The Role of Bosutinib in Chronic Myeloid Leukemia: An Indian Perspective

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Abstract

Management of chronic myeloid leukemia (CML) has been transformed by the use of tyrosine kinase inhibitors (TKIs). Presently in India, five TKIs are approved for the management of CML with distinct safety profiles. The selection of TKIs for chronic phase (CP)-CML patients is based on treatment goals, underlying comorbidities, and specific TKI toxicity profiles. Bosutinib is one of five TKIs indicated for the first-line treatment of CP-CML and patients with intolerance or resistance to prior TKI therapy. It possesses a distinct safety profile among other TKIs, with less cardiovascular adverse events (AEs), albeit the liver-related and gastrointestinal AEs have higher occurrence. The safety and efficacy of bosutinib have been examined in clinical trials; however, there is a paucity of data from Asia. A virtual expert panel meeting was convened to gather expert opinion from India on the selection of bosutinib as a treatment choice for patients with CP-CML. This is a white paper document drafted with the help of an expert panel of 14 oncologists and hematooncologists from India on bosutinib use in CP-CML. The experts concurred that bosutinib has proven efficacy for CP-CML in global randomized clinical trials and is well suited for CP-CML patients with existing cardiovascular comorbidities. However, it was not recommended for patients with gastrointestinal, pancreatic, or renal abnormalities. This review aims to put forth expert opinion and guidance document on key considerations for CP-CML clinical decision-making in India.

Keywords

- chronic myeloid leukemia
- India
- bosutinib
- tyrosine kinase inhibitors
- chronic phase

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Introduction

Chronic myeloid leukemia (CML), a myeloproliferative neoplasm, is characterized by an abnormal increase in circulating granulocytes as well as bone marrow myeloid precursors.[1,2] It is associated with Philadelphia chromosome (Ph+), a reciprocal translocation between a chromosome 9 gene–Abelson murine leukemia (ABL) and a chromosome 22 gene–breakpoint cluster region (BCR) (t[9;22][q34;q11]), forming the BCR–ABL fusion gene.[1,2] The disease presents itself in three stages—chronic phase (CP)-CML, accelerated phase (AP)-CML, and blast phase (BP)-CML. Majority of the patients are diagnosed during the CP-CML phase; however, untreated patients advance to the aggressive forms, AP-CML or BP-CML.[2–4] According to the American Cancer Society, CML constitutes 15% of the total leukemia cases.[3,5] According to a 2009 review, in India, the annual frequency of CML was estimated to be 0.8 to 2.2 per 100,000 population,[6] while a 2011 regional registry study results presented an age-adjusted rate (per 100,000) of 0.53 in females and 0.71 in males.[7] According to the 2018 Globocan survey, the incidence of leukemia in India was estimated to be 42,055 cases and the 5-year prevalence across all ages was 105,592 cases.[8]

The management of CML has been revolutionized by the use of tyrosine kinase inhibitors (TKIs) leading to the reduction in all-cause mortality rate and better long-term outcomes for patients with CML.[9] The TKIs approved for the management of CP-CML have varied safety profiles. The first-generation TKI-imatinib, second-generation TKIs-nilotinib, bosutinib, and dasatinib, and third-generation TKI ponatinib are the approved TKIs in India.[10,11] Bosutinib and ponatinib are the newest additions to the treatment armamentarium of CML.[12,13] The National Comprehensive Cancer Network (NCCN) guidelines recommend determining the risk status of patients with CP-CML using any relevant scoring system before initiating TKI therapy (►**Table 1**).[2] The choice of first-line therapy (bosutinib, imatinib, dasatinib, or nilotinib) for CP-CML is tailored according to the patient's risk profile and existing comorbidities. The ultimate treatment goal of TKI therapy is to achieve major molecular response (MMR) and possibly deep molecular response (DMR). The MMR is equivalent to a 3-log reduction ($\leq$0.1% BCR–ABL1 international scale [IS]) from the 100% baseline for untreated patients that includes molecular response [MR] 3, defined as $\geq$ a 3-log reduction in BCR–ABL1 transcripts from baseline.[14] While DMR is defined as BCR–ABL1 $<$0.01% IS[2] that includes MR 4/MR 4.5 defined as $\geq$ 4 or 4.5log reduction in BCR–ABL1 transcripts from baseline. Recent European LeukemiaNet recommendations 2020 highlight treatment-free remission (TFR) as a vital goal in CML. TFR can be achieved in CP-CML patients with a suitable response to first-line TKI with a duration of $>$5 years) and a DMR duration of over 2 years.[3]

