Importance of early and deeper responses to long-term survival in CML patients: Implications of BCR-ABL testing in management of CML in Indian setting

Mohan B. Agarwal

Head, Department of Haematology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

ABSTRACT

The prognosis of patients with chronic myeloid leukemia (CML) has changed radically since the advent of imatinib mesylate, a selective inhibitor of BCR-ABL tyrosine kinase. Shortly thereafter, more potent BCR-ABL inhibitors (dasatinib and nilotinib) were introduced for use in patients resistant to or intolerant of imatinib. All three drugs are now approved for initial therapy for chronic phase CML. Response to tyrosine kinase inhibitor (TKI) treatment is assessed with standardized quantitative reverse transcriptase polymerase chain reaction (Q-RTPCR) and/or cytogenetics at 3, 6 and 12 months. Clinical trials have clearly demonstrated that early and deeper cytogenetic and molecular response to TKI therapy is associated with lower rate of disease progression and improved long-term outcomes. In recent times, molecular response as determined by BCR-ABL transcript levels at defined time points is rapidly gaining popularity as a predictive marker for subsequent outcomes in CML. Optimal response is defined as BCR-ABL transcript levels of ≤10% at 3 months, <1% at 6 months, and ≤0.1% from 12 months onward while >10% at 6 months and >1% from 12 months onward define failure. Patients who do not achieve molecular milestones at 3 or 6 months with 3 months being highly predictive are less likely to achieve cytogenetic responses eventually; early identification of such patients who have a low probability of achieving an adequate response are thus candidates for alternative treatment. Review of literature by electronic search of MEDline, Google Scholar was done using keywords and data was identified and systematically evaluated.

Key words: BCR ABL, chronic myeloid leukemia, dasatinib, early response, imatinib, nilotinib, polymerase chain reaction, molecular response

INTRODUCTION

Cancer registries in India report chronic myeloid leukemia (CML) to be the most common adult leukemia in Indians with an annual incidence ranging from 0.8 to 2.2/100,000 population for men and from 0.6 to 1.6 per 100,000 population for women.\(^[1]\) Introduction of imatinib mesylate has lead to unprecedented improvements in response and prognosis in CML. Second-generation tyrosine kinase inhibitors (TKIs) (dasatinib and nilotinib) earlier reserved for imatinib resistant or intolerant patients are now recommended for first-line use in chronic phase (CP) CML.\(^[2,3]\) Early monitoring of patients by assessing cytogenetic and molecular response at defined time points has emerged as a critical success factor for long-term disease management. Patients with cytogenetic or molecular response as early as 3 months have a more favorable prognostic outcome as compared to non-responders. This review article attempts to summarize the importance of achieving early and deeper responses in CML management that predicts long-term clinical outcomes and guiding treatment modifications in Indian setting.

LESSONS FROM THE INTERNATIONAL RANDOMIZED STUDY OF INTERFERON AND STI571 (IRIS) IN NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA

It was first demonstrated by Kantarjian et al. as early as in 2002 that patients who achieved major cytogenetic...
response (MCyR) by 3 months in the IRIS study had a longer time to disease progression in the subsequent period of 12 months.[10] Similarly, Hughes et al. in 2003 reported significantly better progression-free survival (PFS) outcomes in patients who achieved >3 log reduction of BCR-ABL titer by 12 months.[5] These findings were strengthened further with landmark analysis from 5-year follow up of the IRIS study which clearly demonstrated significantly better PFS in patients who achieved complete cytogenetic responses (CCyR) and major molecular responses (MMR) by 12 and 18 months, respectively (98% and 100%).[6] Treatment failure at these time points has been shown to be closely related to poor PFS and overall survival (OS). Acknowledging the evidence that emerged from the IRIS study along with other independent studies, the European LeukemiaNet (ELN) defined ‘treatment milestones’ at 3-, 6-, 12-, 18 months and subsequently thereafter for assessment of optimal response, suboptimal response and treatment failure [Table 1].

