The Gray-Zone Concept, Suboptimal Response to Imatinib, Shall be Removed from the ELN-CML Recommendations

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To the Editor,

European LeukemiaNet (ELN) expert panel updated the 2006 CML management recommendations in Blood[1] with minor modifications in Journal of Clinical Oncology.[2] The most important criticism about this update is the preservation of the ambiguous concept "suboptimal response to imatinib".[2] This gray-zone concept has been generated without long-term follow-up data on imatinib and in the absence of second generation TKIs in 2006.[1] Latest evidences indicated that the outcome of "imatinib-suboptimal responders" is very similar and as worse as "imatinib-failure patients".[3] Furthermore, in the Table 7, "Continue imatinib same dose; or test high dose imatinib.." was also recommended as a treatment for "imatinib-suboptimal responders".[2] High dose imatinib, which had inferior efficacy when compared to dasatinib and nilotinib,[2] is not superior to standard dose imatinib too.[4] Removal of the misleading concept "suboptimal response to imatinib" could also simplify Table 6 of the manuscript.[2] Adherences of physicians and patients to previous *ELN-CML* recommendations are not so high.[5] Simplification of recommendations may also increase the compliances and the response to treatment.

CML is a progressive disease and time is important. Even complete cytogenetic responders are not in the "safe heaven".[6] For instance; we followed a 51-year-old female patient admitted to our hospital with the complaints of fatigue and abdominal distension. Her hemoglobin was 9.4 g/dl, platelet count 914.000/mm^3 and white blood cell count 152.800/mm^3 with early myeloid cells in the peripheral blood smear. She had hepatosplenomegaly (7 cm and 15 cm below the right and left costal margins, respectively). The *BCR-ABL* fusion gene transcripts were detected in bone marrow aspiration by fluorescence in situ hybridization (FISH) and reverse-transcriptase polymerase chain reaction (RT-PCR). She was diagnosed as high-Sokal chronic phase CML. 800 mg daily imatinib for *CML* treatment was started. Since edema of the legs and face developed, imatinib dose was temporarily reduced to 400 mg with addition of furosemide 40 mg po two times a week. The drug dosage was again increased to 800 mg by resolution of edema after a month. She achieved complete cytogenetic remission (CCGR) after 3 months of imatinib. She remained in CCGR for one month until she developed a sudden blastic transformation after 7 months of diagnosis. She had hypercellular marrow with 90% myeloid blasts. Morphologic and immunophenotyping studies (CD7, CD13, CD22, CD34, CD117, HLA-DR positive) were consistent with myeloid blast crisis.

Simultaneous conventional and molecular cytogenetic (FISH) analysis of the bone marrow aspirate revealed the clonal evolution with 48,XX,+8,+19, t(9;22)(q34;q11.2)t and nucish 9q34(ABLx2) 22q11.2(BCRx2)/9q34(ABLx3)22q11.2(BCRx2) (BCRconABLx1)/9q34(ABLx2)22q11.2(BCRx2) (BCRconABLx1). Remission induction chemotherapy with idarubicin 12 mg/m^2 for 2 days and Ara-C 100 mg/m^2 for 5 days was given. She achieved hematologic remission and was taken to a maintenance therapy with Ara-C 10 mg/day sc plus imatinib 400 mg/day. One month later, leukemic relapse occurred. Further, cytogenetic and FISH analyses revealed the persistence of trisomy 8, trisomy 19 and *Ph** chromosome and 93% of *BCR-ABL* fusion gene, respectively and T315I mutation. This unique case is another example of sudden blastic transformation even in "complete imatinib responders".[6]

START-B trial showed that dasatinib 70 mg twice daily demonstrated high levels of hematologic and cytogenetic responses in patients with blastic phase of *CML* includes the full cohort of 157 patients.[7,8] HR rates were higher in the *MBP-CML* cohort, whereas CyR rates were higher in the *LBP-CML* cohort. The MCyR rate actually exceeded the major HR in *LBP-CML* patients. All responses were obtained rapidly, and 81 and 47% of those patients who achieved a major HR, and 77 and 40% of those who achieved a MCyR remained progression free at the time of evaluation, for the *MBP-CML* and *LBP-CML* cohorts, respectively.[8] Dasatinib, which is the only approved second generation TKI for blastic phase *CML*, may create the opportunity for patients with advanced phase *CML* disease and not eligible for transplant. It would be important to explore options such as dasatinib-based combinations to try to improve long-term outcome.

The expectations in the second generation TKI era of *CML* is high and all treatment recommendations should be established on the basis of long-term patient survival.

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