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Blood Laboratory Study in Acute Promyelocytic Leukemia Patients with FLT3-ITD Mutation

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Abstract

Background: Acute Promyelocytic Leukemia (APL) is a well-defined subtype of Acute Myelocytic Leukemia (AML) and known by t (15;17) (PML-RARA) mutation. 20%-40% of AML patients indicate FMS-Like Tyrosine kinase 3 (FLT3) mutations. FLT3 mutations contain two famous mutations: FLT3-ITD (Internal Tandem Duplication) and FLT3-TKD (Tyrosine Kinase II Domain).

Objectives: Many studies have been done on FLT3-ITD. These studies have been acknowledged that the FLT3-ITD mutation had poor prognosis of on AML patients. This study was performed on two APL and APL+FLT3-ITD groups. This study aimed to compare differences in blood laboratory assays between APL and APL+FLT3-ITD patients.

Methods: This study contained 73 patients which divided in two groups: Acute promyelocytic leukemia and FLT3-ITD+acute promyelocytic leukemia. The study methods included: Cell counting and Peripheral Blood Smear (PBS), karyotype, extraction of mRNA and DNA, cDNA synthesis electrophoresis.

Results: This study was ruled out on patients involved with acute promyelocytic leukemia in GHAEM hospital Mashhad, Iran. All patients were diagnosed with t (15; 17) (PML-RARA). The age range of patients was 7-63 (mean: 30.86) and 58 (79.5%) (Male: 22, Female: 36) of patients were involved solely with APL and 15 (20.5%) (Male: 10, Female: 5) of them were APL+FLT3-ITD mutation. Blood parameters that were analyzed included: White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin (Hb), Hematocrit (Hct), Mean Cell Volume (MCV) and Platelet (PLT) count. Each group of patients' population was categorized into HIGH Risk factors and LOW Risk factors.

Conclusion: The consequence of current study demonstrated that FLT3-ITD mutation had a bad effect on laboratory assays in patients involved with Acute Promyelocytic Leukemia.

Keywords: Acute promyelocytic leukemia • Fms-like tyrosine kinase • Internal tandem duplication • Blood cells • Laboratory assays

Introduction

Acute Myeloid Leukemia (AML) is the most common acute leukemia in adults. The first classification of AML was French-American-British (FAB) that classified the AML into M0-M7 subgroups. FAB category was depended on the predominant cell morphology in bone marrow aspiration or Peripheral Blood Smear (PBS) [1]. The new classification of blood disorders is presented by the World Health Organization (WHO).

WHO classified the AML in new categories such as cytogenetic assays, molecular pathology, and Immune-Histo-Chemistry (IHC) [2].

Acute Promyelocytic Leukemia (APL) is a well-known sub-type of AML which occurs in 15%-20% of whole AML disorders [3]. 7%-8% of APL happening is because of de novo mutations [4]. APL is characterized by the dominance of promyelocytic cells in the bone marrow and peripheral blood smears and translocation between chromosomes 15 and 17 [t (15;17) (q22;q21)] that joint two genes on these chromosomes together and make the PML-RARA complex. This genetic disorder occurs in over 98% of APL patients [5]. PML-RARA chimeric proteins block the differentiation process by the reduction of maturation transcription in progenitor cells. The immunophenotype of the APL cells shows a heterogeneous CD13, strong expression of CD33 and CD34, negative for HLA-DR and the