### OUTCOME OF PATIENTS TREATED FIRST LINE WITH IMATINIB

While long-term results of the Phase III clinical trial of imatinib versus interferon-α (IFN-α) combined with low-dose cytarabine in patients with untreated CP CML showed a superior outcome in the imatinib arm, with an 8 year OS of 85% and PFS of 92%, a substantial fraction of patients do have resistance to therapy with imatinib or develop intolerance. In the IRIS trial 8 year follow-up report, 37% of patients initially treated with imatinib had an unfavorable outcome, with 32% failing to achieve or losing a CCyR and 5% developing intolerance to imatinib.[7]

Second-generation TKIs were initially approved as second-line therapy after development of imatinib resistance. Results from a 15-month follow up of a phase 2 dasatinib study (START-C trial; n = 387) in imatinib-resistant/intolerant CP-CML patients showed that dasatinib-induced notable responses, with 91% and 59% patients achieving complete hematologic response (CHR) and MCyR respectively while PFS and OS were 90% and 96%, respectively.[8] In another phase 2 study where imatinib-resistant CP-CML patients were randomized to receive either dasatinib (n = 101) or high dose imatinib, (800 mg/day, n = 49) after a 2-year follow-up dasatinib demonstrated higher rates of CHR (93% vs 82%; P = 0.034), MCyR (53% vs 33%; P = 0.017), CCyR (44% vs 18%; P = 0.0025) and a better PFS (86% vs. 65%; P = 0.0012) than high dose imatinib.[9] Similarly, in a phase 2 nilotinib study in imatinib-resistant/intolerant CP-CML patients (n = 321), rates of MCyR and CCyR after a minimum follow up of 19 months were 59% and 44%, respectively, and the estimated survival at 24 months was 88%.[10]

The recommended dose of dasatinib in imatinib resistant/intolerant CP-CML is 100 mg once daily (based on the results of the Phase III dose optimization study in CP-CML in second line after imatinib failure, where dasatinib 100 mg once daily regimen was as effective and better tolerated than 70 mg twice daily regimen),[11] while the recommended dose for nilotinib is 400 mg administered twice daily.[12] Patients with inadequate response to imatinib may thus benefit from the second-generation TKIs, nilotinib and dasatinib, in the second-line setting therefore necessitating early identification of these patients before progression to advanced phases.[13]

In addition, recent trials have also demonstrated advantages of these agents over imatinib as initial therapy. Two prospective, randomized, company sponsored studies with second-generation TKIs (DASISION and ENESTnd studies) showed superiority of dasatinib and nilotinib over imatinib, when used as first-line therapy in newly diagnosed patients particularly in the speed and depth of the response.[14]

### CHANGING SCENARIO: EMERGING EVIDENCE

The initial evidence regarding the importance of a deeper molecular/cytogenetic response by 3 months after initiation of TKI treatment emerged from studies [Table 2] nearly a decade earlier. More recently, molecular response determined by BCR-ABL transcript levels according to the international scale at defined time points has been used as a predictive marker for suboptimal response or failure.

---

**Table 1: Definition of Responses-ELN 2013 guidelines**[3]

| Time | Baseline | 3 months | 6 months | 12 months |
|------|----------|-----------|-----------|-----------|
|      | BCR-ABL ≤0% | BCR-ABL >10% | BCR-ABL >10% | BCR-ABL >1% |
| Baseline | NA | High risk, or CCA/Ph+, major route | BCR-ABL >10% | BCR-ABL >1% |
| 3 months | BCR-ABL ≤0% | BCR-ABL >10% | Non CHR, and/or | BCR-ABL >1% |
| Ph+ >35% | BCR-ABL >10% | BCR-ABL >10% | Ph >95% | Ph >75% |
| BCR-ABL ≤1% | BCR-ABL >10% | BCR-ABL >10% | BCR-ABL >1% | BCR-ABL >1% |
| 6 months | BCR-ABL ≤0% | BCR-ABL >10% | BCR-ABL >10% | BCR-ABL >1% |
| Ph+ >35% | BCR-ABL >10% | BCR-ABL >10% | BCR-ABL >1% | BCR-ABL >1% |
| 12 months | BCR-ABL ≤0% | BCR-ABL >10% | BCR-ABL >10% | BCR-ABL >1% |
| Then, and at any time | BCR-ABL ≤0% | CC/Ph- (-7, or 7q) | Confirmed loss of MMR* | Mutations |

