Extending the reach of nilotinib in chronic myeloid leukemia

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Clarity regarding the optimal management of a newly or recently diagnosed patient with chronic phase-chronic myeloid leukemia (CML) continues to evolve years after registration of nilotinib and dasatinib for use as alternatives to imatinib for initial therapy. Multiple decision points exist early on while navigating the path of therapy: choice of initial agent; assessment of early (3-6 month) molecular response; managing early toxicity, as the majority of adverse events (AEs) appear early in treatment; and perhaps the most crucial, navigating change in therapy, be it dose escalation or switch to an alternative. This is, of course, preceded by either hesitation or conviction regarding the inadequacy of response or intensity of toxicity prompting change, with the former (judging 'suboptimal response') driven in large part by guidelines set by the National Comprehensive Cancer Network (NCCN)[1] or European LeukemiaNet (ELN).[2,3] Do we have good counsel on how to manage these situations? Have we covered all the angles yet?

In this issue of *Haematologica*,[4] Timothy Hughes and co-investigators from the ENESTnd trial shed light on an important question arising from this randomized, phase III trial of nilotinib *versus* imatinib in newly diagnosed Philadelphia-positive (Ph^+) CML in chronic phase.[5] Patients in each of the three arms of the trial (imatinib 400 mg QD, nilotinib 300 mg BID, and nilotinib 400 mg BID) with less than optimal response were offered participation in an extension study. While patients receiving imatinib or lower dose nilotinib (300 mg BID) were offered nilotinib 400 mg BID in the extension study, those on nilotinib 400 mg BID were offered imatinib 400 mg BID; the safety, tolerability and efficacy of the alternative regimens were the primary end points. Such an extension design - viewed as controversial by some, as it intervened and thus 'removed' patients from primary treatment arms - was necessary given the trial design and impetus to intervene based on treatment guidelines for less than ideal response.

At the initiation of the ENESTnd trial, the ELN guidelines' definition of suboptimal response and treatment failure at 6, 12 and 18 months (mos),[2] used to identify appropriate patients for the extension trial, differed from current guidelines.[1,3] Inadequate cytogenetic response (>95% Ph^+ (failure) and >35% Ph^+ (suboptimal) at 6 mos; >35% Ph^+ (failure) and 1-35% Ph^+ (suboptimal) at 12 mos) was reason for redirection earlier in treatment onto the extension study. At the 18-month mark, while less than complete cytogenetic response (CCyR) (>0% Ph^+) defined treatment failure, inadequate molecular response (lack of major molecular response (MMR)) defined suboptimal response and thus redirection into the extension study. 'Suboptimal molecular response' remains controversial regarding its implications; data to date more convincingly implicate cytogenetic suboptimal response for both imatinib[6] and 2nd-generation tyrosine kinase inhibitor (TKI) therapy[7] regarding subsequent risk and are less clear regarding the risk of 'suboptimal molecular response'. Given this, what information do we have available regarding the impact of active correction of suboptimal molecular response?

Since the ENESTnd trial, guidelines have evolved and the opportunity to correct molecular response now presents at several time points, ensuring 'early molecular response' (EMR) as well as correcting for lack of subsequent deeper molecular response (lack of MMR). Data on correction for lack of early response have remained elusive, however; initial trials aiming to randomize between dose escalation and switch early in the treatment of chronic phase CML closed for lack of accrual (e.g. NCT00320190, a trial randomizing between higher dose imatinib and dasatinib for suboptimal response to imatinib 400 mg[8]). Now with more impetus to support or refute the impact of EMR, subsequent trials planned and now ongoing should accrue and shed much-needed light on this question.

Regarding optimization of later molecular response, the RENICE study from South Korea[9] continues and will assess the benefits of switch *versus* dose escalation (nilotinib 400 mg BID *vs.* imatinib 400 mg BID after standard imatinib and lack of MMR at 12 mos); in addition, the ENESTcmr study[10] has investigated the potential benefit of change to nilotinib to improve molecular response (including both correcting suboptimal patients lacking MMR and moving patients into deeper molecular response (MR 4.5)) for imatinib patients after two years of therapy. While initial data from ENESTcmr noted failure to reach the primary end point of confirmed complete molecular response at 12 mos, subsequent 36-month follow up shows marked improvement in the speed and proportion of patients able to achieve MR4.5 with switch to nilotinib *versus* maintaining imatinib.