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absence of CD15. One of the most frequent mutations that occur in AML is FMS-Like Tyrosine Kinase 3 (FLT3). FLT3 gene is located on chromosome 13q12 that encodes tyrosine kinase receptor class III (RTKs). Various studies have demonstrated that de novo FLT3-ITD mutation happens in 20% of AML cases. FLT3 expression has an important role in the differentiation and proliferation of hematopoietic stem cells. The structure of FLT3 includes 5 immunoglobulin-like regions termed: An extracellular domain, Juxta-Membrane domain (JM), a transmembrane region and two intracellular tyrosine kinase domain. FLT3 has two well-known mutations: FLT3 with Internal Tandem Duplication mutation (FLT3-ITD) and FLT3 with Tyrosine Kinase II Domain mutation (FLT3-TKD). The possibility of FLT3-ITD and FLT3-TKD occurrence in AML sub-types are 12-38% and 5%-10% respectively. There are different mutations in myeloid disorders and each of them has various effect and prognosis. Many studies have shown that FLT3-ITD has a poor prognosis and a high possibility of recurrence in AML patients. Adversely, some studies acclaimed that the effect of the FLT3-ITD mutation on laboratory outcomes are controversial yet. But, the effect of FLT3-TKD is not so clear and there is no particular prognosis. The purpose of this study is to measure and compare the blood laboratory assays in APL and APL+FLT3-ITD patients to determine the outcome of the FLT3-ITD mutation on laboratory results in APL patients.

Materials and Methods

Patients

The study is performed retrospectively. The sample population was 73 patients from the year 2016 to 2019. The blood samples were related to the hospitalization APL patients in the GHAEM hospital, Mashhad, Iran. The patients have been diagnosed by the hemato-oncology specialist and then the blood samples were referred to the pathology and hematology laboratory. The samples were collected from the patients. The sample can be either bone marrow aspiration or whole blood.

Sample acceptance value: Diagnosis of acute promyelocytic leukemia with t (15; 17) based on WHO 2016 classification. The sample should be sufficient and enough filled. Patients with newly diagnosed or recurrent APL.

Sample rejecting value: Clotted or hemolysis sample. Dubious or uncertain results. Patients without blood disorders. Patients with non-myeloid disorders. Other FLT3 mutations such as FLT3-TKD.

Techniques

Complete Blood Count (CBC): Blood cell count was counted by hematology analyzer SYSMEX. Apparently, these samples were abnormal in analyzing by the analyzer and usually show some errors due to the blasts or precursor cells presence so the blood smear should be checked by pathology specialist or hematology technician. The myeloid precursors especially promyelocytes are dominant in the blood smear. Promyelocytes usually have Auer rods. The other cells (RBCs and platelets) often have no significant abnormality in their morphology [6].

DNA extraction: The DNA extraction was done to analyze patients' genome for FLT3-ITD mutation. DNA molecule was gathered from whole blood samples included EDTA anticoagulant. DNA extraction steps were by the discipline of kit (DENA ZIST ASIA) order: 20 µl protease K and 150 µl of the blood sample and then the addition of BD1, BD2, ethanol 96%, BD3, and BD4 in volume 150 µl , 200 µl , 300 µl , 400 µl and 100 µl consequently. After addition of ethanol 96%, the samples should be transferred to the filter tubes that placed in the kit. The DNA molecule was trapped in the filter tube and after by adding the BD4 solution, The DNA passed through the filter and is dissolved in the lower solution and collected by centrifugation [7].

RNA extraction: RNA was extracted from peripheral blood or bone marrow included EDTA anticoagulant. Then APL blood samples were referred to the cytogenetic department. RNA extraction was done by Yekta Tajhiz Azma kit order (Cat NO: YT9065). mRNA was converted to the cDNA and marker probes were added to cDNA [8].

cDNA synthesis: The cDNA synthesis process was performed by Yekta Tajhiz Azma kit (Cat NO: YT4500) and synthesis steps were by the desired kit. 0.1 ng-5 µl of target RNA and 1 µl of oligo (dT) 18 primer (50 µM) have been mixed with distilled water to make a 13.4 µl complex and then centrifuge for a short time and then 4 µl of 5 x buffer with 0.5 µl inhibitor of RNase (RNasin 40 U/µl) and 1 µl of dNTPs complex and 1 µl of M-MLV (Moloney Murine Leukemia Virus reverse transcriptase) should be added to complete the synthesis of cDNA. The sequence of cDNA primers for t (15; 17) in sense gene chain was F: 5´-AGG CAG TTC A-3´ and in anti-sense gene chain was R: 5´-ATC TCA GGG A-3´. After that, the specified probe (Yekta Tajhiz Azma, Cat NO: YT2505) which contains 5´FAM-AGT GCC CAG CCC TCC CTC GC-TAMRA 3´ sequence was added.