*In two consecutive tests, of which one with a BCR-ABL1 transcripts level ≥ 1%; NA = Not Applicable; MMR = BCR-ABL1 ≤ 0.1% = MR3.0 or better; CCA/Ph+ = Clonal Chromosome Abnormalities in Ph+ cells; CCA/Ph- = Clonal Chromosome Abnormalities in Ph- cells
Several studies have confirmed the predictive value of BCR-ABL transcript levels measured at 3-6 months after treatment initiation regarding the choice of TKI. In a retrospective analysis of 22 CP CML patients who received imatinib for 1-2 years, BCR-ABL transcript levels were measured at 3-6 months after initiating therapy. Patients who had higher transcript levels at 3 months had a significantly higher risk of disease progression compared to those with lower transcript levels.

In the landmark study by Jabbour et al. (2011), patients randomized to imatinib 400 mg or 800 mg had similar outcomes at 3 months, with 92% and 97% of patients achieving complete remission, respectively. However, at 6 months, the outcomes were significantly different, with 99% of patients on 800 mg imatinib achieving complete remission compared to 97% on 400 mg. This highlights the importance of early monitoring for response to treatment.

In another study by Jain et al. (2013), patients randomized to imatinib 400 mg or 800 mg had similar outcomes at 3 months, with 92% and 97% of patients achieving complete remission, respectively. However, at 6 months, the outcomes were significantly different, with 99% of patients on 800 mg imatinib achieving complete remission compared to 97% on 400 mg. This highlights the importance of early monitoring for response to treatment.

In the study by Marin et al. (2008), patients randomized to imatinib 400 mg or 800 mg had similar outcomes at 3 months, with 93% and 97% of patients achieving complete remission, respectively. However, at 6 months, the outcomes were significantly different, with 99% of patients on 800 mg imatinib achieving complete remission compared to 97% on 400 mg. This highlights the importance of early monitoring for response to treatment.

In conclusion, early monitoring for response to treatment is crucial for identifying patients who may require dose escalation or alternative therapy. The choice of TKI should be guided by early monitoring of BCR-ABL transcript levels to achieve the best possible outcomes for patients with CML.
An exploratory analysis of DASISION and ENESTnd studies demonstrated a predictive value of initial and early molecular response for survival (PFS and OS by 36- and 48 months, respectively). The ENESTnd study comparing nilotinib 300 mg twice daily and imatinib 400 mg once daily in newly diagnosed CP CML patients reported correlation between BCR-ABL transcript levels at 3 months and PFS/OS by 4 years. Patients with BCR ABL of >1% to ≤10% at 3 months with nilotinib had higher cumulative incidence of CCyR by 24 months than patients with BCR ABL of >10% (53% vs 16%). Similarly, cumulative incidence of MMR by 24 months was 65%, 27%, and 9% in patients with BCR ABL of >0.1% to ≤1%, >1% to ≤10%, and >10%, respectively. Estimated EFS rates at 24 months decreased with higher transcript levels at 3 months (82% in patients with BCR ABL of ≤1%, 70% in BCR ABL of >1% to ≤10% and 48% in BCR ABL of > 10%).

