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# The effect of imatinib and nilotinib on blood calcium and blood potassium levels in chronic myeloid leukemia patients: a literature review

Muhammad Darwin Prenggono,<sup>1</sup> Alfi Yasmina,<sup>2</sup> Misna Ariyah,<sup>3</sup> Tenri Ashari Wanahari,<sup>4</sup> Nuvita Hasrianti<sup>4</sup>

<sup>1</sup>Division of Medical Oncology-Hematology, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat/Ulin General Hospital, Banjarmasin; <sup>2</sup>Department of Pharmacology, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin; <sup>3</sup>Medical Education Study Program, Faculty of Medicine, Universitas Lambung Mangkurat/Ulin General Hospital, Banjarmasin, Indonesia

## Abstract

Imatinib and nilotinib are first-line treatments for chronic myeloid leukemia (CML) patients, which act specifically against target cells. However, these drugs may cause side effects, such as electrolyte disturbances. This literature review aimed to provide a comparison of the effects of imatinib and nilotinib on blood potassium and calcium levels. It also summarized their hypothetical mechanism. A comprehensive electronic search of the different

databases was conducted using 'chronic myeloid leukemia', 'tyrosine kinase inhibitors', 'imatinib', 'nilotinib', 'potassium', 'calcium', 'electrolytes' as keywords. This review used PubMed-MEDLINE, Cochrane Library, and Google Scholar as the source databases. Sixteen articles published from 2006 to 2020 were reviewed. Changes in blood potassium levels range from increased to decreased levels, while changes in blood calcium levels range from the lower normal values to below normal values (hypocalcemia). Tyrosine kinase inhibitors (TKIs), including imatinib and nilotinib, have a non-specific target, namely platelet-derived growth factor receptor (PDGFR), which indirectly affects blood potassium and calcium levels in CML patients. The clinical manifestations of these changes vary from being visible only in laboratory tests to displaying a variety of clinical signs and symptoms.

Correspondence: Muhammad Darwin Prenggono, Division of Medical Oncology-Hematology, Department of Internal Medicine, Faculty of Medicine, Universitas Lambung Mangkurat/Ulin General Hospital, Jalan A. Yani No.43, 70233, Banjarmasin, South Kalimantan, Indonesia. Tel. +62.85349532323.  
E-mail: muh.darwin.prenggono@gmail.com.

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## Introduction

The Global Cancer Observatory (GCO) database from International Agency for Research on Cancer (IARC) establishes estimates for all malignancies worldwide. Leukemia was the 15<sup>th</sup> most commonly diagnosed cancer and 11<sup>th</sup> main cause of cancer death globally, according to the GCO database.<sup>1</sup> Chronic myeloid leukemia (CML) accounts for about 15% of new adult leukemia cases, with an incidence of 1-2 cases per 100,000 individuals; while people under the age of 20 accounts for around 2.7% of all new CML cases. CML is characterized by an excessive proliferation of myeloid tissues which usually affects men between 55 to 60 years old.<sup>2</sup>

Imatinib and nilotinib, which belong to the tyrosine kinase inhibitor (TKI) class of drugs, are the first-line treatments for CML patients. Imatinib is the first-generation TKI that acts specifically on CML target cells; whereas nilotinib is a structural analog of imatinib with an effect 20-50 times stronger than imatinib.<sup>3</sup> However, these drugs can act outside the main target cells, through non-selective inhibition of other tyrosine kinase receptors, causing side effects such as blood electrolyte disturbances, nausea, vomiting, and muscle spasm.<sup>4</sup>

Blood electrolyte disturbances that often occur in patients are the decreased level of potassium and calcium, which cause clinical manifestations such as weakness and muscle spasms.<sup>5</sup> These can affect the patient's quality of life, especially if TKIs are used for a prolonged time. Therefore, it is necessary to consider the side effects that may occur during the treatment when determining which TKIs to use.

This literature review is aimed to provide an overview and

identify the processes involved in causing changes in blood potassium and calcium levels after treatment with imatinib or nilotinib and the clinical manifestations that may arise from these changes.

