Chronic myeloid leukemia: Review of our Indian experience

The treatment of patients with chronic myeloid leukemia (CML) has seen the most evolution in terms of diagnosis, therapeutics, monitoring and assessment of disease. The discovery and use of tyrosine kinase inhibitors (TKIs) has changed the treatment algorithm of CML especially chronic phase (CP) toward a safer non-transplant option. With the availability of better monitoring of the BCR-ABL by fluorescence in situ hybridization (FISH) and Polymerase chain reaction, we could now comment on the achievement of major molecular response (MMR) and complete molecular response (CMR) in our patients with analysis of BCR-ABL transcripts in peripheral blood being the very practical advance for monitoring the disease.[1,2] However, the technique and standardization are still issues that need to be addressed and hence unfortunately, subject to availability and reliability. We now have reached a stage of being able to assess the resistance to Imatinib and also to second generation TKIs. This journey has been rapid and exciting.

To add to the excitement is the approval of the second generation TKIs as upfront treatment. With the European Leukaemia Net ELN guidelines in place, our ability to assess the clinical responses in terms of optimal, suboptimal, intolerance and failure have helped us to increase or upgrade the TKIs in practice to continue to achieve the desired MMR/CMR for better disease free survival (DFS).

Although, we accept that in our country, standard dose Imatinib (400 mg) remains the best first-line therapy for most patients with first CP CML, the science of the second generation TKIs is knocking furiously on our doors, promising faster, deeper and higher rates of complete cytogenetic response (CCyR) and MMR, the impediment being cost and the fact that long-term data of overall survival (OS), event-free survival and progression-free survival is still to mature. This brings with it the issues of when to use which agent in the upfront setting, balancing benefits and cost to the Indian consumer. This still needs to be worked out on a practical level.

In this journal, there are several articles on the Indian experience in CML treatment from various centers across the country, with patients from diverse backgrounds. I have looked at about 1600 patient data studied in centers from Delhi, Mumbai, and Jaipur. These were retrospective studies and showed interestingly, there is uniformity in the following points in the Indian patients studied:

Younger age of onset of CML-CP, most patients diagnosed in CP, higher counts at presentation, more organomegaly, more cases of high risk Sokal score and similar difficulties in molecular monitoring either on account of cost or non-availability or lack of standardization of process were a common pattern.

The predominantly used molecule is Imatinib mesylate, a large number through the good offices of Novartis Glivec International Patient Assistance Program and a similar large number on the Indian generic brands. All studies reported Imatinib as a safe and well tolerated drug. We note that in the era preceding Imatinib, the duration of therapy, response to therapy and remission rates were short and inadequate, as well as a far more rapid rate of transformation was evidenced in the report of Dr. Pravas Mishra et al. from AIIMS. Furthermore, high drug toxicity impact on patients affected the compliance and follow-up. The starting dose iwas uniformly 400 mg in all the studies with all the authors preferring to increase the dose of Imatinib if inadequate response, probably the alternatives being too expensive.

It was interesting to note that patients in lower SE class presented with higher Sokal scores and with more disease burden as described by Dr. Hemant Malhotra et al. from SMS Medical College Hospital, Jaipur, indicating probably a late diagnosis. However, the data from Tata Memorial
Hospital, Mumbai, Dr. Purvish Parikh et al. showed that irrespective of the Sokal score, the CCyR for low risk (76.3%), intermediate risk (73.8%), high risk (77.3%) was no different, suggesting that Imatinib can overcome this aspect of disease.

Dr. Hemant Malhotra et al. also compared the responses of Innovator Glivec to the Indian Imatinib and found similar hematological responses. Unfortunately, he could not comment on the molecular response between the two groups as a significant number of patients in the Glivec arm were not tested for economic reasons. All the reports show complete hematological response of 85-98.7% between 1 and 3 months of therapy with most managing to keep the hematological remissions for at least 2-3 years. Although data on complete cytogenetic response was forthcoming in all the series, approximately 77%, the data on molecular assessment is patchy and incomplete. This is an area that we have to improve upon to be able to provide evidence based medicine.

Data from Dr. Pravas Mishra et al. from AIIMs showed that a log 1-2 reduction was achieved in 16% and more than 3 log reduction in 28% of the studied patients with a CMR of 16%. A Cytogenetic response rate of 34-42% was documented by Dr. Hemant Malhotra et al. from SMS Medical College Hospital, Jaipur.

Dr. Purvish Parikh et al. from TMH experience showed Glivec CCyR in 72% while with the Indian generic Veenat CCyR was seen in 75% of patients, indicating its efficacy is similar.

Any drug taken on a long-term basis will have compliance issues and it is imperative that our patients are counseled the need to be compliant. The importance of compliance was emphasized by Dr. Purvish Parikh et al., where the CCyR rate in patients taken with more than or less than 4 weeks gaps irrespective of brands was 57-80%.

At TMH Dr. Purvish Parikh et al. documented resistance or relapse in 372 (38%). Dr. Shweta Bansal et al. data from Asian Institute of Oncology, showed that primary and secondary resistance was significantly high in the patients registered as old cases but were not affected by Sokal scoring. The reson for this is not clear.

Several issues need to be addressed by us for our patients. While the appropriate molecule upfront would appear to be Imatinib mesylate for cost reasons, identifying a subset early that may not be responsive after an adequate trial is essential to prevent progression of disease, a phenomenon we cannot afford! Strategies of monitoring especially molecular are deficient either due to cost or availability of reliable testing, something that will have to be worked out by an Indian Consortium so that specialized labs in different zones could be referred the samples as per quality control norms for standardized results. While such test should be preferably done in-house, it appears impractical. Inability to routinely perform the molecular tests is highlighted in Dr. Shweta Bansal et al. data from Asian Institute of Oncology, where in her study; maximum patients have been followed with blood counts only, cytogenetic study on follow-up was done in few patients only, who could afford it.

Importantly, to have a national level data bank several variables will have to be sorted out such as appropriate test for assessment of response, time (interval) and frequency of test while on treatment, implementation of uniform response criteria, standardization of tests, criteria for the increase or changeover of treatment and the appropriate use of allogeneic transplantation in the younger population not responsive to therapy. Importantly, our ability to recognize the resistance mutations early as per laid criteria would be important especially in the younger population to preempt change of therapy. The role of allogeneic bone marrow transplant should be put in its proper perspective for our population.

It appears from these studies that our CML OS, pattern of response in CP, CCyR with compliance (or non-compliance) is similar to the western population. Where we lack is probably monitoring by molecular tests and uniform implementation of response criteria. These studies also reiterate the stand that the innovator and generic are similar in their efficacy, a thought to cheer a large number of patients who may not be able to afford the innovator brand.

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