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Initial decline of BCR-ABL transcript levels as early prognostic marker for patients with chronic myeloid leukemia (CML) treated with imatinib

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Early assessment of molecular and cytogenetic response at 3 months of imatinib treatment has been shown to predict survival and might trigger treatment intensification in slow responders at risk of treatment failure. The direct biological reasons of insufficient response are still not sufficiently investigated yet. A ratio of 3 month and baseline levels might best reflect individual response kinetics and help to establish the early prognosis of CML patients under tyrosine kinase inhibitor (TKI) therapy in the situation of unclear slow response.

Methods: A total of 408 patients were investigated. 58 patients with imatinib onset before initial blood sampling as well as 49 patients treated with hydroxyurea were excluded from the analysis. A total of 301 evaluable patients (median age 52 years, range 18-85, 59% male) were treated with an imatinibbased therapy consisting of imatinib 400 mg/d (n=75), imatinib 800 mg/d (n=132) and combinations of standard dose imatinib with Interferon alpha (n=78) and low-dose cytarabine (n=16). Median follow-up was 4.8 years. Transcript levels of breakpoint cluster region-Abelson (BCR-ABL), Abelson (ABL) and beta-glucuronidase (GUS) were determined by quantitative real-time polymerase chain reaction from the samples, taken at diagnosis and at 3 months. A landmark analysis was performed for progressionfree survival (PFS) and overall survival (OS).

Aims: Evaluation of the prognostic significance of 1) BCR-ABL/GUS at diagnosis 2) the individual reduction of BCR-ABL transcripts given by (BCR-ABL/GUS at 3 months)/(BCR-ABL/GUS at diagnosis) and 3) the established 10% BCR-ABL/ABLIS landmark. 4) Identification of the optimized 3-month cutoff value, using as a reference gene.

Results: Disease progression was observed in 20 patients (6.6%), 13 of them died (4.3%). The median BCR-ABL/GUSIS ratio (%) was 33 at diagnosis and 1.4 at 3 months reflecting a decline to the 0.04-fold. With regard to the above described parameters the following findings were observed: 1) at diagnosis no prognostic cut-off level could be determined. 2) A reduction to the 0.35-fold of the initial BCR-ABL transcript level at diagnosis (0.46-log reduction) was identified as single best cut-off according to a maximal hazard ratio (HR) of 6.3 for OS and separated a high-risk group of 48 pts (16% of pts, 5-year PFS 77%, 5-year OS 83%) from a good-risk group of 253 pts (84% of pts, 5-year PFS 96%, 5-year OS 98%, $p<0.001$, $p=0.001$, respectively). 3) When the established 10% BCR-ABLIS landmark at 3 months was investigated, 67 pts were at high risk (22% of pts, 5-year PFS 87%, 5-year OS 90%) and 234 were good-risk (78% of pts, 5-year PFS 95%, 5-year OS 97%, p=n.s). 4) The 6% BCR-ABLIS landmark at 3 months was chosen for evaluation as well and is practically equivalent in relation to maximal HR and the proportion of high-risk patients. The resulting stratification was associated with an 5-year OS of 98% in the good-risk group compared to 85% in the high-risk group and discriminated significantly for OS and PFS ($p<0.001$).

Conclusions: The individual reduction of BCR-ABL transcripts to the 0.35-fold of baseline levels identify patients more precisely of being prone to disease progression. In the future the velocity of the transcripts might become a stronger predictor than the 10% BCR-ABLIS landmark since it reflects the natural course of the disease and leukemia elimination under the TKI treatment. Herefore, the use of a BCR-ABL-independent housekeeping gene like GUS is necessary. Our results are in the process to be included into the new version of the recommendations of the European LeukemiaNet for the management and monitoring of CML patients underlining their importance.