Bosutinib Overview

Bosutinib presents BCR–ABL1 kinase inhibitor activity against BCR–ABL1 mutants, except V299L and T315I.[15] Bosutinib inhibits both Src and ABL tyrosine kinases.[16] Bosutinib can ablate BCR–ABL phosphorylation at low concentrations as compared with imatinib.[16] Food and Drug Administration (FDA) approved Bosutinib in 2012 for the treatment of adult patients with chronic, accelerated, or blast phase CML with intolerance or resistance to prior therapy. In 2017, the FDA approved bosutinib for newly diagnosed CP-CML patients.[12] Bosutinib is approved to treat patients with newly diagnosed CP-CML at a dose of 400 mg once daily (QD) and for CP, AP, or BP-CML patients with resistance/intolerance to prior therapy at a dose of 500 mg orally QD.[12]

Methods

A virtual expert panel meeting was convened involving 14 hematooncologists and medical oncologists from across India. All experts possess extensive hematooncology expertise in treating CML patients with approved TKIs. The expert opinion was derived from a moderator-initiated discussion with the panel of experts on bosutinib use in the treatment of CML. The experts discussed diverse topics on bosutinib such as treatment management, risk management, switch from other TKIs in first-line and second-line therapy, use in elderly and vulnerable population, use in patients with comorbidities, and TFR. The opinions gathered from the expert discussions are presented in this publication.

Treatment Decisions for Newly Diagnosed Chronic Myeloid Leukemia

The first-line TKI's approved for patients with CP-CML across all risk categories is Imatinib (400 mg daily), while the second-generation TKIs include dasatinib, 100 mg QD; nilotinib, 300 mg twice daily; and bosutinib, 400 mg daily.[17–19]

The experts discussed treatment initiation with second-generation TKIs, in patients with very recently diagnosed CP-CML in any of the risk groups (low risk, intermediate risk, or high-risk), AP-CML and BP-CML, and the choice of bosutinib in freshly diagnosed CP-CML patients.

With the accessibility to more potent TKIs, second-generation TKIs are preferably chosen for intermediate and high-risk CP-CML patients. The majority of the experts agreed that bosutinib could be the preferred TKI for intermediate and high-risk CP-CML. In BFORE trial, the MMR rate was higher with bosutinib than imatinib at 12 months (47.2 vs. 36.9%, respectively; $p = 0.02$), as was the cytogenetic response (CCyR rate) at 12 months (77.2 vs. 66.4%, respectively; $p = 0.0075$). Cumulative incidence was favorable with bosutinib (MMR: hazard ratio [HR], 1.34; $p = 0.0173$; CCyR: HR, 1.38; $p = 0.001$), with faster response times. Fewer patients experienced disease progression to BP-CML or AP-CML with bosutinib compared with imatinib (1.6 and 2.5%, respectively; ►**Table 2**).[19] Also, for patients with cardiovascular comorbidities (such as arrythmias, high blood cholesterol, coronary artery disease, and thrombosis), vascular abnormalities (such as pulmonary hypertension), and diabetes mellitus, bosutinib could be the preferred choice of TKI owing to its safety profile.[20,21] The panel of experts opined that for recently diagnosed CP-CML patients with existing

Table 1 Scoring systems and risk definitions

Scoring systems	Calculation	Low risk	Intermediate risk	High risk
SOKAL score	Exp $0.0116 \times (\text{age} - 43.4) + 0.0345 \times (\text{spleen size} - 7.51) + 0.188 \times [(\text{platelet count}/700)^2 - 0.563] + 0.0887 \times (\text{blood blasts} - 2.10)$	<0.8	0.8–1.2	>1.2
ELTS score	$0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen size} + 0.1052 \times \text{peripheral blood blasts} + 0.4104 \times (\text{platelet count}/1000)^{0.5}$	<1.5680	1.5680–2.2185	>2.2185
EUTOS score	$4 \times \text{Spleen size} + 7 \times \text{basophil count}$	≤87	NA	>87

Abbreviations: ELTS, European treatment and outcome study for CML long-term survival; EUTOS, European treatment and outcome study; Exp, exponential function.

