Using 2nd generation tyrosine kinase inhibitors in frontline management of chronic phase chronic myeloid leukemia

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Abstract

Choices in medicine come with responsibility. With several TKI's (Tyrosine kinase inhibitors) available for front-line management of CML (Chronic Myeloid Leukemia), an astute clinician has to personalise, rationalise and take a pragmatic approach towards selection of the best drug for the 'patient in question'. Though it is hotly debated as to which TKI will triumph, the truth of this debate lies in individualising treatment rather than a general 'all size fits all' approach with imatinib. I personally believe that the second generation TKI's will suit most patient clinical profiles rather than prescribing imatinib to all and I have strived to make a strong case for them in front line treatment of CML. Though Imatinib may remain the first line choice for some patients, my efforts in this debate are mainly geared towards breaking the myth that imatinib is the sole 'block buster' on the CML landscape

Key words: Chronic myeloid leukemia, tyrosine kinase inhibitor, debate

Introduction

Tyrosine kinase inhibitors (TKI's) are at the cornerstone in the management of patients in chronic phase chronic myeloid leukemia (CML). These patients now boast a near normal life expectancy thanks to the scintillating success of targeted therapy of the BCR-ABL oncogene.[1] Beating cancer with a single non chemotherapy tablet a day in the context of CML has radically changed our perspective, expectations and goals for this patient clientele.

CML is now perceived more like a chronic disease such as hypertension or diabetes rather than a fatal malignancy with various front line agents available for upfront treatment. Though in principle, having choices is associated with a sense of triumph and comfort, choices in medicine come with responsibility and demand a certain level of clinical clarity as to which agent first line and for whom.

In most countries, the 3 drugs available upfront for chronic phase CML are imatinib, nilotinib and dasatinib. Detailed knowledge of the strengths and weaknesses of the 3 most commonly used frontline TKI's coupled with therapeutic goals and patient co-morbidities will assist treatment decision.

This article will focus on use of imatinib, nilotinib and dasatinib (bosutinib and poanatinib will not be discussed in this review) and will make a strong case for usage of second generation TKI's – nilotinib and dasatinib over imatinib as first line therapy for CML.

The argument against using imatinib as front line will be discussed under the following headings:

1. The imatinib hype; is it really a blockbuster?
2. Data on second generation TKI's-a winner!
3. Toxicity profiles, adherence and mutations
4. Is it wrong to get more ambitious for our patients?
5. Money matters; should we value human life in currency?

The Imatinib Hype; Is it Really a Blockbuster?

Dr. Bansal (my debate colleague) has already cited the well-established long-term The International Randomized Study of Interferon and STI571 (IRIS) data on imatinib.[2]

In the seminal IRIS trial, a complete cytogenic response was achieved in 83% of patients, with a projected 8-year event free survival of 81% and overall survival of 85%.

However, I want to bring to your attention (something that my colleague might have conveniently overlooked!) that in this trial, 17% of patients never achieved complete cytogenetic response (CCyr), 15% achieved CCyr but eventually lost it and nearly 5% were intolerant to imatinib.[3] Thus, approximately one-third of the patients did not have a desired outcome.

The situation is more dire outside the premise of clinical trials. What happens in real life in our busy out-patients is often different from the structured protected environment of clinical trials. One universal concern surrounding clinical trials is the extra commitment of both practitioners and patients to optimal outcomes and the fact that they may give superior results when compared to real-world experiences. Needless to say, the raw data outside the premise of a clinical trial looks more disheartening for imatinib.

Results from the Hammersmith UK data on 204 newly diagnosed chronic phase CML patients estimated that an individual's likelihood of remaining in CCyr while receiving

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imatinib 5 years after diagnosis was approximately 63%.[4]

Lucas *et al*., published a retrospective evaluation of 84 patients where in 51-58% would have been considered to be imatinib-resistant by failing to achieve CCyr at 18 months.[5]

These studies indicate that both primary and secondary resistance to IM remains a venerable challenge in a significant minority of newly-diagnosed chronic phase CML patients, leaving a sizeable room for an improvement.

