ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://indiancancerawarej.com

Indian Cancer Awareness Journal

How I Treat Case-Based Approach

Case-based Roundtable on Management Approach for Newly Diagnosed Chronic Myeloid Leukaemia (CML) Patients

Rajan Kapoor[1], Alpana Gupta[2], Abhishek Pathak[3]

[1]Department of Haematology, Command Hospital (Eastern Command), [2]Transfusion Centre, Eastern Command, [3]Department of Medical Oncology, Command Hospital, Kolkata, India.

***Corresponding author:**
Alpana Gupta,
Transfusion Centre, Eastern Command, Kolkata, India.

alpana.dr@gmail.com

Received : 20 December 2021
Accepted : 21 December 2021
Published : 23 March 2022

DOI
10.25259/ICAJ_9_2021

Quick Response Code:

ABSTRACT

Chronic myeloid leukaemia (CML) is one of the success stories in oncology care. The remarkable activity of tyrosine kinase inhibitors (TKIs) in CML has revolutionised the therapeutic landscape of this cancer which was uniformly fatal till a few decades back. However, with the availability of multiple TKIs, there is a need to have standard guidelines for their selection and optimal use in a particular patient.

Keywords: CML, BCR-ABL1, TKI

INTRODUCTION

Mrs. AK, a 32-year-old female during routine evaluation, was found to have splenomegaly (4 cm below the left coastal margin), leucocytosis, and basophilia with myelocyte peak. Molecular studies of peripheral blood revealed a BCR-ABL1 RT-qPCR result of 90% international scale (IS).

Chronic myeloid leukaemia (CML) is a form of myeloproliferative neoplasm which is characterised by unregulated production and proliferation of mature and maturing granulocyte series. It is often discovered during routine examination or evaluation of unrelated illness. Confirming the diagnosis is usually straightforward by performing molecular testing for BCR ABL1 fusion gene which is found in all cases. The question which arises is what minimal workup is to be done in all cases of CML at initial diagnosis. Recommended minimal workup in all cases of CML which not only establishes the diagnosis and prognosis but also assesses for the presence of comorbidities that may interfere with treatment at diagnosis is summarised in [Table 1].

At presentation, peripheral smear (PS) shows leucocytosis with a median leucocyte count of 100 × 10^9/L.[1] One of the hints toward the presence of CML is the finding of a greater percentage of myelocytes than meta-myelocytes ('myelocyte bulge').[2] As neutrophils in CML are cytochemically abnormal, finding of low leucocyte alkaline phosphatase score which can be performed on freshly made PS is useful to differentiate from leucocytosis or 'leukaemoid reaction' typically due to infections in which score is typically elevated or normal. Differential counts should be done manually in all cases as a percentage of PS blasts, basophils and eosinophils are not only clues toward diagnosis but also required for prognostication scores (see below).

Table 1: Recommended workup for newly diagnosed chronic myeloid leukaemia.

Laboratory test	Pathology and molecular	Imaging
Complete blood counts with differential counts	Peripheral smear examination	Chest X-ray
Comprehensive chemistry panel that includes liver enzymes, serum creatinine and serum calcium	Bone marrow aspirate and biopsy (for cellularity and fibrosis by reticulin staining)	ECG (particularly in patients planned for nilotinib therapy)
Blood sugars	Conventional cytogenetics Qualitative and real-time quantitative PCR for BCR ABL (RT-PCR)	

RT-PCR: Reverse transcription polymerase chain reaction

Bone marrow (BM) studies

Although BM evaluation is not required for establishing the diagnosis of CML, BM aspirate and biopsy at diagnosis are recommended for the following reasons:

a. Conventional karyotyping: At diagnosis, 10–12% of CML chronic phase (CP) have chromosomal abnormalities other than Ph chromosome, which have been clubbed under additional cytogenetic abnormalities (ACA). They have been subdivided into major and minor route ACA. The major route ACA such as trisomy 8, a second Ph, isochromosome 17q, or trisomy 19 have been associated with poor prognosis.[3] Newer studies have reemphasised the importance of carrying out conventional karyotyping at diagnosis.[4]
b. BM aspirate differential count is essential for determining the disease stage. PB and BM blasts between 10 and 19% are diagnostic of accelerated phase (AP) disease, while blasts over 20% are diagnostic of blast crisis.
c. Trephine biopsy is required to assess the degree of fibrosis which may be seen in up to 40% of patients at diagnosis.[5] The presence of fibrosis was considered to be the marker of AP; however, with the advent of tyrosine kinase inhibitors (TKIs), the prognostic significance of the degree of fibrosis at presentation is debatable.[6] Usually, patients with significant fibrosis do not tolerate higher doses of imatinib and there are reports of the development of BM fibrosis after prolonged imatinib therapy.[7]

