# CHANGES IN SOME HAEMATOLOGICAL AND COAGULATION PROFILE IN CHRONIC MYELOID LEUKAEMIA SUBJECTS ON IMATINIB

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## ABSTRACT

*Chronic Myeloid Leukaemia (CML) is a disease that affects haemopoietic cells of the myeloid series and it is characterized by the presence of Philadelphia chromosome leading to abnormal proliferation of the cells' lineage. The aim of this study was to assess the changes in some haematological and coagulation profile in chronic myeloid leukaemia subjects on imatinib; a Tyrosine Kinase Inhibitor (TKI). This study was carried out at Obafemi Awolowo University Teaching Hospital Complex (OAUTHC). It included 40 CML patients. 22 of them have been recieving imatinib mesylate (400mg) for at least 3 months. They were further divided 3,6, 9 and 12 months of TKI use. The rest (18) have not yet been placed on TKI (Imatinib).*

*Full Blood Count, (FBC), was assayed using Haematology analyzer, Prothrombin Time (PT), and Partial Thromboplastin Time with Kaolin (PTTK) were analyzed using Quick's method, and serum Calcium level was assayed using Arsenazo III method. Mean ± Standard Deviation (SD) was determined using descriptive statistic, while student t-test was used to determine difference between the Mean values at $p<0.05$ level of significance.*

*The mean values of WBC were significantly lower in CML subjects on TKI for 3 months at $p= 0.025$ when compared with that of CML subjects not on TKI. At 6 months of TKI use, mean values of total WBC count were significantly lower at $p= 0.047$ in comparison with that of CML subjects not on TKI. The mean values of total WBC count remained significantly lower after 9 months of TKI use at $p= 0.014$ when compared with CML subjects not on TKI. At 12 months of TKI use, the mean valuesof WBC, Platelets count, and Prothrombin Time (PT), were significantly lower at $p=0.001$, $p=0.042$, and $p=0.042$ respectively when compared with that of CML subjects not on TKI.*

*This study suggests that some haemostatic and haematological parameters are affected in both CML subjects using the TKI (imatinib) and those not yet on TKI. However, this study supports findings that imatinib has the potential to restore normal haemopoietic function thereby improving chances of survival and life expectancy. Monitoring of these parameters may help in the prevention of coagulation related diseases.*

*Word count = 358*

**Keywords:** *Chronic Myeloid Leukaemia, Haematological parameters, Coagulation profile, imatinib*

## INTRODUCTION

Chronic Myeloid Leukaemia (CML) is the consequence of acquired or genetic damage to the bone marrow cell's DNA [1,2]. These mutated cells reproduce into numerous cells (CML cells). The unrestrained development of myeloid series in CML within the bone marrow causes an upsurge in the cellular population of the myeloid series observable in peripheral blood. Development of progenitors of myeloid is facilitated through a definite connection of the growth factors of hematopoietic stem cells with corresponding receptors and the adhesion molecules present on the surfaces of progenitor cells (committed) with the mechanisms of the extracellular matrix [2]. Clinically, CML is categorized using noticeable leucocytosis observed in the peripheral blood due to diverse phases of maturation of the neutrophils. Basophilia is likewise seen together with slight eosinophilia [3]. The number of blasts is sometimes elevated alongside thrombocytosis. Bone marrow hypercellularity is often present as a result of granulopoiesis in different stages of maturation [3].

Partial thromboplastin time with Kaolin (PTTK) is a coagulation assay that helps in the determination of the activity of both the intrinsic factors; I, II, IX, X, XI, and XII and coagulation pathway (common) having clotting factors I, II, V, VIII and X. This analysis is useful in monitoring of unfractionated heparin (UFH) therapy, the deficiency of clotting factors and in lupus anticoagulant diagnosis [4]. Prothrombin Time (PT) is an in vitro test used to measure the level of activities of extrinsic clotting factors (factors I, II, VII, and X) and supplementary clotting factors that form part of the common coagulation pathway cascade. It has been reported to be important in managing CML disease since the use of TKI has been known to cause a reduction in these factors [4,5]. Calcium signaling has been identified as a mechanism that is important to the regulation of tumour immunity together with the promotion of inflammation. Emerging findings have revealed that fluctuations in calcium ion concentration can modify the inflammation cell pathway that plays an important function in the perioperative immune system [5]. However, alterations of calcium concentration in the blood have been associated with numerous proinflammatory cytokines that are related to tumour growth [6]. Various studies have reported that a general reduction in blood calcium level is present in myeloproliferative disorders and also CML patients on Tyrosine Kinase Inhibitors (TKI) have been known to experience hypocalcaemia [7,8]. It has been reported that cancer cells can cause modification in haemostasis by means of the mechanism of direct communication with endothelial cells to develop an environment that is prothrombotic. Venous Thromboembolism (VTE) causes the need for withdrawal or disruption of chemotherapy. This is considered the secondary reason for morbidity and mortality, reduction in quality of life and a financial challenge on cancer patients [9]. Research have shown that VTE is expected to ensue in leukemia patients in comparison to other malignancies [9]. No known studies have been done concerning how haematological and coagulation profile is affected in CML (both with or without treatment) in Nigeria. Lack of understanding of how this treatment affect CML outcome may predispose them to the dangers of coagulation abnormalities.