### Search strategy

A comprehensive electronic search of the different databases was conducted using 'chronic myeloid leukemia', 'tyrosine kinase inhibitors', 'imatinib', 'nilotinib', 'potassium', 'calcium', 'electrolytes' as keywords. This review used PubMed-MEDLINE, Cochran Library, and Google Scholar as the source databases. Sixteen articles published from 2006 to 2020 were reviewed.

### Tyrosine kinase inhibitors and their side effects in patients with chronic myeloid leukemia

CML is a myeloproliferative neoplasm, characterized by the fusion of the Abelson Murine leukemia (*ABL1*) gene on chromosome 9 with the Breakpoint Cluster Region (*BCR*) gene on chromosome 22, producing the *BCR-ABL1* gene. This gene will activate the tyrosine kinase enzyme, which will increase the growth and replication of myeloid cells until leukemia occurs. Until 2000, treatments for CML patients were limited to nonspecific agents such as IFN- $\alpha$ , busulfan, and hydroxyurea. These therapies were developed before TKIs were discovered.<sup>3</sup>

TKIs act specifically on the tyrosine kinase receptor and inhibit the interaction between the *BCR-ABL1* gene and ATP. Consequently, the proliferation of myeloid cells does not occur excessively. Furthermore, TKIs can improve the 10-year survival rate from 20% to 80-90%, hence TKIs become the frontline treatment for CML patients.<sup>3</sup> The first-line TKIs for CML patients are imatinib and nilotinib. Imatinib is the first-generation TKI that acts competitively by occupying the ATP-binding site of the *BCR-ABL1* gene and causes inhibition of the phosphorylation process. As the result, the process of proliferation is slowed. Imatinib also targets C-kit tyrosine kinase and platelet-derived growth factor receptor (PDGFR), as nonspecific targets. The standard dose of imatinib for CML patients is 400 mg once daily. Meanwhile, nilotinib, a second-generation TKI, is a structural analog of imatinib with the affinity to the ATP-binding site of the *BCR-ABL1* gene 30-50 times stronger than imatinib. The dose of nilotinib for CML patients is 300 mg twice daily.<sup>3,6</sup> Most patients will have to continue taking these medications for life.<sup>6</sup>

CML has developed into a chronic condition that is also affected by age-related comorbidities, hence the clinicians should improve their focus on the patient's quality of life and attempt to avoid long-term organ toxicity. The toxicity of a drug is reported under the general heading of 'adverse events' (AEs) which are divided into two, namely hematological and non-hematological AEs. Hematological AEs include symptoms such as neutropenia, anemia, and thrombocytopenia. Meanwhile, non-hematological AEs are divided into 'side effects' that affect tolerability and quality of life which result in treatment change in about 30% of patients, and 'complications' that may affect the patient's health significantly resulting in treatment change in up to 15% of patients.<sup>6</sup>

Information about the patient's quality of life is important to be assessed by clinicians. This information can be assessed objectively through laboratory examinations or directly through patient's medical reports with regard to symptomatic toxicities, such as nausea, fatigue, and muscle spasm.<sup>7</sup>

In general, imatinib and nilotinib have a good safety profile, although the finding of grade 1/2 non-hematological side effects is quite common.<sup>8,9</sup> Nausea, vomiting, diarrhea, fluid retention, fatigue, and muscle spasm are the most prevalent side effects of imatinib treatment<sup>10</sup>, whereas nilotinib treatment frequently results

in an increase in cardiovascular events, particularly QT prolongation, and a skin rash.<sup>11,12</sup>

One of the non-hematological side effects experienced by CML patients taking imatinib or nilotinib is muscle spasm. Saglio *et al.*, in a phase 3 study evaluating the efficacy and safety of using nilotinib as compared with imatinib in 846 CML patients, stated that muscle spasm of all grades was reported more in patients treated with imatinib compared to nilotinib 300 mg and 400 mg (24% vs 7% and 6%).<sup>8</sup> Furthermore, Hochhaus *et al.*, who studied the same population with 5 years of follow-up, reported that muscle spasms of all grades were still found and most prevalent in patients taking imatinib compared to nilotinib 300 mg and 400 mg (33.9% vs 12.2% and 11.6%).<sup>13</sup>