Polymerase Chain Reaction (PCR): The PCR procedure was used to proliferate the FLT3-ITD mutation sequence in the DNA samples. The sequence of FLT3-ITD primer in sense gene chain was F: 5´TGG TGT TTG TCT CCT CTT CAT TGT-3´ and in anti-sense gene chain was R: 5´GTT GCG TTC ATC ACT TTT CCA A-3´. The program of the thermal cycle was: holding in 94 degrees for 5 minutes, cycling section (include: 30 seconds in 94 degrees then 30 seconds in 61 degrees and then 30 seconds in 72 degrees) and terminal holding in 72 degrees for 5 minutes. After that, the proliferated DNA was loaded on the electrophoresis gel [9].

Real-time PCR (RT-PCR): This technique is used to assay the PML-RARA mutation on cDNA chain. The thermal cycler programs were. Holding section: 30 sec in 95 degrees. Thermal cycling: 4 sec in 95 degrees and then 32 sec in 60 degrees. Afterward, if the mutation had occurred in the sequence of the gene the result is demonstrated in a heightened curve and if curve diagram was a straight line it means that there is no mutation happening (Figure 1).

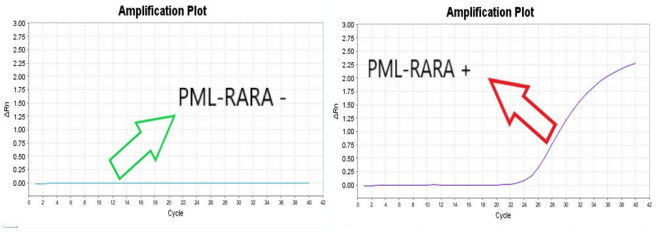

Figure 1. Positive and negative samples for t (15; 17) mutation by ABI step one.

Electrophoresis: Electrophoresis is due to the distinction the FLT3 mutations. So the agarose (2%) and polyacrylamide (5%) gels

were prepared in order to separate the DNA banding pattern. The ladder specification of Agarose gel was YTA 50 bp DNA [10]. The agarose gel electrophoresis voltage system was set on 100-110 volt. After 20 min to 25 min the gel was ready to be read under the UV light. We reached just one banding on the agarose gel. This should be obvious and almost thin. The agarose gel electrophoresis was performed only to ensure that the working process and the gene's proliferation were correct (Figure 2).

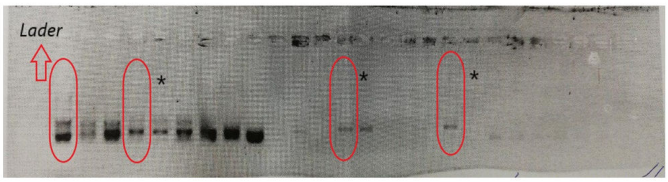

Figure 2: The result of proliferated DNA on agarose gel electrophoresis.

After this step polyacrylamide gel was prepared. The final diagnosis of FLT3-ITD is on the gel polyacrylamide electrophoresis. Then the samples that were clear on agarose gel would mix with 7 µl of Loader solution and then loaded on the polyacrylamide gel. The polyacrylamide gel electrophoresis voltage system was set on 250 volt-260 volt and after 1.5-2 hours gel banding process was ended. The gel was put in ethidium bromide for 5 min to 6 min and then the gel was ready under the UV light. Two-banded samples on polyacrylamide gel were FLT3-ITD positive and negative samples were one banded (Figure 3).