There are three coagulation pathways underlying primary and secondary haemostasis: intrinsic, extrinsic, and common Pathways [10]. While the extrinsic pathway is activated due to the occurrence of external trauma, the intrinsic pathway responds to the vascular endothelium's unprompted internal damage. To maintain coagulation, the common pathway, including intrinsic and extrinsic pathways unite at a same location. Factors XII, XI, IX, and VIII are few of the coagulation factors that are present in the intrinsic route. Factors III an VII are two clotting factors that participate in the extrinsic route. The clotting factors I, II, V, X and XIII are part of the same route [11,12]. Clotting factors are also capable of being described by names other than those with Roman numerals. Factors XII, XI, IX, and VIII are sometimes referred to as the Hageman factor, plasma thromboplastin precursor, Christmas factor, and antihemophilic factor A, respectively, in the intrinsic route. Factors VII and III are also referred to as stabilizing factors and tissue factors in the extrinsic route, respectively [12]. The Stuart-Prower factor, proaccelerin, prothrombin, fibrinogen, and XIII are also referred to as the common pathway factors like factors; X, V, II, I, and XIII, respectively [11]. An important aspect in all 3 routes is played by the calcium ion known as coagulation factor IV. Specific factors like factors; II, VI, IX, and X function like serine proteases [12].

The combination of activated partial thromboplastin time, Prothrombin time, platelet counts, together with the international normalized ratio (INR) are among routine laboratory tests used to assess haemostasis and bleeding risk in trauma patients. Although their use is not common, D-dimer and fibrinogen (FIB) concentrations may offer extra insightful information [13] To evaluate the in vitro activity of particular coagulation factors, PT and APTT were first created [13]. Chronic myeloid leukemia (CML) is a chronic myeloproliferative disease that can be identified by a diversity of nebulous symptoms. Because of its hypercoagulability due to hyperleukocytosis, it may result in various clinical coagulation problems [14].

All three coagulation pathways depend heavily on the calcium ion known as clotting factor IV [12] The strict control of the coagulation cascade, which is essential for maintaining haemostasis, is mostly mediated by calcium ions ($Ca^{2+}$) [15]. Numerous coagulation factors, notably; Factor XIII (FXIII), are fully activated by calcium ions together with platelet activation [15].Covalent clot design and strength are controlled by FXIII [15]. Chelation of

calcium causes structural changes in factors V and VIII, which lead to a reduction of procoagulant activity. Some of these factors, notably factors II, VI, IX, and X, work as serine proteases [12,16]. It is now understood that calcium signaling is essential for the control of the immune system in tumours and the stimulation of inflammation. In addition to remodeling various channels within inflamed cells, which are important components of the immune system of perioperative type, changes in calcium ion concentration can also be related to several tumour-related proinflammatory cytokines, according to newly available data [17]. Prostate, breast, and lung cancers are only a few of the cancers for which previous research has demonstrated the predictive usefulness of serum calcium [18]. Additionally, a study documented that serum calcium could support the development of an inflammation-based modified Glasgow Prognostic Score (mGPS) model for predicting survival in a variety of cancers [6,19]. Individuals with CML are first-line treated with imatinib and nilotinib, which are tyrosine kinase inhibitors (TKIs). While nilotinib is an imatinib structural analogue with an effect 20–50 times stronger than imatinib, imatinib is the first-generation TKI that specifically targets CML target cells [20]. However, these medications have the potential to exert their effects on cells other than the primary target cells by non-selectively inhibiting other tyrosine kinase receptors. As a result, side effects like blood electrolyte disturbances, nausea, vomiting, and muscle spasm can occur [20,21]. Low levels of potassium and calcium in the blood create blood electrolyte abnormalities that frequently affect patients and have clinical symptoms like weakness and muscular spasms [7,8]. These can affect the patient's quality of life, especially if TKIs are used for a prolonged time [8]. The aim of this study is to compare changes in some haematological and coagulation profiles among CML subjects on Imatinib; a tyrosine kinase inhibitor with those of CML subjects not yet on the drug.

## MATERIALS AND METHOD

This study evaluated both haematological parameters and some coagulation profile of CML patients both on TKI and those not on TKI. Thirty (40) CML patients were recruited for this study, eighteen (18) of which had been diagnosed CML patients not yet on TKI (Imatinib) and twenty-two (22) CML patients that have been on the TKI (Imatinib) used for at least 3 months (and further divided into 3, 6, 9 and 12 months). The following haematological parameters were analyzed which includes; White Blood Cell count (WBC), Packed Cell Volume (PCV), Platelet (PLT), While the following coagulation profiles were also considered; Prothrombin time (PT), International Normalized Ratio (INR), Partial Thromboplastin Time with Kaolin (PTTK), and serum Calcium (Ca). A questionnaire was given to them to fill which will help identify when the disease was diagnosed, when treatment commenced, drugs being used and duration of use, among other details.

