

Is imatinib still the best choice as first-line oral TKI

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Abstract

Targeted therapy is the buzz word these days. A decade back the emergence of tyrosine kinase inhibitor Imatinib on the horizon, as the targeted therapy, had captured the imagination of everyone in the field of cancer. It is encouraging to see a large number of patients getting relief from deadly CML disease and leading a good quality of life with the help of this drug. However, sky is not the limit and now we have second and third generation tyrosine kinase inhibitors. I still remember the sagacious smile on the face of late Dr. John Goldman, when I asked him about his preferred choice and he replied and I quote "this is going to be the debate of the decade." Here I take the opportunity to contribute to this debate. I have scrutinized various aspects of the three TKIs, now recommended, for the treatment of CML. I'm still convinced it is too early to shift our practice completely towards 2G TKI as more time is required to make a clear recommendation.

Key words: Frontline therapy, imatinib, Chronic myeloid leukemia

Chronic myeloid leukemia (CML) treatment has become an exemplary model for targeted therapy, which only few malignant diseases are able to match. In the early 80's, the mainstay of treatment was drugs like busulphan, hydroxyurea, interferon, and low dose cytarabine, with which the overall survival was never better than 30-40%.^[1,2] Introduction of imatinib (IM) changed the landscape for patients with Philadelphia-positive CML.^[1] The excellent results of the IRIS trial showed distinct efficacy and safety of IM over interferon with low dose cytarabine and established IM as an undisputed choice for the treatment of newly diagnosed CML patients.^[2]

There is always a relentless pursuit to find the perfect cure and in case of CML, the result is the advent of second-generation tyrosine kinase inhibitors (2G TKI) like dasatinib, nilotinib, bosutinib, and ponatinib. These new agents on the scene have been the subject of much debate on the choice of superior frontline therapy in present era.

The most important thing to be remembered is that all the TKIs approved for treatment of CML are not curative in nature and are required to be taken almost for lifetime. The decision regarding the choice of which TKI is to be used for a particular patient should take into account not only its effectiveness but also its impact on quality of life, the drug affordability, accessibility, and ease of compliance.

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The reasons why IM should still be considered as first choice:

1. 'OLD IS GOLD' well established track record: As per the IRIS trial ($n = 1106$) at 60 months, 87% CML patients taking IM were in complete cytogenetic remission (CCyR) and only 7% progressed to accelerated phase (AP) or blast crisis (BC). At 8 years of follow up, the progression-free survival (PFS) to AP/BC was 92% and overall survival (OS) was 85% for all causes and 93% in case of only CML-related deaths.^[3,4] IM is the only agent where trials are ongoing regarding the stopping the drug in case of sustained molecular response.^[5]
2. 'All that glitters is not gold': Better cytogenetic and molecular responses but no survival advantage so far: So far, the much hyped early and deeper cytogenetic and molecular responses as a result of the 2G TKI have not translated into better OS and PFS compared to IM.
 - a. Trial comparing nilotinib with IM: ENESTnd (Evaluating nilotinib efficacy and safety in clinical trials of newly diagnosed patients) was a 3-arm study comparing nilotinib 300 mg twice a day (BD), nilotinib 400 mg BD with IM 400 mg once a day (OD). Pertinent results and study updates at 4 years are highlighted here.^[6]
 - (1) Here, I have compared only nilotinib 300 mg BD with IM as nilotinib 400 mg BD is still not recommended as first-line therapy. The study showed significant difference in molecular response 4.5 i.e., MR^[4,5] for intermediate ($P = 0.0004$) and high-risk group ($P = 0.0040$); however, it failed to show any statistical difference for MR^[4,5] in patients with low Sokal risk (nilotinib 300 mg BD ($n = 103$) vs IM (104): 38% vs. 29, $P = NS$)^[6,7]
 - (2) The estimated 4-year event free survival and OS with nilotinib 300 mg BD versus IM was 94.5% and 92.6% ($P = 0.1845$)

and 94.3% and 93.3% ($P = 0.4636$), respectively. Similarly, the estimated 4-year PFS with nilotinib 300 mg BD was 96.1% while for IM, it was 94.7% ($P = 0.1995$).^[7,8]

b. Trials comparing dasatinib with IM

(1) The DASISION trial (dasatinib versus IM in newly diagnosed chronic phase CML) compared dasatinib with IM and at 12 months; the CCyR rates for dasatinib ($n = 259$) were significantly higher as compared to IM ($n = 260$) i.e., 77% vs. 66% [Relative risk (RR) = 1.16, confidence interval (CI) 1.04 to 1.30] but not at 24 months as CCyR was 80% on dasatinib arm while 74% on IM arm with RR = 1.08, CI = 0.98 to 1.19.^[9,10]

(2) Fewer patients transformed to accelerated phase/blast crisis when treated with dasatinib (3.5%) compared to IM (5.8%). However, the 24-month OS and PFS were similar for dasatinib as compared to IM: 95.4% versus 95.2% and 93.7% versus 92.1%, respectively.^[9,10]

Similarly, in another trial comparing dasatinib with IM, 15 patients relapsed (6 on dasatinib, 9 on IM), but the OS at 3 years was 97% in both dasatinib and IM arms and PFS at 3 years was 93% for dasatinib arm and 90% for IM arm.^[11]

3. Adverse events

a. Nilotinib: In the ENESTnd study, dose reductions and interruptions occurred in 59% patients receiving nilotinib 300 mg BD as opposed to only 52% of the patients receiving IM. The discontinuation rates were 6% for nilotinib and 9% for IM at 24 months follow-up.