Based on the two studies above, it can be concluded that muscle spasm is more common in patients taking imatinib. This may occur due to biochemical changes in patients, one of which is disturbances in blood calcium levels. Other musculoskeletal symptoms that may be associated with this disorder are bone pain, arthralgia, and myalgia.<sup>14</sup>

In the same study, Hochhaus *et al.* reported symptomatic QT prolongation cases of all grades in 2.9% patients treated with imatinib and 1.8% and 2.5% patients treated with nilotinib 300 mg and 400 mg, respectively. Syncope and seizures are among the symptoms reported; whereas other symptoms such as ventricular flutter, ventricular fibrillation, ventricular tachycardia, torsade de pointes, and sudden death are not reported.<sup>13</sup> Inhibition of the potassium channel's hERG subunit causes QT prolongation in the cardiac organ. Any change in blood potassium levels, specifically hypokalemia, can trigger this event. Nilotinib should be avoided in those who have a long QT syndrome.<sup>14,15</sup> A summary of literature related to side effects of TKIs in CML patients is shown in Table 1.<sup>7,8,11,13,14,16,17,18</sup>

Considering that TKIs can be administered for a prolonged time, low-level side effects can also affect the patient's quality of life. Therefore, when choosing the first treatment to be administered, the clinician must consider the efficacy, tolerability, and toxicity of the drug.<sup>6,16</sup>

### Effects of tyrosine kinase inhibitors on blood potassium level

Imatinib and nilotinib, in addition to act on the main target cell, namely the *BCR-ABL1* gene, also act on the PDGFR which may cause kidney disorders and affect blood potassium levels.<sup>3,19</sup> Marcolino *et al.* did a retrospective investigation in 100 CML in chronic phase (CML-CP) patients, and Yilmaz *et al.* in 253 patients with CML-CP treated with imatinib, reported the incidence of acute kidney injury in 7 and 19 patients, respectively, with blood potassium levels remain below the level considered for diagnostic criteria of tumor lysis syndrome, hence it can be concluded that the patient's blood potassium level was not increased. The result of this study also did not mention whether blood potassium levels were within normal range or had decreased, thus the effect of imatinib treatment on blood potassium levels in CML patients was less known.<sup>19,20</sup>

In contrast to the above studies, a phase 3 study conducted by Chuah *et al.*, in comparison of the safety of dasatinib and imatinib treatment in 260 patients with CML-CP in East Asian and non-East Asian populations, reported the incidence of grade 3/4 decreased blood potassium levels in 2 of 48 patients from the East Asian population and 4 of 210 patients from the non-East Asian population.<sup>21</sup>

Moreover, Wang *et al.* completed a phase 3 trial which evalu-

Table 1. Literature related to side effects of tyrosine kinase inhibitors in patients with chronic myeloid leukemia.