Although a majority of patients on imatinib will fare well, a significant proportion will need a change of therapy due to unsatisfactory responses or side effects.

First and foremost, let me bust the glided imatinib myth that it is blockbuster drug for all CML patients. How wise is it to continue the same drug just because of 13 years of familiarity especially when more potent options are available?

"Old is gold" in this clinical context is pure slothful complacency!

Data on Second Generation Tki's: A Winner!

One of the major drawbacks for imatinib is that it is significantly less potent than nilotinib and dasatinib. Evidence for this comes from *in vitro* studies and the clinical observation that inadequate kinase inhibition in patients receiving imatinib is not uncommon and is associated with inferior response.[6] Failure to achieve adequate blood levels is one example. Susceptibility to inadequate cellular uptake even in the presence of adequate drug levels is mainly due to reduced activity of the organic cation transporter 1 (OCT-1) influx pump. The activity of this pump is highly variable and the majority of patients who fail to achieve optimal response to imatinib have evidence of low activity, as measured by the OCT-1 activity assay.[7]

Nilotinib is a BCR-ABL 1 inhibitor that was rationally designed to be more potent and selective than imatinib. Dastinib is a multitarget kinase inhibitor that is more than 300 times more potent than imatinib in inhibiting the BCR-ABL 1 oncoprotein *in vitro*.[8]

In patients with true resistance to imatinib in chronic phase, second generation TKI cause a CCyr in 50% of cases with durable responses at the end of 2 years.[9]

If a drug can salvage half of imatinib resistant patients, it doesn't take an Archimedes to guess that these second generation TKI's are clinically more potent than imatinib *in vivo* as well.

The proof of the pudding lies in the outstanding results of the ENEST and DASISION trial which were head to head comparisons between imatinib and the two second generation TKI's.

In the multi-center phase 3 randomized study Evaluating nilotinib efficacy and safety in clinical trials in newly diagnosed patients (ENESTnd), achievement of CCyr by 24 months was significantly higher for nilotinib 300 mg BD compared with IM 400 mg daily (87% vs. 77%, $P = 0.0018$). The Major molecular response (MMR) by 24 months remained significantly higher for nilotinib 300 mg BD (71%, $P < 0.001$) and nilotinib 400 mg BD (67%, $P < 0.001$) compared with IM 400 mg/day (44%).[10]

In the multinational dasatinib versus imatinib study in treatment-naïve CML patients, 519 patients were randomized to receive either 100 mg dasatinib daily or IM 400 mg daily.[6]

At 24 months, the rates of MMR were significantly higher for dasatinib (64% vs. 46%, $P < 0.001$) when compared to standard dose IM. CCyr rates at 18 months were higher for dasatinib (78% vs. 70%, $P = 0.037$).

The main argument is that though these milestones are achieved much earlier with second generation TKI's, there is no difference in overall survival and PFS in these patient groups (a valid point rightfully highlighted by Dr. Bansal).

Hence, nilotinib and dasatinib achieve treatment milestones much earlier than imatinib but it doesn't seem to matter in the long run since all 3 drugs will get you there (CCyr and MMR) eventually.

Why is there this mad rush to achieve these milestones so quickly when imatinib will also achieve them, albeit at a slower pace? Why does early response matter?

Does slow and steady not win the race? NO is the confirmed answer for CML.

The reason for this is the following:

Both the DASISION and ENESTnd trials have shown that fewer patients in the nilotinib and dasatinib arms progressed to accelerated phase (AP) and/or blast crisis (BC) when compared to standard dose Imatinb within the first 24 months [Figure 1].

This certainly provides strong evidence for advocation of the notion that achieving CCyr and MMR earlier in the temporal profile is of clinical benefit to the patients by minimizing risk of disease progression. I thereby strongly assert the fact that fewer patients will progress to accelerated and blastic phases if we use second generation TKI's upfront, an outcome immensely desirable (hopefully my opponent will agree!).