Molecular diagnosis

Signature reciprocal translocation [(t9; 22) (q34:q11.2)] results in the generation of BCR ABL fusion transcript which is pathognomic of CML. Genetic testing for the Philadelphia chromosome, the BCR-ABL1 fusion gene, or the fusion mRNA gene product is done by conventional cytogenetic analysis (karyotyping), fluorescence *in situ* hybridisation (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR). The transcript generated from the BCR-ABL fusion gene is dependent on the site of breakage in BCR. PCR is the most sensitive technique and it is recommended that multiplex PCR which detects the presence of different transcripts (p210, p190, and p230) be done at initial diagnosis for all cases. We do not recommend FISH testing for diagnosing CML. Although not essential, it is recommended that quantification of BCR ABL1 transcripts according to the IS be done before initiation of TKI therapy as the kinetics of decline of these transcripts is emerging as an important decision-making tool.[8]

Prognostic scores

Various scoring systems have been devised to predict disease outcomes in CML. Sokal score which takes into account spleen size, PB blasts, age, and platelet counts is the most widely used prognostic too at presentation.[9] EUTOS long-term survival score (ELTS) was derived from survival data that reflect the treatment of CML with TKIs and it provides the best discrimination for the probability of CML-specific death.[10] We recommend that Sokal and ELTS scores be calculated and documented for all patients at presentation.

Case

Mrs. AK underwent BM examination and was found to have 100% Ph chromosomes on karyotyping. She fell into the 'low-risk' category as per Sokal scoring. She is concerned about treatment duration and wants to know the effect of the disease and its treatment on her future plans for pregnancy.

With the availability of multiple TKIs, there is a greater responsibility on physicians to discuss various treatment options with patients and their relatives and select the best TKI wisely. Imatinib changed the way CML is treated over the past two decades. Although the second- and third-generation TKIs are available in the market, imatinib remains the initial choice in the majority of patients and is the most cost-effective treatment option. Patients treated upfront with imatinib have probabilities of 65–70% for CCyR at 12 months, 50–55% for MMR at 2 years, and 45–50% for MR4 at 5 years.[11] In all of the randomised studies of imatinib versus a 2GTKI, it is clear that the 2GTKI induces deeper responses more rapidly than

imatinib and probably in a higher proportion of patients.[12,13] However, whether this translates into better survival rates has never been clearly shown in any of the studies. To summarise, if the goal is to attempt treatment-free remission (TFR) at the earliest, it is prudent to use the second-generation TKI at the onset for achieving faster and deeper molecular response.

CONSIDERATIONS FOR CHOICE OF FRONTLINE THERAPY

For the purpose of this review, only imatinib, dasatinib, and nilotinib will be discussed.

Patient-related factors

The decision to choose appropriate TKI is not straightforward due to a multitude of patient-related factors.

Age

A straightforward approach may be to attempt TFR from the beginning in young and fit by starting second-generation TKI and safe effective disease control in the elderly by the use of imatinib. However, on the one end, there is a paucity of data of the second-generation TKI in a very young and paediatric population, and on the other end, TFR is desirable in the elderly too because of multiple comorbidities.

Economic factors

Unless covered by insurance schemes, the second-generation TKIs are out of reach to most of our population. Even if there is an increased chance of TFR in the future by upfront use of the second-generation TKI, they cannot compete with imatinib in developing nations, which remain the only drug available to the majority of CML patients.

Prognostic scores

These scores remain the most precise tools which aid in the choice of TKI (see above). Sokal remains the most commonly used prognostic score. One of the drawbacks is that, on an individual basis, the score cannot predict that a patient with a low score at diagnosis will not develop progression or that a patient with a high score will not respond well to imatinib. Even with these shortcomings, high-risk Sokal patients derive maximum benefit from upfront second-generation TKI when compared to low- and intermediate-risk patients who do equally well with imatinib.[11]

Other factors

Patients with major route ACA at diagnosis are likely to do poorly, thereby making them candidates for upfront second-generation TKI.[14]

Drug-related factors

TKIs are associated with multiple adverse events largely due to the inhibition of off-target tyrosine kinases. Each of the drugs has a specific adverse event profile that should be known to prescribing physician when choosing first-line therapy. Imatinib is generally regarded as the safest of the TKIs, having been in use for more than 20 years, with no significant long-term irreversible adverse effects. In contrast, the newer generation TKIs have individual risk profiles with more serious complications, and data for long-term adverse events are not there. Major potentially life-threatening side effects of newer generation TKIs have been summarised in [Table 2].

Making the 'right' choice in clinical practice

Due to more than 2 decades of experience with imatinib and the wide availability of low-cost generics, it is hard to go wrong in choosing imatinib for all patients with CML-CP. However, approximately half of the patients treated initially with imatinib will have changed their drug at least once 8 years later and will presumably remain on their second or subsequent choice of drug for the rest of their lives.[11] In young patients who are desirous of TFR at the earliest, the second-generation TKIs would be a more attractive proposition. If decision-making is purely on 'biological grounds' and not on 'economic grounds,' the second-generation TKIs may be considered in certain indications which are summarised in [Table 3].

