Imatinib Mesylate Therapy in Chronic Myeloid Leukaemia: The Floodgates Opened

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Chronic myeloid leukaemia (CML) is the first human cancer where non-random cytogenetic abnormality specific to a cancer was discovered. This was Philadelphia (Ph) chromosome which is the result of a reciprocal translocation between chromosome 9 and 22. It was subsequently shown that CML is characterized by the presence of a bcr/abl fusion gene. Today, the world health organization (WHO) defines CML as the bcr/abl+ disease. Everything else is called atypical chronic myeloproliferative disorder.

Imatinib Mesylate (IM) - represents a monumental leap forward in management of oncology patients. It proves a principle. It justifies an approach. It demonstrates that highly specific and non-toxic therapy is possible. IM binds to the inactive conformation of bcr / abl tyrosine kinase, suppressing the Philadelphia chromosome - positive clone in CML. Clinical studies of IM have yielded impressive results in the treatment of all phases of CML.

With the higher rates of complete cytogenetic response following IM, molecular monitoring of disease has become mandatory in assessing response and determining the prognosis. Also, attempts are being made to determine pre-therapeutic predictors of response to imatinib.

In this issue of JAPI, there are two articles discussing these two aspects of IM therapy in CML.

Firstly, Usman M et al from Karachi, Pakistan, in a prospective study from May 2001 to September 2006, have studied 136 patients with CML-chronic phase and analyzed various variables to predict the response to imatinib therapy. These include age, disease duration at time of starting imatinib and Sokal score at the time of initial presentation. They have concluded that low Sokal score predicts higher haematological as well as cytogenetic response while younger age and shorter disease duration prior to therapy had no significant influence on the response to IM therapy.

Various pre-therapy predictors that have been studied to assess the response to IM therapy include: Sokal / Hasford scores, Cytogenetic analysis, mRNA expression profiles, Intrinsic sensitivity to abl kinase inhibitors, Baseline level of bcr / abl mRNA and Sensitive baseline screen for bcr / abl mutations.

Both Sokal and Hasford scores were developed in the pre-IM era. However, they have some value in predicting response to imatinib. High-risk Sokal patients achieving complete cytogenetic response (CCR) at 12 months have a 90% probability of survival at 54 months compared to 97% in low-risk Sokal patients (p = 0.054).

However, even the most unfavorable prognostic score is not sufficiently adverse to justify transplant without a trial of imatinib.

In presence of additional (besides Ph chromosome) chromosomal abnormalities, it has been suggested that IM therapy may be started in a higher dose i.e. 600-800 mg/day. This is what is done for patients with accelerated phase. Prognostic significance of deletions in 9q+ in the imatinib era remains uncertain.

Microarray studies have been conducted on pre-therapy CML blood or marrow cells, with an expectation that they will provide a patient-specific profile which will be predictive of response to IM therapy. At this stage, none have been sufficiently characterized to be incorporated into treatment guidelines.

The sensitivity of CML cells to abl kinase inhibition by IM can be calculated by determining the concentration of IM needed in vitro to inhibit bcr / abl kinase activity by 50% (IC50Imatinib). The prognostic impact of IC50Imatinib has not yet been tested in the setting of conventional IM doses. The notion that variable cellular uptake of IM is a key factor in determining response is supported by certain studies. Currently, there is no evidence that the amount of bcr/abl in the blood at diagnosis has predictive value. Lastly, significance of baseline bcr/abl mutation remains unknown. Duration of disease prior to imatinib therapy, pre-therapy peripheral blood blast cell count and the cytogenetic response at 6 months are all predictive of the risk of developing resistance associated with mutations.

In the second study published in this issue of JAPI, Gupta and Prasad have discussed about molecular response evaluation in 16 patients of CML - chronic phase using RQ-PCR six monthly for one year. They conclude that molecular response evaluation after six months can predict the depth of final molecular response.

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The amount of bcr/abl transcript in the peripheral blood, measured as a ratio of bcr/abl to a control gene, provides an estimate of the number of terminally differentiated cells that are leukemic. The level of bcr/abl is a good predictor of progression free survival (PFS). In the IRIS study, serial RQ-PCR assays indicated that the log reduction in bcr/abl, measured from the standardized baseline, was a good predictor of subsequent response and risk of progression. The achievement of major molecular response (MMR) by 12 months in the IRIS trial was associated with 100% probability of transformation-free survival at 60 months. MMR was achieved by 40% in the IRIS trial by 12 months and by 75% at 44 months.

Success of IM in CML has virtually opened the floodgates for molecularly targeted therapies in oncology. However, it does not guarantee success of similar degree for all cancers because CML is not typical of most other malignancies. Also, we still have to learn about maximizing the value of this approach.

IM has astonishing efficacy in CML and clinical studies have not shown substantial short or long-term toxic effects. However, recently, Kerkela et al described a potential new adverse event: left ventricular dysfunction and congestive heart failure in 10 patients treated with IM. The ejection fraction dropped significantly during IM therapy. Targeting the array of kinases in cancer is a rapidly expanded strategy for developing drugs for the treatment of cancer. Present in vitro testing includes only a subgroup of the entire human kinase complement (518 enzymes). Also, secondary modifications and different conformations that affect kinase activity in vivo make it even more difficult. Therefore, it is critical that the pre-clinical work-up of the novel agents which are molecularly targeted is stringent and systematic. The drugs need work-up of the novel agents which are molecularly targeted for years of work from dedicated and talented scientists in CML, drug design and testing. All these required years of work from dedicated and talented scientists in CML, drug design and testing. All these required years of work from dedicated and talented scientists in CML, drug design and testing. All these required years of work from dedicated and talented scientists in CML, drug design and testing.

In the beginning, during the development days of Glivec of IM, there was enormous skepticism that inhibiting kinases would be a useful strategy. Even with these reservations, congratulations to Brian Druker and his colleagues for accomplishing the equivalent of the 4-minute mile. As anyone who runs knows, breaking the 4-minute mile still remains a formidable task. It requires years of arduous training, dedication and talent and is accomplished by only a handful of elite athletes. Breaking the 4-minute barrier did not make it easier, it just proved it was possible. Similarly, developing a successful agent like IM that targets a causal, molecular event (bcr/abl) in cancer was not easy. It required knowledge of the molecular genetic events in CML, drug design and testing. All these required years of work from dedicated and talented scientists. The success of IM will not have made it easier, but it has proven that the concept of targeting specific molecular genetic events in cancer can result in remarkably effective therapies.

Roger Bannister did not achieve his ground breaking accomplishment alone. He actually was paced by two of his friends for 3 of the 4 laps. Similarly, a successful drug requires contributions from many individuals. Although, the floodgates may not have been opened, it is clear that it is only a matter of time. To me, the floodgates in the fight against cancer using targeted therapy have really opened.

REFERENCES

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