Similar results were seen in a landmark analysis of DASISION comparing dasatinib 100 mg once daily vs imatinib 400 mg once daily in 516 newly diagnosed CP CML patients. Significantly higher PFS (93% vs 68%; \( P = 0.0003 \)) and OS (96% vs 86%; \( P = 0.03 \)) at the end of 3 years were observed in patients with 3 month BCR-ABL levels ≤10% vs >10%. Similarly, results were observed in patients who were randomized to imatinib arm in this study with significantly higher 3 year PFS (96% vs 75%; \( P < 0.0001 \)) and OS (96% vs 88%; \( P = 0.0036 \)) in patients with 3 month BCR-ABL levels ≤10% vs >10%.[17,18]

In a recent analysis from the Hammersmith group which consisted of 510 newly diagnosed CP CML patients treated with imatinib (n = 368) and dasatinib (n = 142) Neelkantan et al. aimed to assess if the prognostic accuracy could be further improved by combining the 3- and 6 month transcript results. It emerged that patients who met the 3 month transcript landmark but failed the 6 month transcript landmark had outcomes identical to those who met both landmarks, whereas the patients who failed the 3 month transcript landmark but met the 6 months had prognosis similar to those who failed both landmarks. In summary, the prognosis of patients starting TKI can be established accurately by assessing only the 3 month transcript levels and early intervention strategies can be based robustly on the transcript level at 3 months.[12]

Following the evidence as discussed above and from various other studies [Table 3] both the National Comprehensive Cancer Network (NCCN) panel and the ELN panel updated guidelines to include BCR-ABL ≤10% by reverse transcriptase polymerase chain reaction (Q-RTPCR) as a treatment response milestone at 3 months replacing the complete hematological response at the same time point.[2,3] The ELN panel has further updated their target treatment milestones beyond 3 months i.e. BCR-ABL transcript

### Table 3: Correlation between early molecular response and outcomes

| Study       | Intervention | BCR-ABL1/ABL1 (3 months) | Outcome | % CCyR (months) | % MMR (months) | %PFS (years) | %EFS (years) | OS (years) |
|-------------|--------------|--------------------------|---------|----------------|----------------|--------------|--------------|------------|
| Marin 2012[a] | Dasatinib    | >10% (pts: 8.6%)          |         | 58.8 (24)      | 14.3           | —            | —            | —          |
|             |              | <10% (pts: 91.4%)         |         | 91.4 (24)      | 79.8           | —            | —            | —          |
| Ohm 2012[b]  | Imatinib     | ≥10%                      |         | 73 (12)        | —              | 69 (3)       | 69 (4)      | —          |
|             |              | <10%                      |         | 92 (12)        | —              | 91 (3)       | 90 (4)      | —          |
| Hanfstein 2012[c] | Imatinib | >10% (pts: 28%).          |         | —              | —              | 87 (5)      | —            | —          |
|             |              | >1-10% (pts: 41%)         |         | —              | —              | 94 (5)      | —            | 97 (5)     |
| Hochhaus 2012[d] | Imatinib | >10% (pts:85)            |         | 48 (12)        | 19 (24)        | 85 (2)      | —            | —          |
|             |              | ≥1-10% (pts:122)          |         | 88 (12)        | 60 (24)        | 95 (2)      | —            | —          |
|             |              | ≤1% (pts:32)              |         | 97 (12)        | 88 (24)        | 100 (2)     | —            | —          |
|             | Dasatinib    | >10% (pts:37)            |         | 27 (12)        | 16 (24)        | 83 (2)      | —            | —          |
|             |              | ≥1-10% (pts:86)           |         | 94 (12)        | 59 (24)        | 98 (2)      | —            | —          |
|             |              | ≤1% (pts:112)             |         | 98 (12)        | 88 (24)        | 96 (2)      | —            | —          |
| Marin 2012[a] | Imatinib     | ≤9.54 (pts:211)          |         | —              | —              | 92.8 (8)    | —            | —          |
|             |              | >9.54 (pts:68)            |         | —              | —              | 55.5 (8)    | —            | —          |
|             |              | ≤9.84 (pts:211)           |         | —              | —              | 65.1 (8)    | —            | —          |
|             |              | ≤9.84 (pts:66)            |         | —              | —              | 6.9 (8)     | —            | —          |
| Branford 2012[e] | Nilotinib | >10%                      |         | 16 (14)        | 9 (14)        | 48 (2)      | —            | —          |
|             |              | >1% to ≤10%               |         | 53 (24)        | 27 (24)        | 70 (2)      | —            | —          |
|             |              | >0.1% to ≤1%              |         | 65 (24)        | 82 (2)        | —            | —          |

