Profile of BCR-ABL Transcript Levels Based on Sokal Prognostic Score in Chronic Myeloid Leukemia Patients Treated with Imatinib

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ABSTRACT

Aim: to elucidate the pattern of molecular response assessed by logarithmic reduction in BCR-ABL transcription levels based on Sokal prognostic score in chronic phase chronic myeloid leukemia (CML) patients receiving Imatinib treatment. Methods: cross-sectional study was conducted in the Hematologic Outpatient Clinic, Dr. Soetomo Hospital Surabaya in all chronic phase CML patients from June 2008 to June 2012. Data on subject characteristics (age and sex), complete blood count with differential and spleen size were collected. Patients were stratified according to Sokal score at diagnosis. Real-time quantitative PCR (RT-qPCR) were used to monitor BCR-ABL levels in patients who fulfilled study. Proportion difference of complete molecular response (MR) was analyzed by chi-square test, while differences of BCR-ABL transcript level among Sokal...
prognostic scale subgroups was analyzed by Kruskal-Wallis test. Results: 40 subjects finished the study. After 18 months of imatinib treatment, the undetected BCR-ABL transcript level (complete MR) were 7(70%), 8(66.7%), and 9(50%) in low-, intermediate-, and high risk group patients, respectively (p=0.417). Although proportion of subjects with complete MR is higher in sokal low risk group compared to in sokal high risk groups (70% vs. 50%), but this difference is not statistically significant (p=0.557). Kruskal-Wallis test showed that there was no significant difference of BCR-ABL transcript level among Sokal prognostic score subgroup (p=0.734). Conclusion: there was no difference of BCR-ABL transcript level among sokal prognostic score risk groups in chronic phase CML patients treated with Imatinib.

**Key words:** CML, Imatinib, Sokal prognostic score, BCR-ABL/G6PDH transcript.

**INTRODUCTION**

Chronic myeloid leukemia (CML) is the first malignancy associated with a specific chromosome abnormality with an annual incidence of 1 to 2 cases per 100,000 per year and a median onset in the fifth or sixth decade of life.12 The Philadelphia (Ph) chromosome is a shortened chromosome 22 that results from a reciprocal translocation between the long arms of chromosomes 9 and 22. The consequence of this translocation is the fusion of the c-abl oncogene from chromosome 9 with bcr gene from chromosome 22, giving rise to a fused bcr-abl gene. The different fusion proteins encoded by BCR-ABL vary in size depending on the breakpoint in the BCR gene and share a high tyrosine kinase activity, in part responsible for the leukemogenesis. The Philadelphia (Ph) chromosome is seen in 95% of patients with CML.23 Tyrosine kinases are enzymes that transfer phosphate from ATP to tyrosine residues on substrate proteins that in turn regulate cellular processes such as proliferation, differentiation, and survival. Therefore, it is not surprising that deregulated tyrosine kinase activity has a central role in malignant transformation. Until the last decade before targeted therapy, the prospect for patients diagnosed with CML had been relatively unfavorable. Imatinib mesylate (STI571/Gleevec) is the first therapy to target tyrosine kinase activity. The introduction of imatinib has led not only to more favorable outcomes, but has driven the development of advances in monitoring response to therapy at molecular level. The total number of leukemia cells in the body is reduced very substantially in CML patients with BCR-ABL-positive responding to imatinib. This reduction is seen first as restoration of Ph negativity in blood and marrow and there after as decreasing BCR-ABL transcript levels assayed by quantitative polymerase chain reaction. Most patients with chronic-phase CML who receive imatinib achieve complete cytogenetic response (CCyR) and low levels of BCR-ABL transcripts, a status that seems to predict for relatively long survival compared with previous treatments.

Cytogenetic remission with monitoring of the percentage of Philadelphia chromosome-positive cells is the best validated system for the assessment of response to interferon-α and tyrosine kinase inhibitors, since the cytogenetic response is the best surrogate marker of survival. For patients who achieve a CCyR to interferon-α, the 10-year survival is about 75%. For patients who achieve a CCyR to imatinib, the 5-year survival rate is close to 100%. The response is conventionally determined by chromosome banding analysis of marrow cell metaphases. If there are fewer than 20 metaphases, the cytogenetic response can be validated by determining the level of BCR-ABL transcripts with quantitative techniques PCR.

More recently, real-time quantitative PCR (RT-qPCR) has been developed. Results of RT-qPCR usually report the ratio of BCR-ABL transcript level to a reference gene (recommended genes include ABL, BCR, and G6PDH). The level of molecular response (MR) at 12-18 months was confirmed to be predictive of long-term clinical outcomes.4,5 Patients treated with 400 mg daily who achieved a reduction in BCR-ABL transcript numbers equal or greater than 3 logs compared with a baseline value have