Table 2 Comparison of treatment outcomes with first-line and second-line TKI therapy

Trial/Source	Tyrosine kinase inhibitors	Median follow-up (years)	Number (*n*)	Disease progression	Treatment outcomes			
					CCyR	MMR	PFS	OS
IRIS[50]	Imatinib 400 mg QD	11	553	7%	83%	–	92%	83%
DASISION[18]	Dasatinib 100 mg QD	5	259	5%	–	76%	85%	91%
	Imatinib 400 mg QD		260	7%	–	64%	86%	90%
ENESTnd[17]	Nilotinib 300 mg bid	5	282	4%	–	77%	92%	94%
	Nilotinib 400 mg bid		281	2%	–	77%	96%	96%
	Imatinib 400 mg QD		283	7%	–	60%	91%	92%
BFORE trial[19]	Bosutinib 400 mg QD	1	268	2%	77%	47%	–	–
	Imatinib 400 mg QD		268	3%	66%	37%	–	–
Shah et al[51]	Dasatinib 100 mg QD	7	Imatinib-R ($n = 124$)	–	–	43%	39%	63%
			Imatinib-I ($n = 43$)	–	–	55%	51%	70%
Giles et al[52]	Nilotinib 400 mg QD	4	Imatinib-R, $n = 226$; Imatinib-I, $n = 95$	–	45%	–	57%	78%
Cortes et al[53]	Bosutinib 400 mg QD	4	Imatinib and dasatinib-R ($n = 38$)	–	22%	–	–	67%
			Imatinib and dasatinib-I ($n = 50$)	–	40%	–	–	80%
			Imatinib and nilotinib-R ($n = 26$)	–	31%	–	–	87%

Abbreviations: CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukemia; I, intolerant; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; QD, once daily; R, resistance; TKI, tyrosine kinase inhibitor

renal toxicities (<30 mL/min/1.73 m^2), preexisting gastrointestinal disorders such as chronic gastritis, gastric ulcer, and inflammatory bowel disorders and with a history of pancreatitis, bosutinib may not be the preferred choice. Bosutinib has shown comparable efficacy with other second-generation TKIs,[22,23] and a better toxicity profile than dasatinib as exhibited in a recent study by Fachi et al.[24]

Switching to Bosutinib from Another Tyrosine Kinase Inhibitors

Treatment failure can occur due to point mutations in BCR–ABL1 kinase domain in CP-CML patients. The mutations E255K/V, F359V/I/C, and Y253F/H are sensitive to dasatinib/bosutinib, whereas the mutation F317L/V/I/C is sensitive to nilotinib/bosutinib; however, the T315I mutation is insensitive to all first and second-generation TKIs except ponatinib.[2,25–28] As per the NCCN guidelines, BCR–ABL kinase domain mutation analysis, drug interactions, and treatment compliance are recommended before initiating second-line TKI therapy.[2]

The experts concurred that switching of TKIs primarily occurs due to the development of drug-resistance, drug-intolerance, or suboptimal response. In a retrospective non-interventional study conducted in the hospitals of United