No.	Author, Year	Research Topic	Research Subject	Research Result	Level of Evidence
1.	Saggio <i>et al.</i> , 2010 <sup>8</sup>	Comparison between nilotinib and imatinib in newly diagnosed CML patients.	846 patients with CML in chronic phase (CML-CP) were randomly assigned in 1:1 ratio to receive TKI treatment in the form of imatinib 400 mg once daily, nilotinib 300 mg twice daily, and nilotinib 400 mg twice daily	Non-hematological adverse events of grades 3/4 were uncommon overall. In imatinib-treated patients, nausea, vomiting, edema, and muscle spasms were more prevalent; while in nilotinib-treated patients, headache, pruritus, rash, and alopecia were more prevalent. Muscle spasms was reported in 20 patients (7%) treated with nilotinib 300 mg; 17 patients (6%) treated with nilotinib 400 mg; and 67 patients (24%) treated with imatinib.	2
2.	Efficace <i>et al.</i> , 2016 <sup>9</sup>	Assessment of quality of life in CML patients receiving tyrosine kinase inhibitors.	This article has no subjects because it is a review.	Information regarding the life quality of CML patients receiving TKIs (imatinib or nilotinib) is important to be assessed. This determination can be achieved objectively using standardized measurements under the National Cancer Institute's CTCAE, such as reporting system in which the reported toxicity is mostly laboratory abnormalities, or directly by considering symptomatic toxicity, such as nausea, fatigue, and muscle spasms. These are reported in patients' medical records.	5
3.	Cortes <i>et al.</i> , 2016 <sup>6</sup>	Evaluation of the effect of switching to nilotinib on chronic low-grade imatinib-related adverse events in CML patients.	After receiving imatinib for at least 3 months, 52 patients with CML-CP experienced grade 1/2 non-hematologic AE. They were switched to nilotinib 300 mg twice daily for 12 cycles (1 cycle = 28 days).	Switching treatment to nilotinib is an effective strategy to reduce or even resolve chronic low-grade adverse events in imatinib-treated patients. In addition, the patients also reported improved quality of life after taking nilotinib.	3
4.	Hochhaus <i>et al.</i> , 2015 <sup>5</sup>	The risks and long-term benefits of nilotinib, as compared with imatinib, in patients with CML-CP after 3 years follow-up.	In 1:1 ratio, 846 patients with CML-CP were given TKI treatment in the form of nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg once daily.	Overall, muscle spasms of all grades were still reported and more prevalent in patients taking imatinib (33.9%) than nilotinib 300 mg (12.2%) and 400 mg (11.6%). In addition, symptomatic QT prolongation was also reported more common in patients taking imatinib (2.9%) than nilotinib 300 mg (1.8%) and nilotinib 400 mg (2.5%).	2
5.	Stegmann <i>et al.</i> , 2016 <sup>4</sup>	Recommendations for the management and avoidance of adverse events in CML treatment.	This article has no subjects because it is a review of prospective and retrospective cohort studies.	Muscle spasms is the most common musculoskeletal side effect and more prevalent in patients taking imatinib than nilotinib. This disorder may occur because of disturbances in calcium regulation in the body. In addition, arrhythmia is often found in the form of QT prolongation and is associated with the patient's blood potassium levels.	1
6.	Shin <i>et al.</i> , 2018 <sup>11</sup>	Evaluation of the efficacy and safety of nilotinib in phase 4 study of patients with CML-CP in South Korea.	110 patients with CML-CP with a mean age of 55 years received nilotinib 300 mg twice daily.	This study represents the elderly population of CML patients. The side effects that frequently occurred in the patients were cardiovascular events, especially QT prolongation, and skin rash.	3

Not using \*: Howick *et al.*, 2011<sup>17</sup>; Using \*: Joanna Briggs Institute, 2014. <sup>8</sup> AE, adverse events; CML, chronic myeloid leukemia; CML-CP, chronic phase CML; CTCAE, common terminology criteria for adverse events; TKI, tyrosine kinase inhibitor.



ated the efficacy and safety of using nilotinib as compared with imatinib in 265 patients with CML-CP in China, reported the incidence of decreased blood potassium levels of all grades was more prevalent in patients treated with imatinib (50%) compared to nilotinib (21.1%).<sup>22</sup>

Meanwhile, Hasan *et al.* performed a prospective study in 30 nilotinib-treated CML patients reported an insignificant decrease in blood potassium levels when compared to the healthy control group. When comparing the blood potassium levels before and after nilotinib treatment, there was also an insignificant decrease in blood potassium levels.<sup>23</sup>

The prospective study of Hochhaus *et al.* about the evaluation of the efficacy and safety of nilotinib treatment in 1089 patients with CML-CP reported changes in the patient's blood potassium levels which include an increase in blood potassium levels of all grades (13.5%) and a decrease in blood potassium levels of all grades (12.5%).<sup>24</sup> A summary of literature on the effects of TKIs on blood potassium levels in CML patients is shown in Table 2.<sup>19,20,21,22,23,24</sup>