**Group 1:** on TKI for 3 months (n=6)

**Group 2**: on TKI for 6 months (n=5)

**Group 3:** on TKI for 9 months (n=4)

**Group 4**: on TKI for 12 months (n=7)

**Ethical consideration**

Ethical approval was obtained for this study from the Institute for Medical Research and Training (IMRAT) ethical committee of the University College Hospitall with the approval number; **NHREC/05/01/2008a.** (Appendix I).

**Inclusion Criteria**

- Adult subjects (18-65 years)
- Individuals who's oral and written informed consent must have been obtained.
- Patients (CML) placed on Imatinib (400mg) treatment (for at least 3 months) and CML patients not yet on the drug in the **chronic phase** of the disease.

**Exclusion Criteria**

- CML patients identified to be resistant to TKI treatment and those at the **accelerated and blast phase** of the disease.
- Severe septic conditions.
- Pregnant women and Children.
- CML patients who are on warfarin or on any anticoagulant treatment.
- Patients with HIV, liver diseases SLE, vitamin K deficiency, and any reported inflammatory condition
- **Blood sample collection and laboratory procedure**

15mls of blood (Venous) was carefully withdrawn from the median cubital vein. 5mls of blood was dispensed into an ethylene diamine tetreacetic sample bottle for haematological analysis. 4.5mls was dispensed into Sodium citrate bottle for coagulation analysis while 5mls was dispensed into plain sample bottle and the serum separated for serum calcium estimation. All samples were analyzed following good laboratory practice procedures.

**Data Management and Analysis**

Data obtained from the analysis was appropriately coded and inputted into the spreadsheet. The analysis was done using SPSS 26.0. the Descriptive statistics used includes; Mean ± Standard Deviation and were used to summarize the results. Student t-tests was used to compare groups at $p<0.05$ level of significance.

**Full Blood Count**

Materials

- Sysmex Haematology analyzer
- EDTA bottles
- Needle and syringe

**Method 1 (Analysis) [22]**

- Blood samples were collected into EDTA bottles and mixed well
- The samples were run using Sysmex XP 300 (3 parts)
- All the results of all parameters were recorded

## Coagulation profile

**Prothrombin Time (PT) [23]**

**Principle:**

The addition of thromboplastin and calcium to citrate plasma precipitates the initiation of the coagulation cascade initiating the cloth formation. it is used to measure extrinsic factors and factors of the common pathways.

**Procedure:**

- The automated coagulation analyzer was allowed it to warm at $37^0$C
- The PT reagents and samples were warmed up to $37^0$C for about 10 minutes
- 200µL of the reagent was pipetted into clean Khan tubes.
- 100µL of the sample was added to the reagents in the tube and the stopwatch was started immediately.
- At the first appearance of clot formation the stopwatch was stopped and the time was recorded in seconds

**Partial Thromboplastin Time with Kaolin PTTK [23].**

**Principle**

The addition of a factor XII activator, platelet, and $CaCl_2$ to a citrated (Anticoagulant) plasma allows for formation of a stable clot.

**Procedure**

- $CaCl_2$ (0.025M) was prewarmed at $37^O$C for about 10 minutes.
- The automated coagulation analyzer was allowed it to warm at $37^0$C.
- The PTTK reagents and samples were warmed up to $37^0$C for about 10 minutes.
- 200µL of the reagent was pipetted into clean Khan tubes.
- 100µL of the sample was added to the reagents in the tube and was then allowed to react together for 2-3 minutes.

- 100µL of CaCl2 was added to the reagents in the tube and the stopwatch was started immediately.
- At the first appearance of clot formation the stopwatch was stopped and the time was recorded in seconds.

**Calcium (Arsenazo III Method)**

Materials

- Calcium kit (Lot 142220009)
- Mindray Chemistry analyzer

**Principle**

Calcium +Arsenazo III ⟶ a blue coloured complex

**Method:**

| | Blank | Sample |
|---|---|---|
| Reagent | 1000µL | 1000µL |
| Sample | - | 10µL |

Absorbance was read at 630nm

**Calculation**

$$\text{Concentration} = \frac{\text{Absorbance of sample}}{\text{Absorbance of calibration}} \times \text{Conc. Of calibration}$$

## RESULTS

**Table 1:** Frequency of the two categories of CML patients, those on-TKI and those not-on-TKI (Imatinib).

| TKI (400mg Imatinib) | | Frequency | Percentage | Valid Percentage | Cumulative Percentage |
|---|---|---|---|---|---|
| **Patients not-on-TKI** | N | 18 | 45 | 45 | 45 |
| **Patients on-TKI** | Y | 22 | 55 | 55 | 100.0 |
| | Total | 40 | 100.0 | 100.0 | |

Table 1 is a frequency distribution of CML patients on TKI (imatinib) and those not yet on TKI. 22 (55%) were observed to be on 400mg of Imatinib for at least 3 months while 18 (45%) of the participant.