Kingdom and the Netherlands, 57% patients switched to bosutinib due to intolerance and 26% switched to bosutinib due to resistance to previous TKIs.[29] In a multicenter study in CML patients, the complete MR and MMR rates were 3.8 versus 27% for patients with imatinib and 41.5% versus 69% for patients switching to second-generation TKI, respectively, demonstrating increased chances of achieving DMR in switching to a second-generation TKI in CML patients demonstrating late suboptimal response with imatinib.[30] Development of nonhematological toxicities can also lead the physician to switch TKI. In a retrospective database study on CP-CML patients to assess toxicities with nilotinib and dasatinib, 29% patients experience treatment discontinuation owing to AEs (23%), disease progression (1%), or suboptimal response (2%).[31] AEs of grade 3 or 4 were observed in 54% on dasatinib and 22% of patients on nilotinib.[31] The most prevalent AEs with nilotinib were hyperbilirubinemia (47%) and Q-wave to T-wave (QT) interval prolongation (15%), whereas with dasatinib was pleural effusion.[31] Recent real-world and meta-analysis studies have shown that the new generation TKIs, dasatinib, nilotinib, and ponatinib pose a greater risk of cardiovascular toxicities than imatinib.[32–34] The experts agreed that BCR–ABL1 mutational status, the higher grade AEs, 1-log increase in BCR–ABL transcript level, and loss of MMR are reviewed while switching TKI.

The outcomes from a 2-year follow-up of a phase-I/II open-label study on bosutinib as a second-line TKI reported that 85% of patients achieved/maintained complete hematological response, 35% achieved MMR, and 59% achieved/maintained major cytogenetic response (MCyR), including 48% with CCyR. Moreover, the overall survival (OS) and progression-free survival (PFS) rates were 91 and 81%, respectively, after 2 years of treatment.[35] In another mature analysis of the phase-I/II open-label trial, which assessed factors that may influence long-term outcomes, BCR–ABL1 mutations were identified as a significant predictor of decreased OS (HR of 3.35).[36] In a comparison study of dasatinib, nilotinib, and bosutinib in second-line CML, bosutinib showed significantly greater PFS than dasatinib and nilotinib. In comparison to dasatinib, bosutinib resulted in HR for PFS and OS of 0.63 (0.44–0.90, $p < 0.05$) and 0.82 (0.54–1.26, $p = 0.37$), respectively, and an odds ratio (OR) for MCyR of 0.78 (0.53–1.16). However, in comparison with nilotinib, bosutinib demonstrated a significant HR of 0.54 (0.38–0.76, $p < 0.01$) in favor of bosutinib for PFS and a nonsignificant HR of 0.72 (0.46–1.13, $p = 0.16$) for OS (►**Table 2**).[37] Even in the advanced stages of CML (i.e., AP-CML or BP-CML), bosutinib has reported stable long-term efficacy and safety in patients experiencing prior treatment failure, as evident in the phase-I/II trial.[38] This trial indicated that 57 and 28% attained or maintained an overall hematologic response among AP-CML and BP-CML patients, and 40 and 37% attained or maintained MCyR by 4 years. The most commonly reported AEs were GI—low-grade diarrhea (any grade, 74%; maximum grade 1/2, 69%), while serious AEs occurred in 59% patients, most common being pneumonia (10%) and pyrexia (7%).[38]

Considering the switch to bosutinib from another TKI in second-line CP-CML, the experts agreed that loss of MMR, 1-log reduction in BCR–ABL percentage, or evolving BCR–ABL kinase mutations are the primary factors in switching to bosutinib from another TKI in second-line therapy. The experts highlighted that comorbidities and risk of potential AEs in the patient were also considered while choosing bosutinib over other TKIs.

Management of Adverse Events in Patients on Bosutinib

Skin rashes were reported in approximately 30% of the patients administered with bosutinib. However, they were usually short-lasting and well manageable. A study by Ault et al suggests comprehensive skincare and the use of topical agents, immunomodulatory agents, or systemic antibiotics for severe cases.[39] Diarrhea was reported as the most common AE in the Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial (67.7% patients),[20] BFORE trial (70.1% patients),[19] and in a recent real-world study on bosutinib (55% patients).[29]

Myelosuppression was comparable between bosutinib and imatinib arm in the BFORE trial (45.5 vs. 43.4%)[19] and BELA trial, where the incidence of thrombocytopenia was experienced in a similar percentage of patients (28 vs. 28%) as was the incidence of anemia (25 vs. 23%), while the incidence of neutropenia was lower in the bosutinib versus the imatinib arm (13 vs. 30%).[20] In the BFORE trial, musculoskeletal AEs were observed in fewer patients in the bosutinib arm (29.5%) than patients in imatinib arm (58.5%).[19]