There are 3 scoring systems that are currently being applied in CML, the Sokal, Hasford and EUTOS systems and there is no clear indication that one is superior to the others. Regardless of which scoring system is used, a high score is associated with a higher risk of progression to AP or BC. Because both nilotinib and dasatinib have been shown to reduce the risk of CML progression, these drugs might be preferred over imatinib in this group of high-risk patients.[11]

The other strong argument for early response is reflected by recent changes to the NCCN and ELN guidelines for monitoring of CML patients. Both the ELN and NCCN guidelines published in 2013 have strongly advocated early achievement of cytogenetic and molecular milestones. The

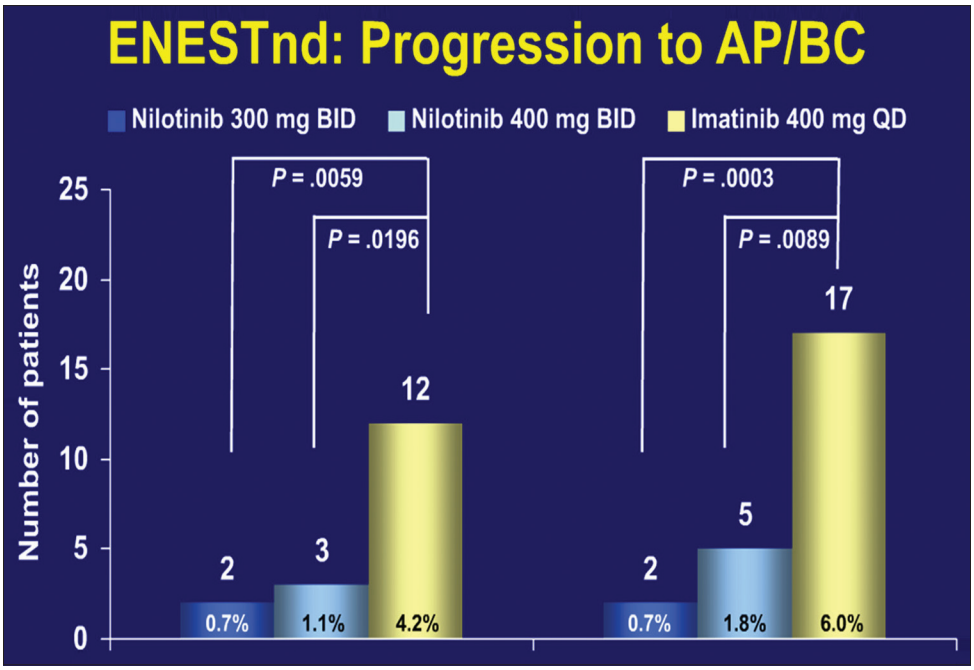

Figure 1: Evaluating nilotinib efficacy and safety in clinical trials newly diagnosed patients results demonstrating lesser patients progressing to accelerated phase or blast crisis with nilotinib 300 mg BD compared to imatinib 400 mg daily

ELN guidelines would recommend using any of the 3 TKI's as first line treatment for CML patients. BCR-ABL1 transcript levels <10% at 3 months, <1% at 6 months and <0.1% from 12 months onward define optimal response, whereas >10% at 6 months and >1% from 12 months onward define failure, mandating a change in treatment. Similarly, partial cytogenetic response (PCyR) at 3 months and CCyR from 6 months onward define optimal response, whereas no CyR (Philadelphia chromosome – positive [Ph 1] >95%) at 3 months, less than PCyR at 6 months and less than CCyR from 12 months onward define failure.[12]

Both the German CML IV study and the Hammersmith hospital, London data show that BCR-ABL >10% at 3 months was the strongest predictor of poorer event free survival (EFS), progression free survival (PFS) and overall survival (OS).[13,14]

When the DASSISON and ENEST data was looked at carefully, more patients in the nilotinib and dasatinib arms achieved this 3 month milestone as opposed to imatinib.[15]

It would be rational to extrapolate that if the second generation TKI's achieve this 3 month milestone earlier than imatinib, then it will eventually transform in to better PFS and OS for our patients.

