification have been defined as follows (4);

Chronic phase (CP)- CML
This is the myeloproliferative neoplasm (MPN) characterized by the chromosomal translocation t(9;22) (q34.1;q11.2) resulting BCR-ABL1 fusion gene and formation of Philadelphia Chromosome (Ph*), which causes increase in blood granulocytes and bone marrow myeloid precursors as the major proliferative component. Cryptic and variant form Philadelphia chromosome as well as additional cytogenetic abnormalities (ACA) may complicate the disease pathobiology. Therefore, interphase fluorescence in situ hybridization (FISH), chromosome banding analysis, and PCR shall be integrated for the diagnosis and follow-up of CML (5, 6).

The disease is described in three main clinical phases which were significantly prognostic before the tyrosine kinase inhibitor (TKI) treatment era. Chronic phase (CP) as the initial phase. The disease progression is described in two phases as accelerated phase (AP) and Blastic phase (BP). Accelerated phase is characterized by 10-19% blasts in bone marrow or peripheral blood. The transformed BP criteria is examining more than 20% blasts either in the blood or in the bone marrow, or at the extramedullary sites (4).

Typical peripheral blood findings in CP-CML is characterized by increased neutrophils with the various early stage granulocytic precursors. The diagnosis needs to be proved by demonstrating the molecular abnormality BCR-ABL1 fusion. Typical bone marrow (BM) histopathology, is demonstrated in Figure 2 panels A-D.
The presence of t(9;22)(q34.1;q11.2) or BCR-ABL1 abnormality could be demonstrated by karyotype analysis, FISH or PCR based methods. The most reliable and sensitive method is real time PCR. This method is important and should be preferred especially for routine monitoring for the evaluation of the response to the TKI treatment (7).

Complete responders to TKI treatment are defined with <10x10⁹/L blood cell count, and <450x10⁹/L platelet count without any immature granulocytes in differentiation and nonpalpable spleen (4). The bone marrow features and cellular compositions are normal with the appearance of erythrocytic precursors. A case is demonstrated on Figure 2 panels E-H.

**Accelerated phase (AP)- CML**

Typical BM histopathology for AP was described before the TKI treatment era. Following the TKI era, the criteria is modified considering the therapy. The cases responded to the TKI treatment are characterized by normalization of the cellular composition of the bone marrow demonstrated in Figure 2 panels I-M. Abnormal megakaryocytes associated with marked reticulin or collagen fibrosis in accordance with the typical AP-CML could be present (Figure 2 panel K). The AP criteria are described below (4).

- The presence of t(9;22)(q34.1;q11.2) or BCR-ABL1 (via molecular biology or karyotype analyses) together with genomic cytogenetic evolution and/or TKI resistance
- Genomic evolution may include second Ph*, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or 3q26.2 abnormalities
- Persistent or increasing abnormal blood counts despite TKI treatment (leukocytosis (>10 X 10⁹/L), thrombocytosis (>1000 X 10⁹/L) or thrombocytopenia (<100 X 10⁹/L) unrelated to therapy, 20% or more basophils, 10-19% blasts).
- Persistent or increasing splenomegaly
- Occurrence of clinically significant driver mutations in BCR-ABL1 during TKI therapy (particularly T315I)
- Additional clonal chromosomal abnormalities such as trisomy 8 isochromosome 17q, trisomy 19 or any new entity complex karyotype, and 3q26.2 abnormalities or any new chromosomal abnormality in BCR-ABL fusion positive cells occur during TKI treatment are the accepted criteria.

There are also provisional response criteria to TKI treatment described in WHO 2016 classification. These are 1- Failure to achieve complete response to the TKI treatment or hematological resistance. 2- Any hematological, cytogenetic or molecular indications of resistance to TKI treatment. 3- Occurrence of two or more mutations in the BCR-ABL fusion gene during TKI therapy (4).

**Blastic phase (BP)- CML**

Typical BM histopathology, is presented on Figure 2 panels N-S with increased blastic infiltration in accordance with the typical BP-CML clinical presentation

- The presence of t(9;22)(q34.1;q11.2) or BCR-ABL1 (via molecular biology or karyotype analyses) together with genomic cytogenetic evolution and/or TKI resistance
- Genomic evolution may include second Ph* chromosome, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype, or 3q26.2 abnormalities
- The presence of at least 20% blasts in the peripheral blood and/or BM or the presence of extramedullary blastic infiltration in any organ or tissue.
• Persistent or increasing splenomegaly (4)

Frontline strategies in CML Patients

TKI drug treatment should be initiated as soon as possible in a newly diagnosed patient with CML. The aim of chronic TKI therapy in CML is the restoration of normal hematopoiesis instead of the neoplastic BCR-ABL1-induced myeloid neoplastic proliferation and the prevention of BCR-ABL1-associated genomic instability (8). Distinct TKI frontline strategy pathways may be chosen to obtain long-term treatment end-points in the personalized treatment of de novo CML. Patient age, CML risk (based on Sokal, Euro/ Hasford, EUTOS, ELTS scoring systems), comorbidities and long-term purpose of TKI treatment (mainly prevention of disease progression with life-long TKI drug administration or treatment-free remission) are the main cornerstones for deciding the frontline TKI strategy in CML (2, 9).