Cardiac AEs (including atrial fibrillation, QT prolongation, and additional arrhythmias) were also comparable between the bosutinib arm and imatinib arm in BFORE trial with 5.2 versus 5.3% patients, respectively, and in phase-III BELA trial as 8 versus 6%, respectively.[19,20] After analysis of 4-year data from BELA trial, it was revealed that there is no increased risk of cardiovascular events with long-term bosutinib versus imatinib treatment.[20]

The experts concurred that diarrhea occurred early during bosutinib treatment, with the majority of patients experiencing transient, mild-to-moderate diarrhea. However, it is self-limiting in most cases and ceases to be a concern with time. In phase-II clinical trial results of bosutinib, only 10% of patients on bosutinib experienced grade 3/4 diarrhea, while others had mild (grade 1/2) diarrhea.[40] The practical management of bosutinib also suggests withholding bosutinib if a patient experience grade 3/4 diarrhea, that is, $\geq$7 stools/day during baseline/pretreatment until recovery to grade $\leq$1. Bosutinib can be resumed at 400 mg QD dose as patients recover to grade $\leq$1 diarrhea.[41]

The experts agreed that fewer cardiovascular AEs with bosutinib in trials and clinical experience may outweigh the safety concerns associated with bosutinib. Furthermore, the treatment regimen and dosage of bosutinib can be adjusted to manage the side effects. In routine clinical practice, bosutinib was either withdrawn for 2 weeks or the dose reduced by 100 mg when a patient experienced a hematological AE. The practical management of bosutinib also suggests withdrawing bosutinib when hematological AEs occur and resuming it at the same dose if patients recover

within 2 weeks. However, if the recovery takes more than 2 weeks, bosutinib dose must be reduced by 100 mg.[41,42] A phase-I/II study assessing the safety of bosutinib in the management of CML patients also reported toxicities such as alanine transaminase (ALT) elevations and lipase increases. However, these toxicities were successfully managed by treatment interruptions and dose reductions.[40] In hepatic toxicity, bosutinib is not withdrawn until the aspartate aminotransferase (AST) or ALT level increases by four to five times, and discontinued if the AST/ALT level increases further.[41,42]

According to experts, the renal profile of patients with CP-CML must be considered during treatment initiation and bosutinib dose must be recommended accordingly. Furthermore, the creatinine clearance level of the CP-CML patient should be regularly monitored during treatment. For creatinine clearance of 30 to 50 mL/min, a starting dose of 400 mg/d bosutinib is recommended, whereas for creatinine clearance <30 mL/min, it is 300 mg/d.[41]

Bosutinib in Patients with Underlying Comorbidities

Data suggest that patients diagnosed with CP-CML have at least one comorbidity during diagnosis. In an observational study conducted in patients with CP-CML, 78.1% patients had a Charlson comorbidity index (CCI) of 2. In comparison, 15.9% patients had a CCI of 3.[43] Most common comorbidities associated with patients with CP-CML were diabetes mellitus, peptic ulcer disease, peripheral vascular disease, liver impairment, renal insufficiency, myocardial infarction, tumors other than CML, cerebrovascular disease, or chronic pulmonary disease.[43,44] Accounting underlying comorbidities among patients with CP-CML at diagnosis is pivotal in therapy selection.

The experts agreed that bosutinib could be recommended for CP-CML patients with cardiovascular comorbidities, underlying diabetes, and pulmonary hypertension. They have observed positive outcomes in such patients with bosutinib use in routine clinical practice.