Two more (not so strong) comments on the PFS/OS data are as follows:

Both these trials were powered for attainment of CCyr and MMR and not primarily designed for PFS and OS.

Secondly, these results have been received with surprise in the hematology community and the speculation is that with more maturity of this data these curves for PFS and OS might start separating out favoring the second generation TKI's.

Toxicity Profiles, Adherence and Mutations

Toxicity

Nearly all patients on imatinib experience some impairment in quality of life, such as excessive fluid retention, muscle pains and cramps, or gastrointestinal disturbances.[11]

The second generation TKI's also have a toxicity profile but my debate colleague Dr. Bansal. seems to have painted it in unreasonably gaudy colors.

The day-to-day toxicity of Nilotinib is generally quite favorable; edema is rare and gastrointestinal toxicity is uncommon. Elevated lipase and abnormal liver function tests are observed in 5-10% of patients, but do not lead to discontinuation of therapy.

I acknowledge that there are sporadic reports from single centers of cases with serious progressive vascular events with Nilotinib, but most patients had multiple vascular risk factors for vascular disease.[16]

I would use nilotinib with caution in diabetic patients due to the associated hyperglycaemia (20% for nilotinib vs. 9% for imatinib in the ENEST trial).[17]

Only 10% of patients have withdrawn from dasatinib arm of the DASISION study because of adverse events, the major concern relating to pleural effusions. Most studies report an incidence lower than 25%, usually grade I-II, easily managed by diuretics and/or steroids with reduction of the dasatinib dose.[18]

I think the pleural effusion toxicity is over rated, more so since thoracocentesis is seldom warranted. Of more concern are rare reports of pulmonary arterial hypertension (Nine cases reported to the French pulmonary hypertension registry over a 4-year period).[19]

I would use dasatinib with caution in patients with Congestive cardiac failure or low pulmonary reserve.

All drugs have a risk/benefit profile, but if we choose our patients correctly and carefully we can certainly skew the benefit/risk ratio favorably toward benefit and second generation TKI's are no exception to that.

Although imatinib appears to be a safe drug over the course of 10-15 years of exposure, significant organ toxicities may be revealed with lifelong exposure.

It would be clinically gullible to dismiss the more potent second generation TKI's as upfront agents due to their toxicities, more so since the toxicity profile is very reasonable and manageable with astute monitoring.

Adherence

Non-adherence to IM is a much bigger problem than initially conceived.

In a study performed at Hammersmith London, 87 patients with chronic phase CML treated with 400 mg imatinib for a median of 59.7 months had adherence monitored during a 3-month period within CCyr using a microelectronic monitoring device. Nearly 26.4% had adherence of <90% and 14% had adherence of <80%.

Multivariate analysis identified adherence and OCT-1 levels as the only independent predictors of MMR. Further, poor adherence is the principal factor contributing to the loss of cytogenetic responses and treatment failures in patients on long-term therapy.

This can certainly happen with the second generation TKI's, but I personally believe that compliance is an issue that should be addressed with more physician commitment and patient education. Drug-delivery devices with reminder function, diaries, or text-messaging reminders may help to increase an adherence. Physicians and pharmacists have an important role in patient education to improve "TKI truancy" since improving an adherence may not only optimize clinical outcomes, but may also reduce the economic burden of CML.

Not considering a drug upfront because of anxiety surrounding adherence (more so with nilotinib since it is a BD dose when compared with dasatinib and imatinib which are taken OD) is a failing on the part of the treating team for not educating and encouraging their patients for strict compliance.

Using this as an argument for deciding the first line choice is lame and needs physician introspection.

