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Tyrosine Kinase level and White Blood Cells Count in Untreated and Treated Chronic Myelogenous Leukemia Patients with *BCR ABL* gene

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Abstract: ***Background:*** ***Molecularly, Chronic Myelogenus Leukemia (CML) is defined by the Philadelphia chromosome, t(9;22) (q34;q11.2), which encodes the BCR-ABL1 fusion protein, that disturb the function of tyrosine kinase. Role of tyrosine kinase activity in the cell, include cell-cycle control, transcription process, and mitogenesis, or induction of cell's mitosis. These properties generate the use of Tyrosine Kinase Inhibitor for CML treatment through inhibition of signal transduction. The aim of this study is to find out the correlation between Tyrosine Kinase level as a mediator of signal transduction with the white blood cells count in untreatedand treated patients with CML.*** ***Subject and methods:*** ***This study was held on January–July 2014 in Clinical Pathology Laboratory of Dr Hasan Sadikin General Hospital Bandung, Indonesia. Subjects were divided into two groups: untreated group and treated group after treatments for CML. Chronic Myelogenus Leukemia is diagnosed if BCR-ABL gene is detected using Reverse Transcriptase-Polymerase Chain Reaction technique. Complete blood count was done using Sysmex XT2100i, while tyrosine kinase level was analyzed by Enzyme-linked Immunosorbent Assay technique. Data were analyzed with Wilcoxon signed-rank test, and Spearman's analysis.*** ***Results:*** ***Subject enrolled in this study were 57 CML patients, consist of 34 male and 23 female. We found a significant positive correlation between the number of white blood cell with Tyrosine Kinase level ($r= 0.456$; $p<0.001$) in both untreated and treated group. The level of Tyrosine Kinase and white blood cells count significantly higher in untreated CML patients compared to treated group. No significant different were found in, Red Blood Cells and platelet cells count within two groups.*** ***Conclusions:*** ***This study shown correlation between the numbers of WBC with level of Tyrosine Kinase, in untreated and treated CML patients.***

Keywords: CML, Tyrosine kinase, white blood cells count

1. Introduction

In 1951 William Dameshek stated that Chronic myelogenous leukemia (CML) are included in the class of myeloproliferative disorder characterized by an increase number of cells in the peripheral blood as a result of increase activity of bone marrow proliferation. Chronic myelogenous leukemia (CML) is the first malignancy known associated with genetic lesions, Philadelphia (Ph) chromosome, in more than 95% of CML patients, which was discovered by Rowley in 1973.[1,2] Philadelphia chromosome is formed by translocation between the 3' *Abelson murine leukemia (ABL)* gene which is considered to be an oncogen on the long arm of chromosome 9 band 9q34 (9q34) with the 5' *Breakpoint Cluster Region (BCR)* geneat chromosome 22with a breaking pointon band q11:22 (22q11) resulting *chimeric Breakpoint Cluster Region-Abelson (BCR-ABL)* gene which in virtually all cases results in the formation of a BCR-ABL protein. [3-8] The BCR-ABL protein with a molecular mass of 210 kDa, contains the active tyrosine kinase region of ABL, produces a cytokine-independent, constitutive proliferative signal and affects a variety of down-stream pathways. Overexpression of BCR-ABL protein resulted in disregulation of Tyrosine Kinase (TK) activity and trigger leukemogenesis.[6,9-11] Tyrosine Kinases are enzymes that play a role as mediator in the process of signal transduction for cell proliferation, differentiation migration, metabolism and apoptosis.[12,13]

Chronic myelogenous leukemia is characterized by loss of control of the process of hematopoiesis leading to excessive proliferation and differentiation on myeloid elements at all stages of maturation. Clinically, the patient will experience chronic phase, accelerated phase CML, and blast phase. The chronic phase is characterized by an abnormal proliferation of myeloid precursors. This is occurred due to small differences in maturation imbalances, and then excessive cell growth without abnormality of morphology.[2]

Tyrosine kinase inhibitors (TKIs) have proved to be a great advantage in the management of patients with CML in chronic phase. The drugs are a highly selective inhibitor of the protein tyrosine kinase family, which includes BCR–ABL protein, the platelet-derived growth factor (PDGF) receptor and the c-kit receptor.[14] Treatment monitoring to TKI consist of hematology response (HR), Cytogenetic response (CyR), and molecular respons (MR). Fusion transcript levels of *BCR-ABL* until a >3 log reduction (1000 fold reduction; 0.1% *BCR-ABL* gene according to the international scale (IS)) from the baseline mean, defined as a major molecular response (MMR). In term of treatment responses, it has been reported that this BCR-ABL kinase inhibitor produces a complete HR in 98% of patients. A laboratories complete HR was defined as, a white blood cell (WBC) count of less than $10\times10^3/\mu L$, a platelet cells count of less than $450\times10^3/\mu L$, and no detected mieloblast cells.[15,16]The purpose of this study is to find out the relationship between TK enzyme activity level as a mediator of signal transduction and the WBC count in treated and untreated CML patients.

2. Subject and Methods

The study was conducted between December 2013 and July 2014. The subjects were 57 adult patients diagnosed with CML in the chronic phase and being examined for *BCR ABL* gene quantification ratio in the laboratory of Clinical Pathology Department Dr. HasanSadikin General Hospital,