Bosutinib in Elderly and Vulnerable Population

CML is usually diagnosed at a median age of 57 to 60 years[45]; consequently, substantial proportion of patients with CML have achieved elderly status or are likely to achieve it during treatment. Increased age affects the OS of patients with CML. Bosutinib has proven effectiveness and favorable safety profile in elderly patients. In a retrospective real-world study of bosutinib use in 91 elderly (>65 years) patients with CP-CML, all grade hematological and extrahematological toxicities were reported in 13.1 and 49.4% patients, respectively, after 18.1 months median period of treatment.[46] Among the 86 elderly patients evaluable for response, approximately 4.6% achieved hematological response and 82.5% achieved CCyR (MCyR: 4.7%, CCyR: 77.9%).[46] Furthermore, bosutinib may be better tolerated at lower doses (300 mg QD) in elderly patients. In a prospective phase-II study in 63 elderly CML patients after intolerance/failure of first-line TKIs, bosutinib was initiated at a dose of 200 mg QD, increased to 300 mg QD after 3 months, and further to 400 mg QD in patients with BCR–ABL transcript >1%. Overall, 60% of the cohort achieved MR3 by 12 months, while 38 and 19% achieved MR4 and MR4.5, respectively.[47]

For younger patients, especially women, bosutinib which is a second-generation TKI may be preferred over imatinib, particularly because the achievement of a deep and rapid MR may allow eventual discontinuation of TKI therapy for fertility purpose. With the currently available management options for CP-CML, effective contraception is encouraged with all TKIs due to the risk of fetal complications with drug exposure in women of reproductive age. Overall, the experts agreed that bosutinib can be recommended for elderly patients, women of reproductive age, and patients with comorbidities such as cardiovascular disease, pulmonary hypertension, or diabetes mellitus.

Treatment-Free Remission with Bosutinib

In recent years, the treatment goals in CML have evolved, a group of patients successfully treated with TKI may experience a period of TFR. For patients with CML achieving DMR on TKI therapy, TFR is a safe treatment goal. TKI discontinuation involving imatinib, dasatinib, and nilotinib has been examined in recent studies, though there are limited data exploring TKI discontinuation with bosutinib. A U.S. study that evaluated the molecular recurrence of CML and patient-reported outcomes after discontinuation of TKI for patients in TFR at 6 months observed a moderate improvement in fatigue, diarrhea, and minimal increase in pain interference, while some patients reported substantial improvements in fatigue and diarrhea.[48] However, failing to achieve MR 4.5 before TKI discontinuation proved as a strong predictor of relapse with HR 40.23 in a single center study involving 15 patients with ponatinib/bosutinib discontinuation.[49]

The experts discussed their clinical experience with dasatinib and nilotinib and their opinion on the discontinuation of bosutinib once DMR is sustained for a certain period. The experts acknowledged that there is limited published literature on TFR with bosutinib and a pressing need for further research in this area. However, experts opined that based on NCCN guidelines, the data on TFR for other second-generation TKIs could be extrapolated for bosutinib.[2]

Conclusion

The article accentuates the unmet needs in CP-CML management in the country. The clinical opinions gathered from the participating experts may guide Indian oncologists in their day-to-day clinical decision-making for CP-CML. Bosutinib has a better safety and tolerability profile than other second-generation TKIs. Most AEs with bosutinib are low grade and controllable over time. Bosutinib has proven efficacy over imatinib in clinical trials and is an efficacious alternative for CP-CML patients in India. It emerged as a favored treatment of choice among the experts for CP-CML patients with underlying comorbidities and those at the risk of developing serious cardiac and pulmonary AEs.

Authors' Contributions

All authors adhered to the ICMJE authorship criteria. All authors reviewed and revised the manuscript for important intellectual content.

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Conflict of Interest

M.J.J. received grants from Viatris (Mylan) during the conduct of the study; he has also received grants from Novo Nordisk, Pfizer, Takeda, Grifols, Dr Reddy's Laboratory, Janssen and Janssen, and Mylan outside the submitted work. A.T.S. was an employee of Viatris (Mylan India) during the conduct of the study. N.R. is currently an employee of Viatris (Mylan India). A.T.S. was an employee of Viatris during the conduct of the study. M.J.J. reports grants from Viatris (Mylan), during the conduct of the study and others from Novonordisk, Pfizer, Takeda, Grifols, Dr Reddy's Laboratory, Janssen and Janssen, and Mylan, outside the submitted work. N.R. is an employee of Viatris that funded the study.