Overall, the above discussion suggests that changes in blood potassium levels can occur in CML patients treated with imatinib or nilotinib. In imatinib treatment, blood potassium levels tend to decrease; whereas, in nilotinib treatment, blood potassium levels can increase or decrease. When the two TKIs were compared, the decrease in blood potassium levels was more prevalent in imatinib-treated patients; whereas patients treated with nilotinib had a higher rate of increased blood potassium levels. It is unclear what causes changes in blood potassium levels due to imatinib and nilotinib treatment, but there are several mechanisms associated with damage to the kidneys that might be involved in these alterations.

The reabsorption process of chemical substances, including potassium, in the renal tubules, is an active process that depends on energy (ATP). ATP is produced from the mitochondria contained in renal tubular cells, thus the demands of energy in the reabsorption process is always guaranteed. ATP will be used by the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump to maintain the electrochemical gradient needed in the potassium reabsorption process.<sup>25</sup> Emadi *et al.* in his experimental study on imatinib-treated rats reported a disturbance in mitochondrial membrane function which might be the result of imatinib cellular toxicity, thereby reducing the production of ATP.<sup>25</sup>

About 25% of blood from the total cardiac output will flow from the heart to the kidneys. The blood flow of patients taking imatinib and nilotinib contains the drugs' metabolites. When these metabolites are exposed to the cells along the renal tubules, the cell's sensitivity to injury will increase upon subsequent exposure to nephrotoxic substances because the cells are located in a relatively hypoxic environment, due to the high metabolic requirements associated with active solute transport by Na<sup>+</sup>/K<sup>+</sup>-ATPase pumps. These metabolites will then be reabsorbed by renal tubular cells through human organic anion transporter (HOAT) and human organic cation transporter (HOCT) in peritubular capillaries. Because of competition for apical secretory transporters and loss of function mutations in these transporters, toxin excretion in the urine is reduced. Meanwhile, the high accumulation of toxins in lysosomes will be released into the cytoplasm of the cells and results in mitochondrial injury and dysfunction of the phospholipid membrane which eventually leads to apoptosis and necrosis of proximal tubular cells.<sup>26</sup>

Under normal conditions, injury to the renal tubules will enhance the expression of PDGFR for renal tubular regeneration. PDGF increases mesangial cell proliferation and the formation of the extracellular matrix. However, PDGFR can be inhibited by imatinib and nilotinib through an inhibitory effect outside the main

target cells.<sup>19</sup> Several studies have stated that imatinib inhibits the tubulogenesis process (tubular regeneration) in the kidney through the PDGFβ/PDGFR axis after acute kidney injury, thus the number of active tubular cells in the kidney is reduced. This will interfere with the reabsorption of glomerular filtrate, including potassium. The potassium that is not reabsorbed will be excreted into the urine and if it occurs continuously, it can cause a decrease in blood potassium levels. The reabsorption process will continue to be disrupted as long as the regeneration of the renal tubules is inhibited by imatinib.<sup>19,20</sup>

Meanwhile, the consequence of nilotinib treatment on the kidney organ is still unknown. Iyoda *et al.* who studied nilotinib in people with chronic kidney disease stated that nilotinib has a protective effect on the kidneys, by attenuating kidney injury through the reduction of upregulation of fibrosis-associated genes, such as collagen type-I, fibronectin, and PDGF-β. Thus, the inhibition effect of PDGFR by nilotinib is milder than imatinib. However, the tubulogenesis process may remain disrupted after injury but with less intensity.<sup>27</sup> As a result, the reduction in blood potassium levels is milder. The mechanism associated with an increase in blood potassium levels in CML patients treated with imatinib and nilotinib is still unknown.<sup>27</sup>