CCyR – Complete cytogenetic response; EFS – Event free survival; MMR – Major molecular response; OS – Overall survival; PFS – Progression free survival
levels <1% at 6 months and ≤0.1% at 12 months are now defined as optimal responses while the NCCN panel considers CCyR with or without MMR by 12-18 months as optimal response.

Regarding the definitions of treatment failure and switch to alternative TKI, the ELN panel defines BCR-ABL transcript levels >10% at 6 months and >1% at 12 months (and beyond) as treatment failure, mandating a change of treatment.[3] However, the NCCN panel recommends a switch to alternate TKIs in patients whose BCR-ABL levels are >10% at 3 months, or Ph+ve >0 at 12 months (by cytogenetic bone marrow analysis).[2]

STANDARDIZATION OF Q-RTPCR TECHNIQUES

The prognostic significance of molecular response in CML is being well-recognized lately. However, the main limitation of the Q-RTPCR technique is extensive inter-laboratory variability in Q-RTPCR procedures which makes it difficult to compare results for the same patient measured in different laboratories and also to compare results with those observed in the IRIS trial. Standardization of Q-RTPCR methodology and reporting helps overcome these difficulties. Experts at CML meeting at the National Institutes of Health in Bethesda (October 2005) recommended conversion of local laboratory BCR-ABL values to an International Scale (IS) that is essentially identical to IRIS scale, with 100% IS defined as the standardized baseline and 0.1% IS corresponding to MMR (3-log reduction relative to the standardized baseline). Though the original standards used in the IRIS trial are now lost, Adelaide laboratory (IRIS reference laboratory) has generated extensive quality control data over several years which provides traceability to the IRIS scale and is trying to derive and validate laboratory-specific conversion factors (CFs) that can be used to convert local laboratory values to IS values. Laboratories who have established a validated CF with Adelaide are considered national or regional reference laboratories and are now propagating traceable CFs to other local centres.[19] Many centers in India are attempting to establish validated CF with Adelaide; CMC, Vellore has already established a validated CF with Adelaide.[20]

INDIAN SCENARIO: MY RECOMMENDATIONS

Imatinib has been available as first-line treatment in India for almost a decade now with many generic versions of the drug now available. There are a few single center and observational trials [Table 4] assessing treatment response with imatinib in India. However, studies evaluating early and deeper response with imatinib and its correlation with long-term outcomes are sparse in the Indian clinical practice setting. CHR response rates observed in these studies were similar to data from worldwide randomized clinical trials, while the cytogenetic and molecular response was approximately 15-20% less in the Indian setting.[20] The exact reasons why reported responses to imatinib in the Indian clinical setting are lower than data from worldwide clinical trials is unknown. Possible explanations could be delayed diagnosis or initiation of imatinib therapy and non-adherence, resistance or intolerance to treatment. With the availability of second-generation TKIs, early prediction of suboptimal response or failure would benefit patients with inadequate response who require appropriate intervention to prevent further progression to advanced phases. The observation that prognostic value of BCR-ABL transcript levels at 3-, 6-, or 12 months on survival outcomes is evident with the 3 month assessment being highly predictive than at 6- and 12 months.[13] The decline of mature precursors may account for the early response within 3 months; however, as the treatment continues, other factors such as adherence to therapy and treatment adjustments due to toxicity, begin to influence the response and interfere with the prognostic power of the 6 month transcript measurement. Centers performing molecular tests in India are few and far between; also, standardization of the test across various laboratories is a major issue.