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References

1 Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–2405
2 Radich JP, Deininger M, Abboud CN, et al. Chronic Myeloid Leukemia, Version 1.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16(09):1108–1135
3 Hochhaus A, Saussele S, Rosti G, et al; ESMO Guidelines Committee. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28 (Suppl 4):iv41–iv51
4 Sawyers CL. Chronic myeloid leukemia. N Engl J Med 1999;340 (17):1330–1340
5 ACS. American Cancer Society; Chronic myeloid leukemia. Accessed August 26, 2020 at: https://www.cancer.org/cancer/chronic-myeloid-leukemia.html
6 Au WY, Caguioa PB, Chuah C, et al. Chronic myeloid leukemia in Asia. Int J Hematol 2009;89(01):14–23
7 Dikshit RP, Nagrani R, Yeole B, Koyande S, Banawali S. Changing trends of chronic myeloid leukemia in greater Mumbai, India over a period of 30 years. Indian J Med Paediatr Oncol 2011;32(02): 96–100
8 WHO. World Health Organization; International Agency for Research on cancer; India Source: Globocan 2018. 2018. Accessed October 01, 2020, at: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
9 Kennedy JA, Hobbs G. Tyrosine kinase inhibitors in the treatment of chronic-phase CML: strategies for frontline decision-making. Curr Hematol Malig Rep 2018;13(03):202–211
10 Ganesan P, Kumar L. Chronic myeloid leukemia in India. J Glob Oncol 2016;3(01):64–71
11 Yanamandra U, Malhotra P. CML in India: are we there yet? Indian J Hematol Blood Transfus 2019;35(01):1–2
12 Labs P. BOSULIF® (bosutinib) tablets, Prescribing Information. 2017. Accessed August 10, 2022, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203341s009lbl.pdf
13 USFDA. ARIAD Pharmaceuticals, Inc. ICLUSIG® (ponatinib) tablets for oral use 2012. Accessed October 01, 2020, at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf
14 Hughes TP, Kaeda J, Branford S, et al; International Randomised Study of Interferon versus STI571 (IRIS) Study Group. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349(15):1423–1432
15 Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol 2009;27(03):469–471
16 Steinbach A, Clark SM, Clemmons AB. Bosutinib: a novel src/abl kinase inhibitor for chronic myelogenous leukemia. J Adv Pract Oncol 2013;4(06):451–455
17 Hochhaus A, Saglio G, Hughes TP, 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(05):1044–1054
18 Cortes JE, Saglio G, Kantarjian HM, 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(20):2333–2340
19 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 (03):231–237
20 Cortes JE, Kim D-W, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol 2012;30(28): 3486–3492
21 Smith G, Apperley J, Milojkovic D, et al; British Society for Haematology. A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia. Br J Haematol 2020;191(02):171–193
22 Chen K-K, Du T-F, Wu K-S, Yang W. First-line treatment strategies for newly diagnosed chronic myeloid leukemia: a network meta-analysis. Cancer Manag Res 2018;10:3891–3910
23 Fachi MM, Tonin FS, Leonart LP, et al. Comparative efficacy and safety of tyrosine kinase inhibitors for chronic myeloid leukaemia: a systematic review and network meta-analysis. Eur J Cancer 2018;104:9–20
24 Fachi MM, Tonin FS, Leonart LP, Rotta I, Fernandez-Llimos F, Pontarolo R. Haematological adverse events associated with tyrosine kinase inhibitors in chronic myeloid leukaemia: a network meta-analysis. Br J Clin Pharmacol 2019;85(10):2280–2291
25 Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J Clin Oncol 2009;27(25): 4204–4210
26 Müller MC, Cortes JE, Kim D-W, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. Blood 2009;114 (24):4944–4953
27 Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118(17):4567–4576
28 O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 2009;16(05):401–412
29 Apperley JF, Byrne JL, Smith G, et al. The real world use of bosutinib in patients with chronic myeloid leukaemia. Blood 2016;128(22):5435–5435

