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COMPARISON OF INSULIN LIKE GROWTH FACTOR-1 LEVELS IN CHRONIC MYELOCYTIC LEUKEMIA PATIENTS RECEIVING IMATINIB AND NILOTINIB THERAPY WITH HEALTHY POPULATIONS

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Abstract
Introduction. CML is the most common form of chronic leukemia in Indonesia, whereas in Western countries it is more commonly found in the form of chronic lymphocytic leukemia (CLL). Chronic myelocytic leukemia (CML) is a chronic myeloproliferative disease with clonal abnormalities due to genetic changes in stem cell pluripotence. This disease is characterized by proliferation of granulocyte series without differentiation disorders. On the CML, the Philadelphia chromosome (Ph1 chr) is found in a reciprocal translocation 9.22 (t9; 22). Insulin-like Growth Factor-1 is a natural polypeptide in the human body that has similarities with insulin. IGF-1 plays an important role in the growth and development of tissues. As such, several studies have shown an association between IGF-1 and -2 circulation rates. IGF-1 plays an important role in terms of stimulating cell proliferation and inhibition of apoptosis. This affects the regulation of the body's physiological growth as well as pathological growth such as cancer. Until now there has been no research on IGF-1 levels in CML patients with imatinib and nilotinib treatment.
Methods. This research is a cross-sectional study, by observing the status of exposure and simultaneous disease in individuals from a single population, in one period. The study was conducted in December 2019 at the Outpatient Clinic of H Adam Malik General Hospital Medan with the approval of the North Sumatera University Research Ethics Commission. Data were analyzed using SPSS where $p < 0.05$ was considered significant.
Results. This study showed that there were no differences in IGF-1 levels between CML patients who received imatinib and nilotinib therapy. The mean IGF-1 results were obtained in the imatinib group 107.43±19.70 and nilotinib 107.43±18.09. While the healthy population is 138.60±52.85.
Conclusion. No significant differences were found in IGF-1 levels between CML patients receiving imatinib and nilotinib therapy with healthy populations.

Introduction
Chronic myelocytic leukemia (CML) is a chronic myeloproliferative disease with clonal disorders due to genetic changes in stem cell pluripotent. The disorder affects the myeloid lineage, monocytes, erythroids, and megakaryocytes. Pathological changes that occur in the form of adhesion disorders of immature cells in the bone marrow, activation of stem cell mitosis and inhibition of apoptosis which results in the proliferation of immature myeloid cells in the bone marrow, peripheral blood and extramedular hematopoiesis.[1]

The incidence of chronic myelocytic leukemia (CML reaches 20% of all leukemia in adults, second only to chronic lymphocytic leukemia. Generally attacks the age of 40-50 years, although it can be found at a young age and is usually more progressive.[1] In children it can be found with CML juvenile form. The incidence in male to female is 3: 2, that in general of 1 - 1.5 / 100,000 population in the entire country.[1]

CML is a form of chronic leukemia that is most often found in Indonesia, while in Western countries it is more often found in the form of chronic lymphocytic leukemia (CLL). Some reported the cause of CML apart from radiation exposure, the atomic bomb was post-radiation ankylosing spondylitis.[1,2]

In CML we found the Philadelphia chromosome (Ph1 chr) a reciprocal translocation of 9.22 (t9; 22). The Philadelphia chromosome is an abnormal chromosome 22 caused by translocation of some genetic material on the long arm (q) of chromosome 22 chromosome 9, and reciprocal translocation of chromosome 9, including the

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ABL oncogene, to the breakpoint cluster region (BCR) which is the point the separation of the place where the chromosome breaks which is specifically found on chromosome 22.

Polymorphonuclear cells and monocytes normally are formed only in the bone marrow. While lymphocytes and plasma cells are produced in various lymphogen organs (lymph nodes, spleen, thymus, tonsils). Some of the white blood cells that are formed in the bone marrow, particularly granulocytes, are stored in the bone marrow until they are needed in circulation. If there is damage to the bone marrow, for example due to radiation or chemicals, there will be an excessive and immature proliferation of white blood cells.