The adverse events profile was not much different in the two arms. However, there is an emerging concern regarding the increased incidence of 3 types of vascular events, which include peripheral arterial occlusive disease, coronary artery disease, and cerebrovascular events on treatment with nilotinib.^[12]

There is also a concern regarding the increased incidence of hyperglycemia and hypercholesterolemia in patients treated with nilotinib. An increased incidence of deranged liver enzymes were seen in patients (12%) treated with nilotinib 300 mg BD compared to 3.6% in IM arm.^[8]

Another important side-effect is that nilotinib causes hyperglycemia, possibly by inducing insulin resistance. In the ENESTnd trial, about 20% of non-diabetic patients on nilotinib 300 mg BD developed diabetes compared to 9% on the IM arm.^[6,13]

b. Dasatinib: In DASISION study, adverse events requiring therapy discontinuation in patients

treated with dasatinib vs. IM were 4% and 5%, respectively. However, grade 4 thrombocytopenia was seen in twice as many patients (19%) receiving dasatinib compared to 10% receiving IM.^[11]

Pleural effusion was seen in 26 patients (10%) treated with dasatinib, out of which 8% were grade 2 while none on IM developed pleural effusion. Among these 26 patients, 19 required therapy interruption and in 8 patients, dose reduction was done.

Another major concern is the development of pulmonary hypertension reported in a French study with incidence of 0.45%. The most worrying part was that although there was marked improvement after cessation of therapy, pulmonary pressures did not return to normal levels and led to death of 2 patients.^[11,14,15]

In another trial among 245 patients, 15% (18/122) patients treated with dasatinib and only 2% (2/123) patients treated with IM had grade 4 toxicities ($P = 0.0001$). The grade 4 non-hematologic toxicities in the dasatinib arm were febrile neutropenia, cardiac ischemia, asyctole, pericardial effusion, sensory neuropathy, and metabolic abnormalities (lactate dehydrogenase elevation).^[11]

4. Kinase domain mutations:

1. Nilotinib: In the ENESTnd trial, patients in all the 3 arms developed mutations. However, a statistically significant assessment of difference in occurrence of mutations as a result of the drug or schedule was not possible due to small number patients in each group. One out of 2 patients on nilotinib 300 mg BD arm and 7 out of 12 patients on IM arm who progressed to AP/BC developed mutations. These mutations were more frequently seen in patients with intermediate and high Sokal score.^[7,8,16]

2. Dasatinib: In the DASISION trial, a similar number of mutations were seen in both the dasatinib and IM arms. The number of T315I mutations was higher in the dasatinib arm.^[9,17]

Practical issues to be considered in deciding first-line therapy.

1. Management of treatment toxicity: There is well established data of side-effects of IM available from both clinical trials and real life reports. However, for both nilotinib and dasatinib, long-term data are still evolving and more real life reports are needed to confirm their safety. So far, we know that both dasatinib and nilotinib require more careful and regular monitoring compared to IM. On follow-up, CML patients on IM are usually monitored with a single complete blood test; however, seeing the adverse events list with nilotinib and dasatinib, it will be important to monitor the liver function tests, lipid profile, glucose levels, electrocardiogram, and chest

X-ray, which adds to the cost.

2. Compliance issues - Adherence to drug schedule: In CML, drug adherence is extremely important, and missing more than two doses can have an impact on the outcome.^[18] Therefore, looking into compliance issues and simplicity of drug schedule is very important. Adherence to drug schedule will not only depend on the better education of patients but also on the safety profile of the drug. As in one study, toxicity of dasatinib was more compared to IM, which led to more drug interruptions and dose adjustments. Similarly, nilotinib is required to be taken twice a day compared to once a day dosing for IM will require careful consideration of patient profile while deciding the therapy.
3. Cost-effectiveness: Since generic IM is easily available in India, and soon in other countries (as IM patent expiry will be in the year 2016), the cost of dasatinib and nilotinib will be the main hindrance for using them as first-line therapy.
4. Lack of second choice after 2G TKI: The EFS with IM at 7 years is 81%, and patients who lose response can be salvaged with second-line TKI making the current EFS 88%.^[10] However, if dasatinib and nilotinib is used as frontline, the main option for second-line therapy will be stem cell transplantation as ponatinib has been withdrawn from the markets due to severe side-effects. Hence, it will be important to have a good strategic plan before deciding the therapy for an individual.

Conclusions

The trials comparing dasatinib and nilotinib are still in immature stages with no clear benefit on survival, and more real life reports are required to gain confidence regarding the treatment toxicity and clinical efficacy of these drugs. Both European Leukemia Network 2013 and National comprehensive cancer network version 2.2012 treatment recommendations do not indicate preference for any of the three drugs as frontline therapy.^[19,20] The choice of the drug, therefore, should be made on the basis of the following considerations:

1. Careful selection based on risk category: High-risk patients or patients with additional chromosomal abnormalities may be more benefitted with 2G TKI
2. Considering co-morbidity status: In India, cardiac ailments, diabetes, and hypertension are on the rise. Using nilotinib in these set of patients will require careful monitoring and involvement of specialists from other fields, for holistic management. Similarly, dasatinib should be used carefully in patients with pulmonary disease. However, with IM, no such restrictions are indicated
3. Management of adverse events: IM in clinical practice is seen to be well tolerated with fewer side-effects requiring intervention. In India, where the major population lives in villages and patients come for follow-up only after

3 months, regular monitoring of side-effects is also an issue worth considering before deciding the drug

4. Compliance/Adherence issues: Need to be addressed
5. Cost factor: With effective IM generic available, it would be difficult to prescribe 2G TKI as frontline. Consideration of the treatment efficacy and cost-effectiveness on individual basis need to be account while making a decision.

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