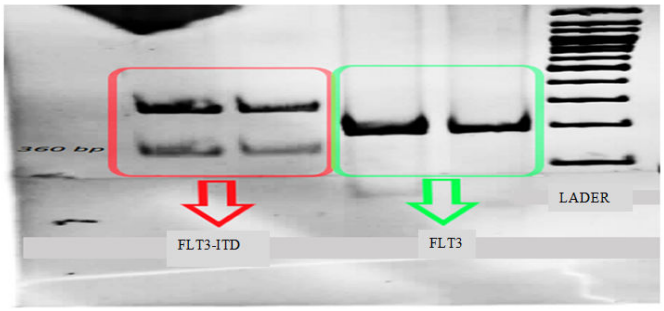

Figure 3. Positive and negative FLT3-ITD mutation by Polyacrylamide Gel Electrophoresis (PAGE).

Statistical analysis: The statistical analysis was done by SPSS ver.22. The normality of parameters was checked by nonparametric tests in two independent parameters (Kolmogorov Smirnov test). No parameters were normal. The comparing between quantitative parameters (blood parameters) and qualitative parameters (FLT3-ITD mutation) were checked by MANN WHITNEY U test. P. value 0.05 was considered meaningful.

Results and Discussion

This study was done on 73 APL patients with age range 7-63 (mean: 32) years old. There were 32 (43.8%) male patients and 41 (56.2%) female patients. 100% of patients had t (15;17) (PML-RARA). 58 (79.5%) patients involved just with APL and 15 (20.5%) of whole patients had APL+FLT3-ITD mutation. although many scientific articles revealed that FLT3-ITD is a bad factor in acute myeloid leukemia malignancies but some studies are dubious about FL3-ITD consequence. Patients' blood results in Tables 1 and 2 demonstrate the potency of FLT3-ITD mutation to make a poor outcome in laboratory blood tests results more than APL without FLT3-ITD mutation.

Parameters	Non-FLT3 APL (Median)	P. value	APL +FLT3-ITD (Median)	P. value	Total (Median)
Age (year)	7-63 (31.00)	0.22	26-55 (37.66)	0.22	7-63 (31.00)
Gender (male-female)	22-36	-	44691	-	32-41 (73)
WBC (x103/µl)	0.4-253 (7.50)	<0.001	3-167 (73.00)	<0.001	0.4-253 (9.70)
0.25	3.7		18.7		4.75
0.5	7.5		73		9.7
0.75	31.65		119.5		49.1
RBC (x106/µl)	1.2-6.07 (3.50)	0.002	1.9-4.41 (2.63)	0.004	1.2-6.07 (3.01)
0.25	2.68		2.44		2.56
0.5	3.35		2.63		3.01
0.75	4.37		2.74		4.18
Hb (g/dl)	5.4-17.5 (10.20)	<0.001	6.1-13.6 (7.70)	0.001	5.4-17.5 (9.30)
0.25	8.4		7.1		7.75
0.5	10.2		7.7		9.3
0.75	13.82		8.5		13.3
Hct (L/L)	17.30-48.5 0 (32.05)	<0.001	19.80-40.5 0 (23.80)	0.003	17.3-48.5 (28.50)
0.25	25.9		22		23.65
0.5	32.05		23.8		28.5
0.75	40.6		27		40.25
MCV (fl)	73-108 (86.50)	0.001	78-108 (90.00)	0.093	73-108 (87.00)
0.25	83		86		83.65
0.5	86.5		90		87
0.75	92		98		92.3
PLT (x103/µl)	11-454 (123.00)	<0.001	11-208 (60.00)	0.047	11-454 (96.00)
0.25	37.75		21		33
0.5	123.5		60		96
0.75	228		124		211

Table 1. Quartiles of characteristics of patients with APL and APL + FLT3-ITD mutation and both together. Note: WBC: White Blood Cell; RBC: Red Blood Cell; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean Cell Volume; PLT: Platelet.