30 Garcia-Gutierrez JV, Maestro BA, Casado LF, et al. Switching to a second generation TKI in chronic myeloid leukemia patients with late suboptimal response with imatinib obtained better molecular responses that the "watch and wait" approach. an experience of a multicenter registry in patients outside clinical trials. Blood 2012;120(21):3768–3768
31 Suh KJ, Lee JY, Shin DY, et al. Analysis of adverse events associated with dasatinib and nilotinib treatments in chronic-phase chronic myeloid leukemia patients outside clinical trials. Int J Hematol 2017;106(02):229–239
32 Haguet H, Douxfils J, Mullier F, Chatelain C, Graux C, Dogné JM. Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis. Expert Opin Drug Saf 2017;16(01):5–12
33 Novo G, Di Lisi D, Bronte E, et al. Cardiovascular toxicity in cancer patients treated with tyrosine kinase inhibitors: a real-world single-center experience. Oncology 2020;98(07):445–451
34 Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné JM. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. JAMA Oncol 2016;2(05):625–632
35 Gambacorti-Passerini C, Brümmendorf TH, Kim D-W, et al. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: minimum 24-month follow-up. Am J Hematol 2014;89(07):732–742
36 Brümmendorf TH, Cortes JE, Khoury HJ, et al. Factors influencing long-term efficacy and tolerability of bosutinib in chronic phase chronic myeloid leukaemia resistant or intolerant to imatinib. Br J Haematol 2016;172(01):97–110
37 Cortes JE, Muresan B, Mamolo C, et al. Matching-adjusted indirect comparison of bosutinib, dasatinib and nilotinib effect on survival and major cytogenetic response in treatment of second-line chronic phase chronic myeloid leukemia. Curr Med Res Opin 2019;35(09):1615–1622
38 Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am J Hematol 2015;90(09):755–768
39 Ault PS, Rose PharmD J, Nodzon PhD LA, Kaled ES. Bosutinib therapy in patients with chronic myeloid leukemia: practical considerations for management of side effects. J Adv Pract Oncol 2016;7(02):160–175
40 Kantarjian HM, Cortes JE, Kim DW, et al. Bosutinib safety and management of toxicity in leukemia patients with resistance or intolerance to imatinib and other tyrosine kinase inhibitors. Blood 2014;123(09):1309–1318
41 Khoury HJ, Gambacorti-Passerini C, Brümmendorf TH. Practical management of toxicities associated with bosutinib in patients with Philadelphia chromosome-positive chronic myeloid leukemia. Ann Oncol 2018;29(03):578–587
42 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(01):143–143
43 Ono T, Takahashi N, Kizaki M, et al. Prognostic effect of comorbidities in patients with chronic myeloid leukemia treated with a tyrosine kinase inhibitor. Cancer Sci 2020;111(10):3714–3725
44 Saussele S, Krauss M-P, Hehlmann R, et al; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and the German CML Study Group. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood 2015;126(01):42–49
45 Höglund M, Sandin F, Simonsson B. Epidemiology of chronic myeloid leukaemia: an update. Ann Hematol 2015;94(2, Suppl 2):S241–S247
46 Latagliata R, Attolico I, Trawinska MM, et al. Bosutinib in the real-life treatment of chronic phase chronic myeloid leukemia (CML) patients aged >65 years resistant/intolerant to frontline tyrosine-kynase inhibitors. Blood 2019;134(Supplement_1):1649–1649
47 Castagnetti F, Gugliotta G, Bocchia M, et al. Dose optimization in elderly CML patients treated with bosutinib after intolerance or failure of first-line tyrosine kinase inhibitors. Blood 2019;134 (Supplement_1):496–496
48 Flynn KE, Weinfurt KP, Lin L, et al. Patient-reported outcome results from the U.S. life after stopping TKIs (LAST) study in patients with chronic myeloid leukemia. Blood 2019;134 (Supplement_1):705–705
49 Alfayez M, Kantarjian HM, Kadia TM, et al. Ponatinib and bosutinib discontinuation in chronic myeloid leukemia (CML): single center experience. Blood 2018;132(Supplement 1):5447–5447
50 Hochhaus A, Larson RA, Guilhot F, et al; IRIS Investigators. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376(10):917–927
51 Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180–034. 2016;91(09):869–874
52 Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. Leukemia 2013;27(01):107–112
53 Cortes JE, Khoury HJ, Kantarjian HM, et al. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol 2016;91(12): 1206–1214