Pathway 1 (Imatinib as the frontline TKI for CML): The treatment of oral generic imatinib mesylate 400 mg daily can be prescribed to any patient with CML as the initial therapy. Switching to a second generation TKI may be considered in case of resistance or intolerance during the CML follow-up period. The rational aspects about following this path are pharmacoeconomy, better tolerability and less toxicity of imatinib with regard to 2nd generation TKIs. Furthermore, there is no difference of frontline dasatinib/ nilotinib/ bosutinib over imatinib in terms of survival (2).

Pathway 2 (Second generation TKI as the frontline drug for CML): Second generation TKIs (nilotinib, dasatinib, bosutinib) may be administered to the patients at high Sokal disease risk of CML for the prevention of disease progression and blastic crisis. The determination of disease risk may be defined via using Sokal, Euro/ Hasford, EUTOS, ELTS scoring systems (10). The rational of this path is the prevention of disease progression, occurrence of accelerated disease and blastic crisis in high risk patients. CML patients with higher percentage of blasts, basophils, eosinophils, with thrombocytosis, BM fibrosis and massive splenomegaly are candidates for frontline second generation TKI therapy (11). Relatively young CML patients representing the target subpopulation of ‘treatment-free remission’ (TFR) should also be selected for the frontline nilotinib or dasatinib approach. However, there is no overall survival advantage between frontline imatinib and second generation TKI approaches (12-14). Therefore, imatinib 400 mg treatment shall be chosen for the patients with drug/ disease-associated comorbidities, of which ‘treatment-free remission’ is not a target (2).

During the clinical practice, any TKI (imatinib, nilotinib, bosutinib or dasatinib) as the frontline therapy can be chosen with the optimization of their dosages with regard to the individual disease/ patient characteristics, life expectancies, lifestyles, and comorbidities. TKI dosages (for example; imatinib 300 vs. 400 vs. 600 mg; dasatinib 50 vs. 100 vs. 140 mg; nilotinib 600 vs. 800 mg; ponatinib 15 mg vs 30 mg; bosutinib 300 mg vs. 500 mg) could be tailored based on the tolerability, side effects and BCR-ABL1 level of CML. The doses of TKIs shall be adopted based on the phase of CML and the line of TKI therapy. Lower starting TKI doses for the sake of tolerability should be up-titrated to the standard doses in order to get hematological, cytogenetic, molecular responses with the observation of toxicity, compliance and tolerability. The rational of TFR path, i.e; frontline second generation TKI frontline, is to obtain faster and deeper molecular responses including MR4.5 for TKI drug cessations (14, 15). EURO-SKI trial had been performed in molecular responders of MR4 TKI-free long term remissions represent an advantage of survival without TKI toxicities, which may be named as the ‘functional cure’ (16). Although the greatest literature experience with TKI discontinuation
is with imatinib, the patients with two-year administration of 2nd generation TKI and a two-year duration of MR4.5 are ideal candidates for the TKI drug discontinuation (2, 16, 17).

The response to TKI drug treatment in the patient with CML must be monitored to check full hematological (CHR), complete cytogenetic (CCyR), and major molecular (MMR) remissions whatever the path had been chosen. The clinicobiological signs of normal hematopoiesis replacing Ph*(+) myeloid neoplasia shall be searched. Next generation molecular analyses (18) may be incorporated to the follow-up of CML patients to search genomic stability in a given disease. Current disease guidelines such ELN or NCCN require CHR within the first month, CCyR within the first year, and MMR within the 18 months of TKI therapy. BCR-ABL1 less than 10% within the three months just after TKI is a very good prognostic sign, named early molecular response (EMR). However, there is little evidence that switching to 2nd generation TKI in the absence of EMR might produce better disease outcome and prevention of disease progression (19, 20). Preliminary results of DASCERN study implied that CML patients without EMR to imatinib at 3 months who switched to dasatinib had a significantly increased rate of MMR at 12 months when compared to the patients receiving imatinib mesylate. Longer follow-up duration is certainly required to assess the impact of early switching of dasatinib at 3 months to the overall survival of patients (21).