**Table 2:** Comparison of parameters between CML patient on-TKI and those not-on-TKI**.**

| | CML (On-TKI) (n=22) | CML subjects (not-on-TKI) (n=18) | t value | P value |
|---|---|---|---|---|
| **PCV (%)** | 32.58±1.74 | 30.30±4.37 | -0.228 | 0.826 |
| **WBC (cumm)** | 17529.41±6418.53 | 191037.50±78391.00 | 6.504 | **0.000*** |
| **PLT (cumm)** | 269117.64±53443.40 | 363250.00±146611.00 | -0.232 | 0.823 |
| **PT (secs)** | 14.50±0.27 | 15.72±1.35 | 2.333 | 0.052 |
| **INR** | 1.06±0.02 | 1.17±0.12 | 2.183 | 0.065 |
| **PTTK (Secs)** | 34.24±1.02 | 34.53±3.98 | 1.182 | 0.276 |
| **$Ca^{2+}$ (mmol/L)** | 1.83±0.093 | 2.03±0.19 | 0.462 | 0.658 |

* Significant at P<0.05 level of significance.

Table 2 represents the comparison of all measured parameters in CML patients on TKI (Imatinib) and not on TKI. It shows the Mean ± S.D. of Haematological and Coagulation profile in CML patients and the control group with their levels of significance. The PCV in the on-TKI group was observed to be higher (32.58±1.74%) when compared with that of the group not-on-TKI (30.30±4.37%) with no significant difference. The total WBC in on TKI group was observed to be significantly lower (17529.41±6418.53 $mm^3$) when compared with that of the group not on TKI (191037.50±78391.00 $mm^3$) at P= 0.000. Platelet count in the on-TKI group was observed to be lower (269117.64±53443.40 $mm^3$) when compared with that of the group not-on-TKI (363250.00±146611.00 $mm^3$) with no significant.

The PT in the on-TKI group was observed to be significantly lower in CML patients (14.50±0.27secs) when compared with that of the not-on-TKI group (15.73±1.35 secs) at P= 0.003. The INR in the on-TKI group was observed to be significantly lower (1.06±0.02) when compared with that of the not-on-drug group (1.17±0.12) at P= 0.020. The PTTK in the CML group was observed to be lower in the on-drug group (34.24±1.02 secs) when compared with that of the not-on-TKI category (34.54±3.98 secs) with no significant difference. serum Calcium in the on-TKI group was observed to be lower (1.83±0.93) when compared with that of those not-on-TKI (2.03±0.19) with no significant difference.

Table 3: Comparison of measured values between CML patients on TKI for three (3) months and CML patients not on TKI

* Significant at P<0.05 level of significance.

Table 3 represents the comparison of all measured parameters in CML patients on TKI (Imatinib)for about three (3) months and CML patients not yet on TKI. It shows the Mean ± S.D. of Haematological and Coagulation

| Parameters | Not on TKI Mean±S. D. (n=18) | On TKI Mean±S. D. (n=6) | t | df | Sig. diff. |
|---|---|---|---|---|---|
| **PCV (%)** | 30.30±4.37 | 36.00±10.12 | 1.469 | 4 | .216 |
| **WBC (cumm)** | 191037.50±78391.00 | 25960.00±22165.35 | -3.515 | 4 | **.025*** |
| **PLT (cumm)** | 363250.00±146611.00 | 330878.83±147973.33 | .469 | 4 | .663 |
| **PT (secs)** | 15.72±1.35 | 14.30±0.26 | -2.102 | 4 | .103 |
| **INR** | 1.17±0.12 | 1.02±0.44 | -2.714 | 4 | .053 |
| **PTTK (Secs)** | 34.53±3.98 | 35.40±1.91 | .923 | 4 | .408 |
| **Serum Calcium (mmol/L)** | 2.03±0.19 | 1.95±0.48 | -.421 | 4 | .695 |

profile of the two categories. The PCV in the group not yet on TKI was observed to be lower (30.30±4.37%) when compared with that of the group on TKI (for 3 months) (36.00±10.12%) no significant difference. The total WBC was observed to be higher in value (191037.50±78391.00mm$^3$) when compared with that of the group on TKI (25960.00±22165.35 mm3) with a significant difference at p=0.020. Platelet count in the group not yet on TKI was observed to be higher (363250.00±146611.00mm3) when compared with the group on TKI (330878.00±147973.33 mm3) with no significant difference.