Due to neoplastic myeloid proliferation, the production of other blood elements is suppressed due to competition for nutrients for metabolic processes (granulocytopenia, thrombocytopenia occurs). Leukemia cells also invade the surrounding bone causing bone pain and a tendency to fracture easily. The proliferation of leukemia cells in organs results in additional symptoms: pain due to enlarged spleen or liver, lymph gland problems; headache or vomiting due to meningeal leukemia.[3]

Insulin-like Growth Factor-1 is a natural polypeptide in the human body which has similarities with insulin. Insulin-like Growth Factor-1 consists of a single polypeptide chain that has 3 disulfide chains as bridges between molecules. Insulin-like Growth Factor-1 itself is part of a complex system known as the IGF axis.[4]

In humans, IGF-1 levels are undetectable in neonates. Then it will begin to be detected in childhood and increases to its peak at puberty and lasts until the 3rd and 4th decades of age, then decreases slowly. The normal level of IGF-1 in serum is a sign that the GH level in the blood is normal and vice versa.[5]

The role of IGF-1 in general is to stimulate the proliferation of cell growth, anabolic protein, inhibition of apoptosis, reduce levels of GH and the hormone insulin. This role will be inhibited or reduced when IGF-1 is in a bond with IGFBP-3 and vice versa will increase when it is in a bond with IGFBP-1 and IGFBP-2.[6]

Based on previous studies on IGF-1, some of these studies examined IGF-1 levels in chronic myelocytic leukemia patients compared with healthy populations, as well as several other studies comparing IGF-1 levels in CML patients before and after therapy. However, until now there has been no research on IGF-1 levels in CML patients treated with imatinib and nilotinib. For this reason, this study was conducted to determine the differences in IGF-1 levels in the CML receiving imatinib and nilotinib therapy compared to the normal population.

Methods

This study was an observational study with a cross-sectional design on CML patients receiving imatinib and nilotinib therapy at Haji Adam Malik General Hospital Medan. The research was carried out at the outpatient installation of RSUP Haji Adam Malik Medan with the approval of the USU Faculty of Medicine Research Ethics Commission. The research was conducted starting in December 2019. The sampling technique in this study was purposive sampling, the determination of the sample was carried out with certain considerations, which is inclusion criteria and exclusion criteria. The inclusion criteria in this study were: 1) patients who had been diagnosed with CML; 2) aged ≥ 18 years; 3) patients who are willing to be research subjects; 4) patients taking imatinib and nilotinib for 3 months. Meanwhile, an exclusion criterion in this study were : 1) pregnant women; 2) GFR <15; 3) proteinuria +3; 4) severe systemic disease: pulmonary infection, sepsis; 5) history of other chronic diseases: diabetes mellitus, coronary heart disease, stroke, thyroid dysfunction; 6) CML patients in the blast crisis phase; 7) patients who did not meet the inclusion criteria.

The sample size calculation for this study was determined based on the sample formula to test the proportion of two groups in pairs.7 Based on this formula, the minimum required sample size is 7 people in each group. All patients who met the study criteria were then taken anamnesis to obtain data: age, gender, and other personal data, weight loss, anorexia, fatigue. The physical examination includes measurements of height and weight to determine Body Mass Index (BMI). Then the laboratory staff took 5cc of blood to check IGF-1 levels.

The data that has been obtained from the primary data collection process are then analyzed using the SPSS program. Descriptive statistical analysis was used for demographic data. Unpaired analytical statistical analysis of the T test or Wilcoxon was used to test for differences in numerical variables in the CML and healthy groups. Correlation test was conducted to determine the relationship between numerical variables. The difference was

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considered statistically significant if $p < 0.05$. This study has obtained ethical clearance from the Health Research Committee, Faculty of Medicine, University of North Sumatra. Informed consent was requested in writing from research subjects who were willing to participate in the study without coercion after receiving an explanation of the aims and objectives of this study.

Results and discussion

This study was followed by 24 study subjects who had met the inclusion and exclusion criteria. 11 male subjects and 13 female subjects. Subjects with CML totaled 14 people, normal subjects numbered 10 people. There were 7 CML subjects with imatinib treatment, 7 subjects with nilotinib treatment. The mean age of the research subjects was 43.3 ± 9.9 years. The mean body mass index (BMI) was 24.4 ± 3.2 kg / m^2. The characteristics of research subjects can be seen in Table 1.