Parameters	Non-FLT3 APL (Mean)	P. value	APL +FLT3-ITD (Mean)	P. value	Total (Mean)
Age (year)	7-63 (30.86)	0.22	26-55 (37.66)	0.22	7-63 (32.02)
Gender (male-female)	22-36	-	44691	-	32-41 (73)
WBC (x103/µl)	0.4-253 (24.15)	<0.001	3-167 (75.84)	<0.001	0.4-253 (34.77)
<10 (n) (%)	36 (62.1%)		2 (13.3%)		38 (52.1%)
≥10 (n) (%)	22 (37.9%)		13 (86.7%)		35 (47.9%)
RBC (x106/µl)	1.2-6.07 (3.46)	0.002	1.9-4.41 (2.69)	0.004	1.2-6.07 (3.30)
<4 (n) (%)	39 (67.2%)		14 (93%)		57 (70.4%)
≥4 (n) (%)	19 (32.8%)		1 (7%)		24 (29.6)

Hb (g/dl)	5.4-17.5 (10.73)	<0.001	6.1-13.6 (8.20)	<0.001	5.4-17.5 (10.21)
<11 (n) (%) 33 (56.9%)	≥11 (n) (%) 25 (43.1%)		14 (93%)		51 (63%)
			1 (7%)		30 (37%)
Hct (L/L)	17.3-48.5 (32.69)	<0.001	19.8-40.5 (25.62)	0.003	17.3-48.5 (31.23)
<35 (n) (%) 35 (60.3%)	≥35 (n) (%) 23 (39.7%)		14 (93%)		53 (65.4%)
			1 (7%)		28 (34.6%)
MCV (fl)	73- 108 (87.92)	0.001	78-108 (91.47)	0.093	73-108 (88.65)
<92 (n) (%) 46 (79.3%)	≥92 (n) (%) 12 (20.7%)		9 (60%)		55 (75.3%)
			6 (40%)		18 (24.7%)
PLT (x103/µl)	11-454 (147.81)	<0.001	11-208 (72.00)	0.047	11-454 (132.23)
<150 (n) (%)	32 (55.2%)		14 (93%)		51 (63%)
≥150 (n) (%)	26 (44.8%)		1 (7%)		30 (37%)

Table 2. Critical border of patient characteristics dividing in low risk and high risk groups. patients with high risk factors usually show Multi Drugs Resistance (MDR) and significant risk of disease recurrence.

Patients with low risk factors often exhibit minimal risk of disease recurrence. Note: WBC: White Blood Cell, RBC: Red Blood Cell, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean Cell Volume, PLT: Platelet.

In Table 2 patients were divided into low and high risk groups. Low risk factors are WBC 10 × 103/µl, RBC ≥ 4 × 106/µl, Hb ≥ 11 g/dl, Hct ≥ 35 L/L, MCV 92 fl and PLT ≥ 150 × 103/µl. and high risk factors are WBC ≥ 10 × 103/µl, RBC<4 × 106/µl, Hb<11 g/dl, Hct 35 L/L, MCV 92 fl, PLT 150 × 103/µl.

The results show that the outcome of APL+FLT3-ITD malignancies are involved with higher proliferation, increased renewability potency of Hematopoietic Stem Cells (HSC) because of the FLT3-ITD ability to make more and more myeloid precursor cells, increased number of disease recurrence, intricate treatment procedure and significant change in blood parameters count as shown (i.e. conspicuous increase in WBC count whilst decrease in RBCs, HB, HCT, PLTs). 28.82 (49.7%) of APL and 12.46 (83.1%) of APL+ FLT3-ITD mutation patients had high risk factors and 29.1 (50.3%) and 2.52 (16.8%) were low risk (Figures 4-9).

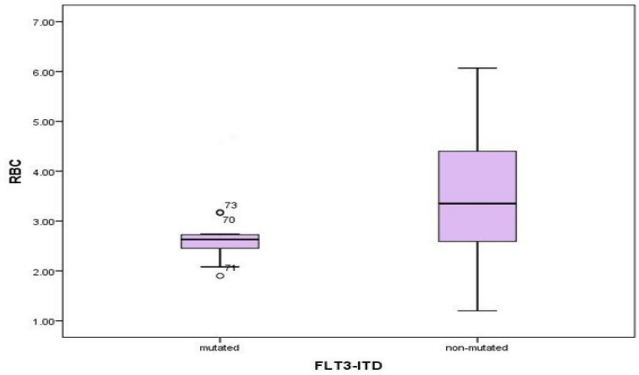

Figure 4. Box-Plot charts to compare the results of two groups of patients: APL+ FLT3-ITD patients and non FLT3-ITD APL patients in RBC.