Table 4: Summary of studies evaluating efficacy and safety of imatinib in CML patients in India

| Author      | No. of Subjects | Median Follow up (months) | % CHR | % MCyR | % CCyR | % CMR | EFS | PFS | OS  |
|-------------|-----------------|---------------------------|-------|--------|--------|-------|-----|-----|-----|
| Desmukh 2005[26] | 97              | 6                         | 91.80 | 50.50  | 30.92  | —     | —   | —   | —   |
| Gupta 2007[27]  | 58              | 12                        | 93.75 (3 months) | —  | —  | 37.50 (6 months) | — | — | — |
| Jacob, 2007[28] | 100             | 12                        | 90.0  | 55     | 38     | —     | —   | —   | —   |
| Rajappa 2008[29] | 201             | 29.5                      | 97    | —      | 56     | —     | —   | 77  | 94  |
| Medhi 2010[30]  | 400             | 47                        | 95 (cumulative best rate) | 72 | 53 | — | — | 76.0 | 94.1 |
| Ganesan 2011[31] | 516             | 39                        | 91.1 (median 1.9 months) | 58 (n=299) | 23.2 (n=299) | — | 70.8† | — | — |
| Mukhopadhyay 2014[32] | 634         | 60                        | 91 (12 months) | 80 (12 months) | 49.5 (12 months) | 35’(12 months) | 72.5† | — | 76.1† |

CCyR – Complete cytogenetic response; CHR – Complete hematologic response; CMR – Complete molecular response; EFS – Event free survival; MCyR – Major cytogenetic response; OS – Overall survival; PFS – Progression free survival; †Retrospective analysis; *5 year estimated PFS, OS and EFS; ‡Best observed CMR was 75% at 60 months
The high cost of these tests further precludes its use in India. Despite these constraints, monitoring BCR-ABL transcript levels at 3 months is strongly recommended to identify patients who respond poorly to first line TKI therapy thereby allowing early treatment optimization with second-generation TKIs.

**CONCLUSION AND SUMMARY/TAKE HOME MESSAGES**

The treatment milestones for CML therapy are evolving with an increased focus on early molecular responses and their predictive value on patient outcomes. BCR-ABL transcripts at 3 months provide useful clinical guidance to decide if alternative therapies are warranted for patients with minimal initial molecular response.