The clinical manifestations of the decreased blood potassium levels differ depending on the severity of the condition. The low decrease may only be seen through laboratory tests, without signs and symptoms; while a moderate decrease will cause mild signs and symptoms, especially in the elderly and people with a history of heart or kidney disease. Furthermore, a large decrease in blood potassium levels may produce a variety of signs and symptoms from muscle spasms to arrhythmias.<sup>28</sup> Meanwhile, the clinical manifestations of an increase in blood potassium levels are similar to the those shown by the decrease in blood potassium levels.<sup>26</sup> Other factors that may affect blood potassium levels in CML patients include a history of diabetes mellitus, hypertension, kidney disorders, and the usage of drugs that might affect the potassium levels such as potassium-sparing diuretics (*e.g.*, spironolactone), ACE inhibitors (*e.g.*, lisinopril), and ARBs (*e.g.*, valsartan).<sup>22,29-31</sup> These drugs will cause potassium retention, and eventually hyperkalemia.<sup>32</sup> To date, hyperkalemia is reported as adverse events of TKI treatment. There is a lack of study about possible interaction between TKIs and the mentioned drugs above. Figure 1 depicts the summary of the mechanism of the TKI influence on the blood potassium level.

### Effect of tyrosine kinase inhibitors on blood calcium level

Besides working on the main target cell, namely the BCR-ABL1 gene, imatinib and nilotinib also acts on the PDGFR which can affect blood calcium levels through alteration on calcium metabolism.<sup>5</sup> A study by Berman *et al.* in 63 CML patients who were treated with imatinib reported that these patients had low-normal blood calcium levels accompanied by low blood phosphate levels when compared to the healthy control group.<sup>33</sup> The prospective study conducted by Hasan *et al.* in 30 nilotinib-treated CML patients reported a significant decrease in blood calcium levels when compared to the healthy control group; whereas the comparison of blood calcium levels before and after taking nilotinib also showed a decrease, but not significantly.<sup>23</sup>

Furthermore, a phase 3 study conducted by Wang *et al.*, evaluating the efficacy and safety of using nilotinib as compared with imatinib in 265 patients with CML-CP in China, reported that the

Table 2. Literature related to the effects of tyrosine kinase inhibitors on blood potassium level in patients with chronic myeloid leukemia.