In the ENESTnd trial and forming the basis for the extension study reported herein by Hughes *et al.*,[4] the occurrence of suboptimal response at earlier time points (6 and 12 mos), again reflecting incomplete cytogenetic response, was modest across the study but more common in the imatinib cohort. Suboptimal response at 18 mos, now reflecting incomplete molecular response, was observed much more often (approx. 25-50% of the patients overall) and again was more common in the imatinib cohort. Among these patients and patients with treatment failure, approximately two-thirds entered the extension study. Perhaps it is not surprising to note that the majority of imatinib-treated patients entered the extension study on the basis of treatment failure, and that overall this group contained more patients with higher Sokal risk disease and had not improved their response with imatinib dose escalation. In contrast, the overwhelming majority of nilotinib-treated patients entered the extension on the basis of suboptimal response, mainly late suboptimal molecular response. Lastly, it is not surprising that very few patients treated initially with nilotinib 400 mg BID in the core study entered the extension study intending to receive high-dose imatinib, and this group was not analyzed.

Rates of salvage in the extension trial using nilotinib 400 mg BID were significant for both patients previously on imatinib 400 mg QD or BID and nilotinib 300 mg BID. After imatinib, higher dose nilotinib engendered CCyR in approximately 60% of cases and MMR in approximately 30%; after lower dose nilotinib, higher dose nilotinib engendered cytogenetic and molecular responses in 30-40% of cases. Of note, despite these interventions and improvements in response milestones, patients in the imatinib cohort still faced significant reduction in subsequent progression-free and overall survival in comparison to the nilotinib 300 mg BID cohort.

Of great importance regarding the recommendation to switch therapy is the potential trade-off regarding toxicity. In the Hughes *et al.* study,[4] the authors note adverse events with switch from imatinib to nilotinib were in line with prior phase II studies, including approximately 10% discontinuation for AEs. In the ENESTcmr study,[10] however, with 36 mos of follow up, authors noted that for those patients switching to nilotinib, rates of AEs and related treatment discontinuation were higher in addition to a numerically higher amount of cardiovascular events observed with nilotinib.

What have we learned from this experience? Clearly we have the option and the means to intervene at several time points to optimize response and rescue treatment failure. Given the increasing amount of data on the benefit of early molecular response and the increased risk associated with non-intervention, guidelines[1,3] encourage intervention in order to recuperate missed milestones. Based on available data, we still cannot fully judge the benefit of correcting failure to achieve early molecular response. From the ENESTnd data,[4] there is confirmation of excellent salvage of imatinib-treated patients with switch to achieve missed cytogenetic response milestones and relevant molecular response (MMR), and the merits of dose escalation of nilotinib for similar missed milestones.

Coupled with data from the ENESTcmr study, we now can expect improvement with switch to nilotinib across the spectrum of missed cytogenetic and molecular milestones, from initial cytogenetic response to complete molecular response (more aptly termed MR4.5). The additional improvement in response observed with dose escalation of nilotinib is consistent with a very subtle difference in primary response and earlier evidence of survival advantage seen in the 400 mg BID nilotinib arm compared to the 300 mg BID arm within the core ENEST trial. However, reflecting the caution advised in the report of the 36-month ENESTcmr data, benefits of switch must be weighed against any risks of new toxicity. Certainly, adjusting to an alternative TKI can be tumultuous for patients and typical toxicities requiring management must not be overlooked. Late toxicities such as cardiovascular/vascular AEs must be carefully considered, as early gains may be offset by subsequent complications. Of course, as we continue to actively pursue the possibility of 'treatment-free remission', the attraction of defined treatment duration may increase our focus on short-term gains assuming long-term risk may be reduced or eliminated.

Philosophically speaking, one may increasingly feel that a double major in biology as well as economics is needed to best help CML patients nowadays navigate these issues of so-called 'risk management'…

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Financial and other disclosures provided by the author using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are available with the full text of this paper at www.haematologica.org.

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Hematologic malignancies in elderly patients

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Over recent decades, global life expectancy has increased remarkably, and further increases are anticipated.[1] Current estimates suggest that the most important changes in world population over the next 40 years will occur within the oldest age groups; the number of people aged 65 years and over worldwide is expect-