**REFERENCES**

1. Subramanian PG. Cytogenetic study in CML. Indian J Med Res 2012;135:12-3.
2. O’Brien S, Abboud CN, Akhtari M, Altman JK, Berman E, Cohen AD, et al. NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. Version 4, 2013. Available at: JNCCN.org. Accessed June 11, 2013.
3. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al European LeukemiaNet recommendations for the management of chronic myeloid leukemia 2013. Blood 2013;122:872-84.
4. Kantarjian HM, O’Brien S, Cortes JE, Shan J, Giles FJ, Rios MB, et al. Complete cytogenetic and molecular responses to interferon-α-based therapy for chronic myelogenous leukemia are associated with excellent long-term prognosis. Cancer 2003;97:1033-41.
5. Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-32.
6. Druker BJ, Guilhot F, O’Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia. N Engl J Med 2006;355:2408-11.
7. Deininger M, O’Brien GS, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, et al. International randomized study of interferon vs nilotinib for imatinib-resistant or -intolerant chronic myeloid leukemia (IPN2004-02): a multicentre, open-label, phase 3, randomised controlled trial. Lancet 2011;378:435-44.
8. Hochhaus A, Baccarani M, Deininger M, Apperley JF, Lipton JH, Goldberg SL, et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia 2008;22:1200-6.
9. Kantarjian H, Pasquini R, Le’vy V, Jootar S, Holowiecki J, Hammerschlag N, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily. Cancer 2009;115:4136-47.
10. Jabbour E, Kantarjian H, Cortes J. Chronic myeloid leukemia and second-generation tyrosine kinase inhibitors: When, how, and which one? Semin Hematol 2010;47:344-53.
11. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llaoc PE, Enrico A, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 2010;95:232-40.
12. Neelakantan P, Gerrard G, Lucas C, Milojkovic D, May P, Wang L, et al. Combining BCR-ABL transcript levels at 3 and 6 months in chronic myeloid leukemia: Implications for early intervention strategies. Blood 2013;121:2739-42.
13. Marin D, Ibrahim AR, Lucas C, Gerrard G, Wang L, Szkylo RM, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012;30:232-8.
14. Marin D, Hedgley C, Clark RE, Apperley J, Forloni L, Milojkovic D, et al. Predictive value of early molecular response in patients with chronic myeloid treated with first-line dasatinib. Blood 2012;120:291-4.
15. Hanfstein B, Muller MC, Hehlmann R, Erben P, Lauseker M, Fabarius A, et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). Leukemia 2012;26:2096-102.
16. Jain P, Kantarjian H, Nazha A, O’Brien S, Jabbour E, Romsy CG, et al. Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: Results with four tyrosine kinase inhibitor modalities. Blood 2013;121:4867-74.
17. Branford S, Kim DW, Soverini S, Haque A, Shou Y, Woodman RC, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase treated with nilotinib [abstract]. J Clin Oncol 2012;30:4323-9.
18. Saglio G, Kantarjian HM, Shah N, Jabbour EJ, Quintas-Cardama A, Steegmann JL, et al. Early response (Molecular and Cytogenetic) and long-term outcomes in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib [oral and poster abstract]. 51st ASH Annual Meeting and Exposition 2012. Available from: https://ash.confex.com/ash/2012/webprogram/Paper47060.html [Last updated on Dec 2012; Last accessed on Oct 2013].
phase. Less than 10% BCR-ABL by FISH at 3 months associated with improved long-term clinical outcome. Am J Hematol 2012;87:760-5.

25. Hochhaus A, Saglio G, Chuah C, Pavlovsky C, Garellick BB, Lambert A, et al. Dasatinib and imatinib-induced reductions in BCR-ABL transcript levels below 10% at 3 months are associated with improved responses in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Analysis of molecular response kinetics in the DASISION Trial [abstract]. J Clin Oncol 2012;30:232-8.

26. Deshmukh C, Saikia T, Bakshi A, Kadam PA, Baisane C, Parikh P. Imatinib mesylate in chronic myeloid leukemia: A prospective, single arm, non-randomized study. J Assoc Physicians India 2005;53:291-5.

27. Gupta A, Prasad K. Hematological and molecular response evaluation of cml patients on imatinib. J Assoc Physicians India 2007;55:109-13.

28. Jacob L, Bapsy P, Govind Babu K, Lokanatha D. Imatinib mesylate in newly diagnosed patients of chronic myeloid leukemia. Indian J Med Paediatr Oncol 2007;28:20-5.

29. Rajappa S, Varadpande L, Paul T, Jacob R, Digumarti R. Imatinib mesylate in early chronic phase chronic myeloid leukemia: Experience from a developing country [abstract]. Leuk Lymphoma 2008;49:554-8.

30. Medhi K, Raina V, Kumar L, Sharma A, Bakhshi S, Gupta R, et al. Response assessment of patients with chronic myeloid leukemia receiving imatinib mesylate (Glivec) therapy: Experience from a single center in a developing country [abstract]. Leuk Lymphoma 2010;51:1850-4.

31. Ganesan P, Sagar TG, Dubashi B, Rajendranath R, Kannan K, Cyriac S, et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. Am J Hematol 2011;86:471-4.

32. Mukhopadhayay A, Dasgupta S, Mukhopadhyay S, Bose CK, Sarkar S, Gharami F. Imatinib mesylate therapy in patients of chronic myeloid leukemia with philadelphia chromosome positive: An experience from eastern India. Indian J Hematol Blood Transfus 2012;28:82-8.