Table 1. Basic characteristics of research subjects

Characteristics	n = 24	%
Gender		
Male	11	45.8
Female	13	54.2
Age (years)[a]	43.3 ± 9.9	
Anthropometry		
BW (kg)[a]	64.9 ± 12.3	
TB (cm)[a]	162.8 ± 7.6	
BMI (kg / m^2)[a]	24.4 ± 3.2	

[a]normal distribution, mean ± SD

Based on the results of the analysis that has been carried out, there were no significant differences in the results of anthropometric and laboratory examinations in patients treated with imatinib or nilotinib. The mean BMI of subjects treated with imatinib was 23.6 ± 2.6 kg / m^2, for subjects treated with nilotinib 23.0 ± 1.7 kg / m^2. The mean IGF-1 level in subjects treated with imatinib was 107.43 ± 19.70 ng / mL, for patients on nilotinib treatment was 107.43 ± 18.09 ng / mL. Comparison of the results of anthropometric and laboratory examinations of CML patients can be seen in Table 2.

Table 2. Comparison of the results of anthropometric examinations of and laboratoryCML subjects

Characteristics of	Imatinib n = 7	Nilotinib n = 7	p
Age (years)	40.3 ± 10.9	46.4 ± 13.2	0.362
Sex			
Male	3 (37.5%)	5 (62.5%)	0.280
Female	4 (66.7%)	2 (33.3%)	
BW[a] (kg)	61.9 ± 6.8	61.6 ± 6.9	0.939
TB[a] (cm)	161.9 ± 5.1	163.6 ± 6.4	0.589
BMI[a] (kg / m^2)	of 23.6 ± 2.6	to 23.0 ± 1.7	0.583
Hemoglobin[a] (g / dL)	12.1 ± 2.8	to 12.2 ± 1.8	0.933
Hematocrit[a] (%)	36.4 ± 8.1	36.5 ± 5.3	0.985
Leukocytes[b] (cells / mm^3)	8110 (5540-23980)	11900 (5740-16390)	0.116
platelets[B] (10^3cells / mm^3)	251 (114-871)	256 (116-792)	0.945
MCV[a] (fL)	92.7 ± 8.9	86.5 ± 5.4	0.152
MCH[a] (%)	30.7 ± 2.8	29.0 ± 2,4	0.246
MCHC[a] (g / dL^3)	33.1 ± 1.1	33.5 ± 1.2	0.621
RDW[a] (%)	15.0 ± 2.3	15.1 ± 0.7	0.955
PDW[a] (%)	9.7 ± 1.1	11.6 ± 3.3	0.224
Neutrophils[a] (%)	58.3 ± 13.6	71.4 ± 13.7	0.116
Lymphocytes[a] (%)	26.6 ± 8.9	19 , 7 ± 12.3	0.284
Monocyte[a] (%)	7.0 ± 1.9	7.0 ± 1.9	0.944
Eosinophil[b] (%)	2.8 (0.7-24.9)	1.4 (0, 3 to 3.1)	0,138
Basophils[b]		(%) 0.7 (0,3-4,9) 0.5 (0,2-1,4	

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BCR-ABL[b] (IS%)	55.3 (0 -64.19)	0.05 (0-34.96)	0.073
IGF-1[a] (ng / mL)	107.43 ± 19.70	107.43 ± 18.09	0.999

[a]normal distribution, mean ± SD; unpaired t test
[b]abnormal distribution, median (min-max); the Mann-Whitney test

Based on the results of the analysis that had been carried out, there were no significant differences in the results of anthropometric and laboratory examinations in patients treated with imatinib, nilotinib, and healthy subjects. The mean BMI of subjects treated with imatinib was 23.6 ± 2.6 kg / m^2, subjects with nilotinib treatment were 23.0 ± 1.7 kg / m^2, healthy subjects were 25.8 ± 4.0 kg / m^2. The mean IGF-1 levels in subjects treated with imatinib was 107.43 ± 19.70 ng / mL, patients on nilotinib treatment were 107.43 ± 18.09 ng / mL, and normal subjects were 138.60 ± 52.85 ng / mL. Comparison of the results of anthropometric and laboratory examinations in CML patients and healthy subjects can be seen in Table 3.