Case

Our patient, although in the low-risk category, would like to achieve TFR before contemplating pregnancy. As none of the TKIs are safe during pregnancy, drug cessation is paramount. Furthermore, her timeframe for conceiving is relatively

Table 2: Major adverse events attributed to the second-generation TKI.

TKI	Adverse event
Dasatinib	Pleural effusions[12]
	Pulmonary arterial hypertension[i]
	Haemorrhagic gastrointestinal colitis[ii]
Nilotinib	Peripheral arterial occlusive disease[13]
	Pancreatitis
	Prolonged QTc interval

TKI: Tyrosine kinase inhibitor.
[i]Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, *et al*. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128-37.
[ii]Nishiwaki S, Maeda M, Yamada M, Okuno S, Harada Y, Suzuki K, *et al*. Clinical efficacy of faecal occult blood test and colonoscopy for dasatinib-induced haemorrhagic colitis in CML patients. Blood 2017;129:126-8.

Table 3: Selected indications where the second-generation TKI may be used as upfront therapy at diagnosis of CML-CP.

1. High- risk Sokal category
2. Presence of ACA on conventional cytogenetics
3. Young patients where the goal of treatment is early TFR*

*This is not applicable to paediatric population where imatinib still remains drug of choice, TKI: Tyrosine kinase inhibitor, CML-CP: Chronic myeloid leukaemia-chronic phase , ACA: additional cytogenetic abnormalities

short; hence, either nilotinib or dasatinib would be a better option for her, with current evidence showing TFR success with second-line second-generation TKI.[15,16] This patient was switched to nilotinib and rapidly achieved MR4.5. She was able to attempt TFR within 2.5 years and has remained off therapy for over 12 months.

To summarise, with the availability of multiple TKIs, the decision to choose wisely has become very important for physicians managing CML patients. The final decision should be taken after a diligent assessment of the patient and his or her disease and comorbidities, a discussion regarding the risks and benefits of each drug, and a clear understanding regarding his or her personal treatment goals.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*., editors. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2008.
2. Spiers AS, Bain BJ, Turner JE. The peripheral blood in chronic granulocytic leukaemia. Study of 50 untreated Philadelphia-positive cases. Scand J Haematol 1977;18:25.
3. Guilhot F. Cytogenetics in CML: More important than you think. Blood 2016;127:2661-2.
4. Wang W, Cortes JE, Tang G, Khoury JD, Wang S, Bueso-Ramos CE, *et al*. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood 2016;127:2742-50.
5. Simsek TE, Eskazan AE, Cengiz M, Ar MC, Ekizoglu S, Salihoglu A, *et al*. Imatinib mesylate reduces bone marrow fibrosis and overwhelms the adverse prognostic impact of reticulin formation in patients with chronic myeloid leukemia. Blood 2015;126:2783.
6. Kantarjian HM, Bueso-Ramos CE, Talpaz M, O'Brien S, Giles F, Rios MB, *et al*. The degree of bone marrow fibrosis in chronic myelogenous leukemia is not a prognostic factor with imatinib mesylate therapy. Leuk Lymphoma 2005;46:993-7.
7. Shanmuganathan M, Branford S, Hughes TP, Hiwase D. Bone marrow fibrosis associated with long-term imatinib therapy: Resolution after switching to second-generation TKI. Blood Adv 2019;12:370-4.
8. Branford S, Yeung DT, Parker WT, Roberts ND, Purins L, Braley JA, *et al*. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. Blood 2014;124:511-8.
9. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, *et al*. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.
10. Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, *et al*. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016;30:48.
11. Claudiani S, Apperley JF. The argument for using imatinib in CML. Hematology Am Soc Hematol Educ Program 2018;2018:161-7.
12. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boqué C, *et al*. Final 5-year study results of DASISION: The dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. J Clin Oncol 2016;34:2333-40.
13. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, *et al*. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia 2016;30:1044-54.
14. Fabarius A, Leitner A, Hochhaus A, Müller MC, Hanfstein B, Haferlach C, *et al*. Impact of additional cytogenetic aberrations at diagnosis on prognosis of CML: Long-term observation of 1151 patients from the randomized CML Study IV. Blood 2011;118:6760-8.
15. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, *et al*. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: Results from the ENESTfreedom study. Leukemia 2017;31:1525-31.
16. Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, *et al*. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: Interim analysis of the STOP 2G-TKI study. Blood 2017;129:846-54.

How to cite this article: Kapoor R, Gupta A, Pathak A. Case-based roundtable on management approach for newly diagnosed chronic myeloid leukaemia (CML) patients. Indian Cancer Awareness J 2022;1:27-30.