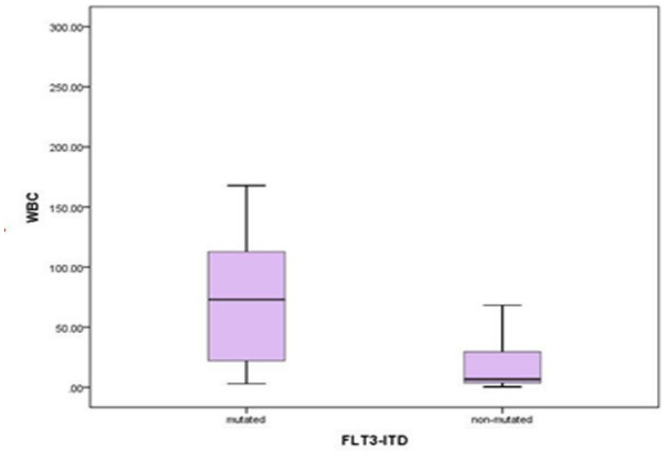

Figure 5. Box-Plot charts to compare the results of two groups of patients: APL+ FLT3-ITD patients and non FLT3-ITD APL patients in WBC.

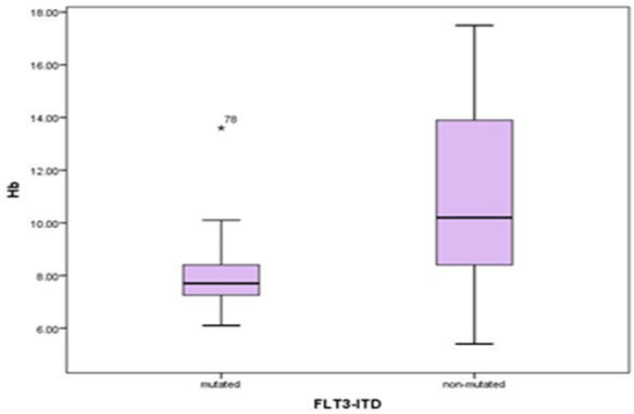

Figure 6. Box-Plot charts to compare the results of two groups of patients: APL+ FLT3-ITD patients and non FLT3-ITD APL patients in Hb.

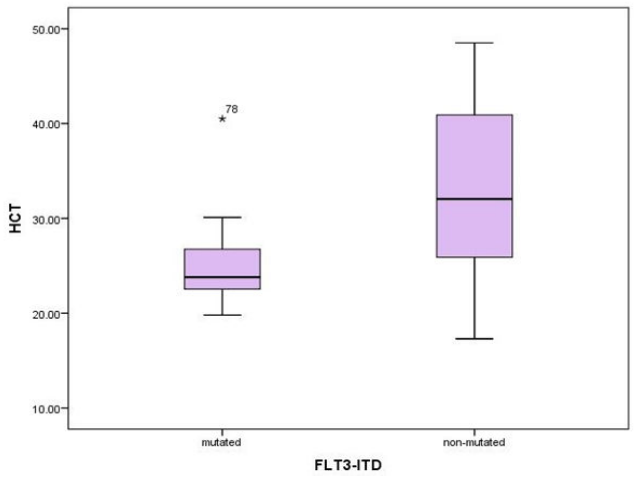

Figure 7. Box-Plot charts to compare the results of two groups of patients: APL+ FLT3-ITD patients and non FLT3-ITD APL patients in HCT.