Table 3. Clinical and laboratory parameters of CML vand healthy subjects

Characteristics of	Imatinib n = 7	Nilotinib n = 7	Control n = 10	p
Age[a] (years)	40.3 ± 10.9	46.4 ± 13.2	43.3 ± 6.4	0,531
Gender				
Male	3 (27.3%)	5 (45.5%)	3 (27.3%)	0.237
Female	4 (30.8%)	2 (15.3%)	7 (53.8%)	
BW[a] (kg)	61.9 ± 6.8	61.6 ± 6.9	69.3 ± 16.9	0.340
TB[a] (cell / mm^3)	161.9 ± 5.1	163.6 ± 6.4	162 , 8 ± 10.1	0.921
BMI[a] (gr / dL)	23.6 ± 2.6	23.0 ± 1.7	25.8 ± 4.0	0.157
IGF-1[a] (ng / mL)	107.43 ± 19 , 70	107.43 ± 18.09	138.60 ± 52.85	0.157

normal distribution, mean ± SD; ANNOVA test
[b]abnormal distribution, median (min-max); Kruskal-Wallis test
* was significant, p <0.05

Insulin-like Growth Factor-1 is a natural polypeptide in the human body which has similarities with insulin.[4] The normal level of IGF-1 in serum is a sign that the GH level in the blood is normal and vice versa.[5] Insulin-like Growth Factor-1 is produced in the liver by regulation by GH. Growth hormone stimulates the synthesis of IGF-1 in the liver and vice versa, IGF-1 levels will require a reverse response to GH production in the pituitary. Several studies have shown a correlation between IGF-1 levels and blood insulin levels. In patients with Diabetes Mellitus (DM) type 1, absolute insulin deficiency was found and there was also a decrease in serum IGF-1 levels. Likewise, during fasting, IGF-1 levels in serum were also found to be lower than those without fasting.[8]

Insulin-like Growth Factor-1 plays an important role in stimulating cell proliferation and inhibition of apoptosis. This affects the regulation of physiological growth in the body as well as pathological growths such as cancer.[4] Insulin-like Growth Factor-1 has a broad and important role in regulating functions in the human body. Research on experimental animals has shown that "knockout" genes of IGF-1-producing mice will show retarded mental growth and low life expectancy. Almost all cells in the human body are affected by the action of IGF-1, especially in muscles, cartilage, bones, liver, kidneys, nerves, skin and lungs. Several recent studies have also shown a link between IGF-1 and the aging process.[5]

In another study, it was shown that insulin-like growth factor-I (IGF-1) delayed spontaneous neutrophil apoptosis in serum-free medium (SFM), and that this effect was not mediated by the neutrophil modulation of cytokine secretion.[9] Previous studies have shown the presence of IGF-1 receptors in lymphocytes and lymphoblasts of leukemia patients.[10]

Insulin-like growth factor (IGF) plays an important role in tissue growth and development. Thus, several studies have shown an association between circulating levels of IGF-1 and -2 and cancer risk.[11] Another study showed a modest association between higher circulating IGF-1 and -2 levels and an increased risk of prostate, breast, colorectal, and ovarian cancer.[12,13,14,15]

Research conducted by O. Shevah and Z Laron,[16] showed that IGF-1 deficiency in early childhood or deficiency in early childhood provides protection against cancer development in the future.[16] Increased IGF-IR expression

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has been reported in many cancer cell lines and human tumor biopsies.[17] However, in recent years, considerable renewed interest has been generated by the results of prospective epidemiological studies linking circulating IGF-I concentrations, measured in samples taken years before the onset of disease, with the subsequent risk of developing clinical cancer.

In this study, it was found that IGF-1 levels in the CML population receiving imatinib and nilotinib therapy were within the normal reference value range. However, it was found that IGF-1 levels were slightly lower than the control population. This may be due to the suppressive effect of IGF-1 with imatinib and nilotinib. Previous animal studies conducted by Lee, et al.[10] showed that administration of 3 out of 4 chemotherapy drugs decreased serum IGF-1 levels in 11 mice within 72 hours after chemotherapy drug administration. The drawback of this study was that it did not allow the investigators to compare IGF-1 levels before the CML patient population received imatinib and nilotinib therapy.

In this study, there were drawbacks in the form of no IGF-1 results before the patient received Imatinib and Nilotinib therapy. Because it cannot be compared to the IGF-1 results in CML patients at RSUP H Adam Malik Medan before receiving therapy and after receiving therapy, but from previous studies, we can see that the IGF-1 levels in CML patients who received therapy tend to decrease and the value IGF-1 could be equivalent to a control i.e. a healthy population. In this study, we also processed various data such as levels of bcr-abl, hemoglobin, leukocytes, platelets, and various other data contained in the table above.

Conclusion

There were no significant differences in IGF-1 levels between CML patients receiving imatinib and nilotinib therapy and healthy populations and no significant differences in IGF-1 levels between CML patients receiving imatinib and nilotinib therapy.

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