The PT in the group that have not been placed on TKI was observed to be lower (15.72±1.35secs) when compared with that of the group on TKI (14.30±0.26 secs) with no significant difference. The INR in the group not yet on TKI was observed to be lower (1.17±0.12) when compared with that of those on TKI (1.02±0.44) with no significant difference. The PTTK in the CML group was observed to be slightly lower in the group not yet on TKI (34.53±3.98secs) when compared with that of the not-on-TKI category (35.40±1.91 secs) with no significant difference. serum Calcium in the group not yet on TKI was observed to be higher (2.03±0.19mmol/L) when compared with that of CML participants on TKI (1.95±0.48mmol/L) with no significant difference.

**Table 4:** Comparison of measured values between CML patients on TKI for six (6) months and CML patients not-on-TKI.

* Significant at P<0.05 level of significance.

| Parameters | Not on TKI Mean±S. D. (n=18) | On TKI Mean±S. D. (n=5) | t | df | Sig. diff. |
|---|---|---|---|---|---|
| **PCV (%)** | 30.30±4.37 | 31.50±1.73 | .827 | 3 | .469 |
| **WBC (cumm)** | 191037.50±78391.00 | 8250.00±2551.00 | -3.273 | 3 | **.047*** |
| **PLT (cumm)** | 363250.00±146611.00 | 301000. 00±270600.56 | -.669 | 3 | .551 |
| **PT (secs)** | 15.72±1.35 | 15.62±1.81 | -.372 | 3 | .735 |
| **INR** | 1.17±0.12 | 1.17±0.17 | -.480 | 3 | .664 |
| **PTTK (Secs)** | 34.53±3.98 | 34.82±6.56 | 1.714 | 3 | .185 |
| **Serum Calcium (mmol/L)** | 2.03±0.19 | 1.78±0.37 | -1.763 | 3 | .176 |

Table 4 represents the comparison of all measured parameters in CML patients on TKI (Imatinib)for about six (6) months and CML patients not yet on TKI. It shows the Mean ± S.D. of Haematological and Coagulation profile of the two categories. The PCV in the group not yet on TKI was observed to be lower (30.30±4.37%) when compared with that of the group on TKI (for 6 months) (31.50±1.73%) no significant difference. The total WBC was observed to remain higher in value (191037.50±78391.00mm3) when compared with that of the group on TKI (8250.00±2551.00mm3) with a significant difference at p=0.04.

Platelet count in the group not yet on TKI was observed to be higher (363250.00±146611.00mm3) when compared with the group on TKI (301000. 00±270600.56mm3) with no significant difference.

The PT in the group that have not been placed on TKI was observed to be lower (15.72±1.35secs) when compared with that of the group on TKI (15.62±1.81 secs) with no significant difference. The INR in the group not yet on TKI was observed to be lower (1.17±0.12) when compared with that of those on TKI (1.17±0.17) with no significant difference. The PTTK in the CML group was observed to be slightly lower in the group not yet on TKI (34.53±3.98secs) when compared with that of those on TKI (34.82±6.56secs) with no significant difference. serum Calcium in the group not yet on TKI was observed to be higher (2.03±0.19mmol/L) when compared with that of CML participants on TKI (1.78±0.37mmol/L) with no significant difference.

Table 5: Comparison of measured values between CML patients on TKI for nine (9) months and CML patients not on TKI

*Significant at p<0.05 level of significance

Table 5 represents the comparison of all measured parameters in CML patients on TKI (Imatinib)for about nine

| Parameters | Not on TKI Mean±S. D. (n=18) | On TKI (n=4) Mean±S. D. | t | df | Sig. diff. |
|---|---|---|---|---|---|
| **PCV (%)** | 30.30±4.37 | 35.20±3.63 | 2.735 | 4 | .052 |
| **WBC (cumm)** | 191037.50±78391.00 | 5080.00±1325.51 | -4.177 | 4 | **.014*** |
| **PLT (cumm)** | 363250.00±146611.00 | 218400.00±712809.4 | -1.425 | 4 | .227 |
| **PT (secs)** | 15.72±1.35 | 14.40±0.64 | -1.652 | 4 | .174 |
| **INR** | 1.17±0.12 | 1.06±0.54 | -1.723 | 4 | .160 |
| **PTTK (Secs)** | 34.53±3.98 | 30.48±5.66 | -.773 | 4 | .482 |
| **Serum Calcium (mmol/L)** | 2.03±0.19 | 1.76±0.35 | -1.137 | 4 | .319 |

(9) months and CML patients not yet on TKI. It shows the Mean ± S.D. of Haematological and Coagulation profile of the two categories. The PCV in the group not yet on TKI was observed to be lower (30.30±4.37%) when compared with that of the group on TKI (for 9 months) (35.20±3.63%) no significant difference. The total WBC was observed to remain higher in value (191037.50±78391.00mm3) when compared with that of the group on TKI (5080.00±1325.51mm3) with a significant difference at p=0.014. Platelet count in the group not yet on TKI was observed to be higher (363250.00±146611.00mm3) when compared with the group on TKI (218400.00±712809.40mm3) with no significant difference.