Long-term adverse events associated with the chronic usage of TKI drugs described by ELN (22) represent an important emerging challenge in everyday clinical practice of CML. Side effects of TKIs are generally mild to moderate and easy-to-manage in mid-terms of CML therapy (22). Provisional discontinuation of the drug may be a choice in case of serious adverse events. Close attention should be paid to drug-drug interactions (23). Cardiovascular toxicity with ponatinib and nilotinib, pulmonary toxicity with dasatinib, and gastrointestinal/metabolic toxicities with bosutinib and nilotinib may require specific follow-up strategies for their early adverse event detection and proper clinical management (24). If properly managed, TKI therapies are well tolerated with improvement of the drug-related symptoms in due course with few dose reductions or short drug holidays (25).

Salvage strategies in CML Patients

Salvage strategy of CML mainly depends upon the alternative unused TKIs and allografting if all of the TKIs had been consumed with a T315I mutation. Decision making in multi-TKI resistant CML should rely on the type of first-line treatment, type of resistance (TKI mutation, TKI failure, TKI intolerance, TKI incompliance), phase of disease and transplant risk score of the patient. Before the consideration of TKI alteration during the life-time management of CML, drug dose adjustments, such as TKI dose decrements within adverse events and increments in the presence of insufficient BCR-ABL1 control, shall be performed. Optimal salvage therapeutic strategy of CML should avoid of both over- and under-treatment. CML Over-treatment may be described as aggressive clinical intervention. For instance; early/inappropriate decision of a very risky hematopoietic stem cell transplantation (HSCT) in a CML patient receiving a given 2nd generation TKI and exhibiting inadequate response, in which a third-generation TKI or dose increments would produce better outcome requires careful consideration. On the other hand, inability to detect relapse/ resistance follow-up warnings resulting in TKI failure and/or blastic crisis may be considered as an inappropriate management. ABL mutations of T315I, Y253H, E255K, E255V, F359V, F359C, F359I are poorly sensitive to nilotinib and T315I, T315A, F317L, F317V, F317I, F317C, V299L are the mutations poorly sensitive to dasatinib. Ponatinib is the only TKI for T315I before HSCT. The most
challenging situations in the patients CML are resistance to all available TKIs and cannot be transplanted, or recurring after HSCT especially into the blastic crisis (26). Fourth generation drug of asciminib, a specific TKI targeting the BCR-ABL1 myristoyl-binding site, an allosteric regulatory domain, and PF-114 Mesylate (27) have potential to treat patients with resistance to ATP-binding-site TKIs, including T315I (28, 29). CML leukemic stem cells expressing IL-1RAP can be targeted by CAR-T cells (chimeric antigen receptor-engineered T lymphocytes) (30). Manipulations of CML stem cell (31), neoplastic bone marrow niche trafficking control (32) and CRISPR/Cas9 system with nanocarriers (33) seem to be the future research areas in the field of CML therapy.
REFERENCES


**FIGURES AND FIGURE LEGENDS**

**Figure 1.** The harmonization of individual disease characteristics, the experience physician/clinic facilities and best clinical evidence is essential for clinical decision making in chronic myeloid leukemia (CML).
Figure 2. Bone marrow biopsy in the chronic phase (CP) CML is usually hypercellular with %100 cellularity (Panel A). The bone marrow cells are almost all
composed of mature granulocytes and their precursors (Panel B). Reticulin could be seen especially the cases with increased megakaryocytes, but usually do not increase (Panel C). Bone marrow aspirate is hypercellular composed of maturing granulocytic precursors with striking decrease in other precursors (Panel D). Cellularity decreases in the bone marrow of the responders of the TKI treatment (Panel E, F). The islands of erythroid precursors and megacaryocytes as well as the granulocytic series reflect the normal composition (Panel G). Aspirate smears can also reflect the normal cellular composition with the erythroid precursors (Panel H) (Green arrows).

**Accelerated phase (AP) CML** is characterized by increased blasts <10-19 and/or megakaryocytes (Panel I, J). Increase in megakaryocyte population promotes reticulin fibrosis (Panel K). The immunohistochemistry is helpful especially for demonstrating blasts by CD34 staining (Panel L). Blasts on the bone marrow aspirates are scattered between myeloid precursors (yellow arrows) (Panel M). The blasts are the dominant cellular component in the bone marrow of the **Blastic phase (BP) CML** (Panel N, P). Presence of strikingly increased in blasts could be demonstrated by CD34 immunohistochemistry (Panel R). On the bone marrow aspirate smears, blastic cells are also dominant (Panel S) (red arrows).