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Nilotinib

A Viewpoint by Gianantonio Rosti

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On 28 May 2001, for the first time a targeted agent against leukaemia reached the cover of *Time* magazine: imatinib, the "new ammunition in the war against cancer" dramatically changed the dismal fate of patients with chronic myeloid leukaemia (CML).

The long-term durability of responses to imatinib in patients with early chronic-phase CML has recently been updated: the cumulative 60-month rate of complete cytogenetic response was 87%, survival without progression to the terminal accelerated and blastic phase was 93%, and event-free survival was 83%.[1] Moreover, the rate of secondary resistance is declining year by year on one hand, while the rate of major molecular response (assuring a virtual 100% response durability in the long term) is, in parallel, increasing.[2] In this scenario, nilotinib, a new aminopyrimidine-derivative tyrosine kinase inhibitor, was developed to overcome its predecessor. Both nilotinib and imatinib switch off BCR-ABL functions through a competitive inhibition at the adenosine triphosphate-binding site, nilotinib being far more specific and selective for BCR-ABL. Moreover, nilotinib is 50- and 7-fold more active on imatinib-sensitive and -resistant cell lines, respectively. These attractive pre-clinical features of nilotinib translated to noteworthy results in imatinib-resistant CML patients in all disease phases. Approximately one-half and one-third of imatinib-resistant CML patients treated with nilotinib 400mg twice daily for ≥6 months obtain a major and complete cytogenetic response, respectively. The durability of the responses is still uncertain until data become available for longer follow-up periods.

Nilotinib is generally well tolerated and most adverse events appear to be transient. Fluid retention is not an issue at all with nilotinib and although the possibility of QT prolongation is still a concern, it appears to be a minor one. Nilotinib, like most of the new tyrosine kinase inhibitors (except MK-0457), is inactive against cells harbouring a T315I ABL kinase domain mutation. Given that responses to nilotinib will be durable, it is unclear how often resistance to nilotinib will emerge through a T315I mutation. Moreover, considering previous results with nilotinib establishing its efficacy in the imatinib-resistant setting, is T315I a real shadow in the hopefully shining future of nilotinib in the treatment of early chronic-phase CML patients? Overcoming imatinib resistance requires a precise strategy that, if 100% successful, will provide a complete and durable response in early chronic-phase CML: my personal feeling is that nilotinib has all the features to achieve these expectations. ▲

References

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