The PT in the group that have not been placed on TKI was observed to be lower (15.72±1.35secs) when compared with that of the group on TKI (14.40±1.64 secs) with no significant difference. The INR in the group not yet on TKI was observed to be lower (1.17±0.12) when compared with that of those on TKI (1.06±0.54) with no significant difference. The PTTK in the CML group was observed to be slightly lower in the group not yet on TKI (34.53±3.98secs) when compared with that of those on TKI (30.48±5.66secs) with no significant difference. serum Calcium in the group not yet on TKI was observed to be higher (2.03±0.19mmol/L) when compared with that of CML participants on TKI (1.76±0.35mmol/L) with no significant difference.

Table 6: Comparison of measured values between CML patients on TKI for twelve (12) months and CML patients not on TKI.

*Significant at p<0.05 level of signficance

Table 6 represents the comparison of all measured parameters in CML patients on TKI (Imatinib)for about twelve (12) months and CML patients not yet on TKI. It shows the Mean ± S.D. of Haematological and Coagulation

| Parameters | Not on TKI Mean±S. D. (n=18) | On TKI Mean±S. D. (n=7) | t | Df | Sig. diff. |
|---|---|---|---|---|---|
| **PCV (%)** | 30.30±4.37 | 31.85±7.31 | .552 | 6 | .601 |
| **WBC (cumm)** | 191037.50±78391.00 | 3814.28±1348.36 | -5.800 | 6 | **.001*** |
| **PLT (cumm)** | 363250.00±146611.00 | 197000.00±101044.54 | -2.580 | 6 | **.042*** |
| **PT (secs)** | 15.72±1.35 | 14.70±0.55 | -2.573 | 6 | **.042*** |
| **INR** | 1.17±0.12 | 1.07±0.04 | -2.489 | 6 | **.047*** |
| **PTTK (Secs)** | 34.53±3.98 | 33.51±3.47 | -.521 | 6 | .621 |
| **Serum Calcium (mmol/L)** | 2.03±0.19 | 1.79±0.50 | -.961 | 6 | .373 |

profile of the two categories. The PCV in the group not yet on TKI was observed to be lower (30.30±4.37%) when compared with that of the group on TKI (for 12 months) (31.85±7.31%) no significant difference. The total WBC was observed to remain higher in value (191037.50±78391.00mm3) when compared with that of the group on TKI (3814.28±1348.36mm3) with a strong significant difference at p=0.001. Platelet count in the group not yet on TKI was observed to be higher (363250.00±146611.00mm3) when compared with the group on TKI (197000.00±101044.54mm3) with a significant difference at p=0.042.

The PT in the group that have not been placed on TKI was observed to be lower (15.72±1.35secs) when compared with that of the group on TKI (14.70±0.55 secs) with a significant difference at p=0.42. The INR in the group not yet on TKI was observed to be lower (1.17±0.12) when compared with that of those on TKI (1.07±0.04) with a significant difference at p=0.047. The PTTK in the CML group was observed to be slightly lower in the group not yet on TKI (34.53±3.98secs) when compared with that of those on TKI (33.51±3.47secs) with no significant difference. serum Calcium in the group not yet on TKI was observed to be higher (2.03±0.19mmol/L) when compared with that of CML participants on TKI (1.79±0.50mmol/L) with no significant difference.

## DISCUSSION

Tyrosine kinase inhibitors has been reported to be connected with the risk of cardiovascular events like thrombosis and also have been known to interfere with electrolyte balance most especially calcium and potassium [7], which are vital to the signaling pathway and the maintenance of immune response to the malignancy [17]. Imatinib, a type of tyrosine kinase inhibitor, is the foremost therapy that targets CML at the molecular level, it helps to achieve a quick resolution of abnormalities of peripheral blood which is associated with CML. Imatinib has been reported to influence changes in haematological parameters as early as four weeks after the commencement of drug use [24].

The stratification of CML subjects on TKI into various categories based on duration of TKI use (3, 6, 9 and 12 months) gave a broad outlook of the long term and short-term effect of Imatinib use on haematological and Haemostatic profile of the patients. In this study, there was an observable change in the haematological parameters as early as three months of TKI used all through till the 12 months group which was supported by the previous findings of Qin et al., [25] and Amleh, [26] who reported that optimal molecular response was achieved in CML subjects within a year and suggested that these reduction in overall values of previously elevated haematological parameter are a good predictor of patients' survival which shows a favourable function of the TKI. Lower values of PCV during drug use suggests that the use of imatinib may negatively impact erythropoiesis. This finding is similar to the works of Bamgboje et al., [27] who also reported a lower PCV during imatinib use with a lowered BCR-ABL gene expression withing 3 months of TKI use which in turn influences the rate of white cells' proliferation in CML subjects. Jain et al., [28] reported that the use of Imatinib has a myelosuppressive effects on platelets which in turn leads to reduction in platelet counts among CML patients on TK this suggests the reason why a lower platelet count was observed among CML subjects on Imatinib for over three months. However, Daher-Reyes et al., [29] reported that prolonged use of Imatinib has the potential to decrease molecular response in CML subjects causing a relapse.