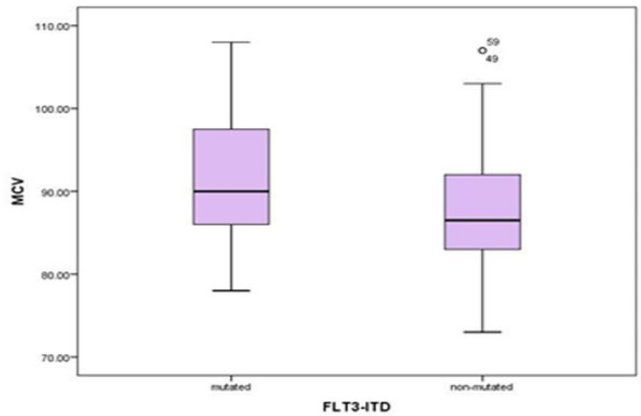

Figure 8. Box-Plot charts to compare the results of two groups of patients: APL+ FLT3-ITD patients and non FLT3-ITD APL patients in MCV.

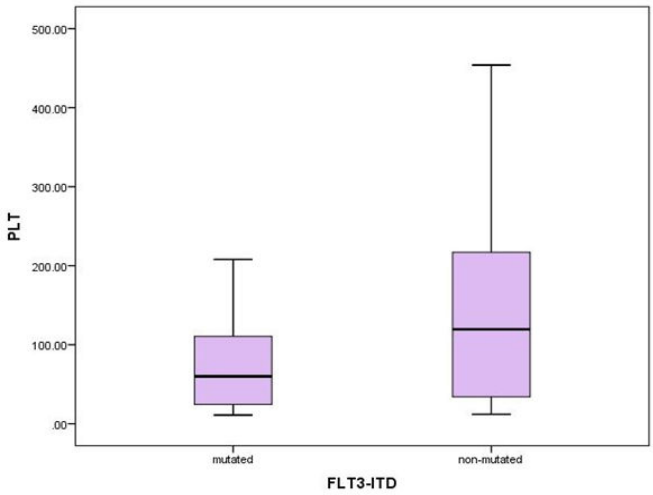

Figure 9. Box-Plot charts to compare the results of two groups of patients: APL+FLT3-ITD patients and non FLT3-ITD APL patients in PLT.

Acute promyelocytic leukemia is a subtype of acute myeloid leukemia and occurs because of t (15; 17) in over 98% situations [11-15]. Other different mutations may occur with this malignancy. One of the major mutations in APL is FLT3-ITD. Many studies have shown that FLT3-ITD mutation has a poor prognosis on patient clinical situations and life longevity but some studies mentioned that the consequence of APL+FLT3-ITD is controversial study in 2014 was done on two groups of patients: APL (n=26) and APL+FLT3-ITD (n=8). The median amount in APL and APL+ FLT3-ITD consequently were: WBC (3.4 and 32.1 × 10^9/L), Hb (8 and 10 g/dl) and PLT (22.5 and 24 × 10^9/L) [16-18]. Study in 2005 on 203 APL patients whom 115 patients were negative for FLT3-ITD mutation and 69 of them were APL+FLT3-ITD. Blood cell characteristics contain median APL and APL+FLT3-ITD in two groups consequently were: WBC (2.2 and 8.9 × 10^9/L) and PLT (23.5 and 23 × 10^9/L). These studies have shown the poor outcome of FLT3-ITD mutation on blood parameters. This study is done on various blood characteristics described risk factors in two different phases: APL without FLT3-ITD mutation and APL+ FLT3-ITD [19].

Conclusion

Results showed that the presence of FLT3-ITD mutation causes: Increase in WBC count and MCV index ratio to the non FLT3-ITD APL. Reduction in RBC/Hb/Hct and PLTs count ratio to the non FLT3-ITD APL in most case. Significant increase in the rate of high risk factors in patient with APL+FLT3-ITD (83.3%) and in APL patients were (54.5%). The complex APL+FLT3-ITD patients need more attention for treatment and FLT inhibitors and if necessary patients should receive blood component products for their cytopenias in RBC and PLT count and when WBC count is so high WBC apheresis is recommended to decline danger of Leukostasis in patients. We assume that the increase in MCV index is due to the presence of blast and precursor cells in blood because these series of cells are larger than typical cells in the blood.

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