Mutations

Another major drawback of imatinib as a frontline drug in CP-CML is the frequency of kinase domain mutations that emerge on imatinib therapy. This became evident in the ENESTnd study, in which the number of mutations detected on the imatinib arm was twice as high as those on the nilotinib arm (7% vs. 3.5%).[20] With regard to kinase domain mutations, there have been similar numbers of mutations on imatinib and dasatinib in the DASISION trial.

Of course, the T315I mutation is an unbeatable one which does not respond to any of the TKI's.

Ponatinib is a potent BCR-ABL inhibitor with activity against the T315I mutation.[21] However on October 31, 2013, the Food and Drug Administration asked the manufacturer of the leukemia chemotherapy drug ponatinib hydrochloride to suspend marketing and sales of this drug because of the risk of life-threatening blood clots and severe narrowing of blood vessels.

Is it Wrong to Get More Ambitious for Our Patients?

Among the most intriguing clinical questions remaining in the management of CML is whether patients could eventually discontinue treatment and be cured?

Improving the prospect of treatment-free remission should now be considered as a desirable and achievable goal. Young women who wish to start a family would also value the achievement of treatment-free remission very highly. The evidence from the STIM trial and the Australian TWISTER trial is fairly convincing. 30-40% of CML patients who achieve a stable deep molecular response (MR) on imatinib can stop therapy and remain polymerase chain reaction (PCR) negative for many years.[22,23] In fact, there has been no evidence of late molecular recurrence in any of the patients who remained PCR negative for the first 27 months after imatinib cessation.

This data will look even more promising for second generation TKI's.

Given that the achievement of deep MRs appears to be higher with second-generation TKIs than with imatinib, the overall rate of treatment-free remission achieved using nilotinib or dasatinib frontline may be significantly higher than the 15% who can achieve it on imatinib. On this basis, we can conclude that, on the balance of probabilities, it is very likely that second-generation drugs used frontline will achieve a higher rate of treatment-free remission overall. However, more mature data are needed before we can say that the case is proven beyond reasonable doubt.[11]

If we are going to render more patients treatment free with second generation TKI's, why should we butcher our ambition with first line imatinib?

Money Matters; Should we Value Human Life in Currency?

Imatinib has not entered the domain of generics in USA or Europe as yet.

Table 1: Annual price estimates, by country, of the 3 TKI's approved for CML (price in thousands of US dollars)-adapted from experts in chronic myeloid leukemia-the price of drugs for CML is a reflection of the unsustainable prices of cancer drugs

Country	Imatinib	Nilotinib	Dasatinib
United States	92	115.5	123.5
United Kingdom	33.5	33.5	48.5
China	46.5	75	61.5
South Korea	28.5	26	22

CML=Chronic myeloid leukemia

Money makes the mare go and unfortunately clinical medicine is no exception to this woefully shallow doctrine. In deciding the relationship between price and worth (or value), by moral necessity, price must reflect worth.

The doctrine of free market economies where prices reflect "what the market bears," or what one is willing to pay for a product is best suited to luxury commodities rather than life saving drugs. A recent article published in blood by experts in CML is a good read for the unsustainable prices of TKI's in CML.[24]

Table 1 shows that in most countries, the second generation tyrosine kinase inhibitors are more expensive than imatinib.[25,26]

Though it is a convenient argument to use a drug that is cheaper, it is not the right argument.

In a profession which demands excellence, it our responsibility as a fraternity to fight for what we think is best for our patients. I find dismissing second generation TKI's because they are more expensive a rather vexing and impotent defence.

We must strive to establish a dialogue with the drug companies by organizing regular meetings, involving all stake holders, to address the reasons behind high cancer drug prices and offer solutions to reduce them rather than rejecting good potent drugs at the face value.

With respect to India, if the government can find the cash to fund Mangalyaan to mars, I am confident that dignitaries will and must find the funds to support their cancer population with the best drug.

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