In this study, general evaluation of the two categories revealed variation in various haematological parameters. The CML patients not yet on TKI had very low PCV value at presentation. this finding is similar to the works of Ngono et al., [30] who documented an 86.4% of CML patients in that study were anaemic this phenomenon can be attributed to "overcrowded" bone marrow (Hypercellularity of Myeloid series stem cells) with a high number on myeloid stem cells making it difficult for erythroid progenitors to thrive. However, the anemic condition

appears to improve in CML patients on Imatinib which supports the submission by Spiess et al., [31] that CML patients have been known to achieve deep molecular response when on imatinib which in turn restores normal haemopoietic functions A significant observation was the markedly elevated total WBC count. This elevation was observed to be more profound in CML patients who have not begun the use of Tyrosine Kinase inhibitor (Imatinib) while those on the drug for three (3) to six (6) months had a significantly lower white cell count. This observation is also supported by a study by Soderlund, [32] and Howlader et al., [1] who credited this elevation of WBC in CML patients to bone marrow hypercellularity precipitated by the B CR-ABL gene formation. However, the CML patients on Imatinib showed a generally favourably outcome with lower WBC, which is credited to the action of Imatinib (Tyrosine kinase Inhibitor) on bone marrow stem cells of the myeloid series as reported by Saglio and Jabbour, [33] who reported that TKI drugs have the potential to restore normal haemopoiesis in CML patients. Also, Abdulmawjood et al., [34] added that CML patients on TKI are likely to achieve a state of deep molecular response (DMR) which causes general remission of the disease and very low chances of relapse if Molecular Response 4 (MR4) is achieved. This level is also known as a treatment-free remission, this is considered the major target of CML treatment [35]. Generally, the platelet count in CML patients was observed to be higher when compared with that of the control group with a significant difference. While the comparison between those on drugs and not on drugs gave a marked increase in platelet count among CML patients not on drugs (Imatinib). This observation is similar to the observation by Findakly and Arslan, [36] who attributed the observed thrombocytosis to bone marrow hypercellularity commonly seen in CML patients. On the other hand, this event is not always seen in all CML patients and reduction in platelet count has been observed in CML patients on imatinib and Ngono et al., [30] supported this in their works where 60.6% of CML patients had normal platelet count. Also, Athale et al., [37] observed a lower platelet count among CML patients on Imatinib (TKI) and attributed this reduction to the inhibition of the production of platelet by the interaction of TKI with platelet growth factors. Conversely, Goa et al., [38] observed an isolated case of thrombocytosis which is rare in CML. And this rare thrombocytosis can be seen in CML patients with the mutation having translocation (9; 22; 11) (q34; q11; q13) on the chromosome.

Lower values of platelets in CML subjects on TKI in comparison to those not on TKI is supported by the works of Goa et al., [38] who submitted that the use of imatinib occasioned a promising outcome in a very occasional case of CML patients with isolated thrombocytosis.

Partial Thromboplastin Time with Kaolin (PTTK), Prothrombin time (PT), International Normalized Ratio (INR) are both methods of analysis for evaluating the activities of various clotting factors [13]. Signs of bleeding generally specify disease progression in the case of the progression of thrombocytic abnormalities which can either be qualitative or quantitative in CML patients and can be determined by evaluating the level of PT, PTTK, and Platelet count [39]. This study discovered a higher PT (with a consequential higher INR) in CML patients when compared with control with a slightly lower PTTK with no significant difference. In comparison between CML patients onTKI and that not-onTKI, PT was observed to be significantly higher (with a consequential significantly higher INR) in diagnosed CML patients (not-onTKI) when compared with that of the CML subjects on TKI. This observation is comparable to a study by Jain et al., [28] who also reported the presence of elevated PT values in some of the CML patients while some had values within the normal range. This elevation was attributed to a likely reduction in factor VII precipitated by both the disease condition and the use of TKI. The lower values of PT observed in CML subjects were similar to a study by Jain et al., [28] who suggested the accomplishment of clinical and haematological remission observed in imatinib users will likely also cause an improvement in the coagulation abnormalities of the extrinsic pathway (Jain *et al.,* [28]. The PTTK in CML subjects not on drugs was observed to be lower when compared with those on TKI with no significant difference. However, both PT and PTTK values remain within the normal range in CML subjects despite the differences in values. These observations are comparable to the works of Ngono et al., [30] who reported in a cross-sectional study a higher PT value among CML patients regardless of their treatment status, this observation was attributed to an increased rate of cellular destruction and inflammatory syndrome and coagulation perturbation observed in patients with CML. However, the same study reported a higher PTTK in CML patients which is at variance with what was observed in this study.

The disturbance of various blood electrolytes like calcium results in various unpleasant symptoms ranging from muscle spasms to coagulation disorders [8, 15]. Calcium ions ($Ca^{2+}$) performs an important role in regulating the cascade of coagulation that is principal to the preservation of haemostasis [15]. Calcium ions are also accountable for the comprehensive activation of numerous coagulation factors, which include coagulation Factor XIII. The factor XIII is in control of the cross-linking preformed fibrin clots which is a covalent bond that prevents their untimely fibrinolysis [15]. This study estimated serum calcium levels among CML subjects both on Imatinib and those who have not started using imatinib yet while also measuring the same parameter in apparently healthy controls. Generally, Calcium level was observed to be lower in CML subjects in comparison with healthy controls with no significant difference. When compared between CML subjects on Imatinib and those not on Imatinib,

calcium level was lower in CML subjects using Imatinib as against those not on drug which suggest a calcium inhibitory effect of Imatinib a concept that is supported by Zacchia et al., [7] and Prenggono et al., [8] submitted that TKI generally cause reduction in plasma Calcium level Matti et al., [40] who also reported a lower calcium level in CML patients on TKI with those on Imatinib having even lower values that those on Nilotinib (a second generation TKI) which indicates that imatinib may possess a higher calcium inhibitory effect than other TKIs. This inhibition may be through the interfering with intestinal absorption, renal reabsorption and bone integrity [40].

**Conclusion**

The outcome of this study suggests a strong correlation between haematological and coagulation parameters in CML subjects and the use of imatinib. Evaluation of the duration of TKI use suggests a gradual improvement of clinical condition and restoration of haemopoiesis with observable changes within three months of imatinib use as reported by previous findings. The general variation in the level of various coagulation parameters suggests that they could be useful as a prognostic marker in the management of CML and as a dependable predictor of the chances of venous thrombosis in CML patients both on TKI and those not yet on TKI. This study suggests that general monitoring of various coagulation and haematological markers may be useful in mitigating the adverse effect of TKI use to avoid the precipitation of a major metabolic imbalance and haemostatic challenges. On the other hand, though some of these parameters are synonymous to previous findings, the pattern of the results suggests a need to be careful in making a definite statement about these parameters since other factors may determine the way these factors affect the pathophysiology of the disease. This study observed a general alteration on the coagulation profile of CML patients both in those using TKI and naïve CML subjects. In addition, this study suggest that erythropoiesis and claicum concentration may be negatively impacted during TKI use and should be monitored during drug use. Due to the fact that very few studies have been done on the changes in some coagulation profiles in CML patients, this study shed more light into the variation in the concentration of these markers which can be used as a predictor of venous thrombosis in CML patients both before and after the commencement of treatment.

**Recommendation**

It is recommended that other markers of coagulation like thrombomodulin and D-dimer should be measured alongside these proteins. In addition, a similar study using a larger sample size would give a far better picture and understanding of haemostatic and haematological changes in CML patient on TKI.

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## APPENDIX II

## ETHICAL APPROVAL

**INSTITUTE FOR ADVANCED MEDICAL RESEARCH AND TRAINING (IAMRAT)**
**College of Medicine, University of Ibadan**
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UI/UCH EC Registration Number: **NHREC/05/01/2008a**

**NOTICE OF FULL APPROVAL AFTER FULL COMMITTEE REVIEW**

**Re: Analysis of protein S, protein C and coagulation profile in chronic myeloid leukaemia**

UI/UCH Ethics Committee assigned number: UI/EC/22/0107
Name of Principal Investigator: **James K. Molade**
Address of Principal Investigator: Department of Biomedical Sciences
College of Health Sciences
Ladoke Akintola University of Technology

Date of receipt of valid application: 05/04/2022

Date of meeting when final determination on ethical approval was made: **N/A•**

This is to inform you that the research described in the submitted protocol, the consent forms, and other participant information materials have been reviewed and *given full approval by the UI/UCH Ethics Committee.*

This approval dates from **16/05/2022 to 15/05/2023.** If there is delay in starting the research, please inform the UI/UCH Ethics Committee so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the* UI/UCH EC *assigned number and duration of* UI/UCH EC *approval of the study.* It is expected that you submit your annual report as well as an annual request for the project renewal to the UI/UCH EC at least four weeks before the expiration of this approval in order to avoid disruption of your research.

*The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the* UI/UCH EC. *No changes are permitted in the research without prior approval by the* UI/UCH EC *except in circumstances outlined in the Code. The* UI/UCH EC *reserves the right to conduct compliance visit to your research site without previous notification.*

UI/UCH EC
15 MAY 2022
APPROVED
COLLEGE OF MEDICINE - U

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