No.	Author, Year	Research Topic	Research Subject	Research Result	Level of Evidence
1.	Marcolino <i>et al.</i> , 2011 <sup>19</sup>	Incidence of acute kidney injury and chronic renal failure in imatinib-treated CML patients; as well as the relation between duration of the treatment and a reduction in the estimated glomerular filtration rate.	105 CML patients who received imatinib treatment, which consisted of 100 chronic phase CML patients, 4 accelerated phase CML patients, and 1 blast crisis CML patient.	During follow-up, 7 patients had acute kidney injury. Uric acid and potassium concentrations remained below the levels considered for diagnostic criteria of tumor lysis syndrome.	4
2.	Chuah <i>et al.</i> , 2014 <sup>21</sup>	Evaluation of the efficacy and safety of dasatinib compared to imatinib in East Asian sub-population of newly diagnosed patients with CML in chronic phase (CML-CP).	519 patients randomized to receive either dasatinib or imatinib. The dasatinib group consisted of 60 patients from the East Asian population and 199 patients from the non-East Asian population; while 48 individuals from East Asian populations and 212 individuals from the non-East Asian population were in the imatinib group.	Patients receiving imatinib treatment who experienced a grade 3/4 decrease in potassium levels in the East Asian population were 2 out of 48 patients (4.2%); whereas a decreased potassium level in the non-East Asian population occurred in 4 out of 210 patients (1.9%).	2
3.	Wang <i>et al.</i> , 2015 <sup>22</sup>	Evaluation of the efficacy and safety of nilotinib as compared with imatinib in a Chinese population.	267 patients with CML-CP were randomly assigned to one of two treatment groups: imatinib or nilotinib. 133 patients received imatinib treatment; whereas 134 patients received nilotinib treatment.	50% of patients treated with imatinib experienced a decrease in blood potassium levels (hypokalemia) of all grades, where 2.3% among them experienced grade 3/4 hypokalemia. Meanwhile, hypokalemia of all grades occurred in 21.1% of patients treated with nilotinib, where 1.5% among them experienced grade 3/4 hypokalemia.	2
4.	Yilmaz <i>et al.</i> , 2015 <sup>13</sup>	Changes in the estimated glomerular filtration rate in CML patients receiving TKI treatment.	468 patients with CML-CP were treated with TKIs. Of all patients, 253 patients received imatinib and 116 patients received nilotinib.	During follow-up, 19 patients had acute kidney injury related to their treatment. Patients on imatinib treatment had a high risk of acute renal injury than those using nilotinib treatment. These patient's uric acid and potassium concentrations remain below the levels considered for diagnostic criteria of tumor lysis syndrome.	4
5.	Hasan <i>et al.</i> , 2015 <sup>23</sup>	Evaluation of electrolyte disturbances in Iraq CML patients receiving nilotinib.	30 CML patients treated with nilotinib, who had previously experienced resistance or no response to imatinib treatment, and 30 healthy people as a control group.	The results in patients treated with nilotinib (before, after) and in the control group were (4.6±0.68, 4.3±0.68, and 4.46±0.76) mmol/L, respectively (p>0.05).	2
6.	Hochhaus <i>et al.</i> , 2016 <sup>24</sup>	Evaluation of the efficacy and safety of nilotinib as first-line treatments in patients with CML-CP.	1089 patients with CML-CP receiving nilotinib treatment.	There were several biochemical abnormalities, one of which was changes in blood potassium levels. The changes included a decrease and an increase in blood potassium levels. A decreased in blood potassium levels of all grades occurred in 136 patients (12.5%) where 9 of them experienced grade 3 decreased potassium levels; while an increase in blood potassium levels of all grades occurred in 147 patients (13.5%), consisting of 31 patients (2.8%) in grade 2, 7 patients (0.6%) in grade 3, and 6 patients (0.6%) in grade 4.	3

Not using <sup>+</sup>; Howick *et al.*, 2011<sup>17</sup>; Using <sup>+</sup>; Joanna Briggs Institute, 2014<sup>18</sup>. CML, chronic myeloid leukemia; CML-CP, chronic myeloid leukemia in chronic phase; TKI, tyrosine kinase inhibitor.

decrease in blood calcium levels of all grades was more common in patients taking imatinib compared to nilotinib (50.8% vs 34.6%).<sup>22</sup>

Matti *et al.* conducted a cross-sectional study in 95 CML patients who were divided into three groups, namely imatinib 400 mg, imatinib 600-800 mg, and nilotinib 800 mg, which aimed to see long-term side effects on blood calcium levels by administering imatinib with the duration ranged between 1-134 months and nilotinib between 2-23 months. This study showed a greater decrease in blood calcium levels in the imatinib group than in the nilotinib group, as well as an insignificant decrease in blood calcium levels in the imatinib group at different doses.<sup>34</sup>

O'Sullivan *et al.* conducted a prospective study of 9 newly diagnosed CML patients receiving imatinib treatment for 24 months and reported significant changes in blood calcium levels

below baseline at 3 months after imatinib treatment. Furthermore, there was no change from the third month to the eighteenth month in blood calcium levels.<sup>35</sup> O'Sullivan *et al.* then conducted a cross-sectional follow-up study in 10 CML patients who were treated with nilotinib for 12-54 months and found that the patients' mean blood calcium levels were in the lower range of normal values. However, it should be noted that these patients had previously received imatinib treatment for 9 months.<sup>36</sup> A summary of literature on the effects of TKIs on blood calcium level in CML patients is shown in Table 3.<sup>22,23,33,34,35,36</sup>

Overall, the above discussion suggests that the blood calcium levels of CML patients taking imatinib or nilotinib tended to decrease and below normal values, where this decrease was more prevalent in imatinib-treated patients. Referring to O'Sullivan *et al.* study in nilotinib-treated patients, changes in blood calcium

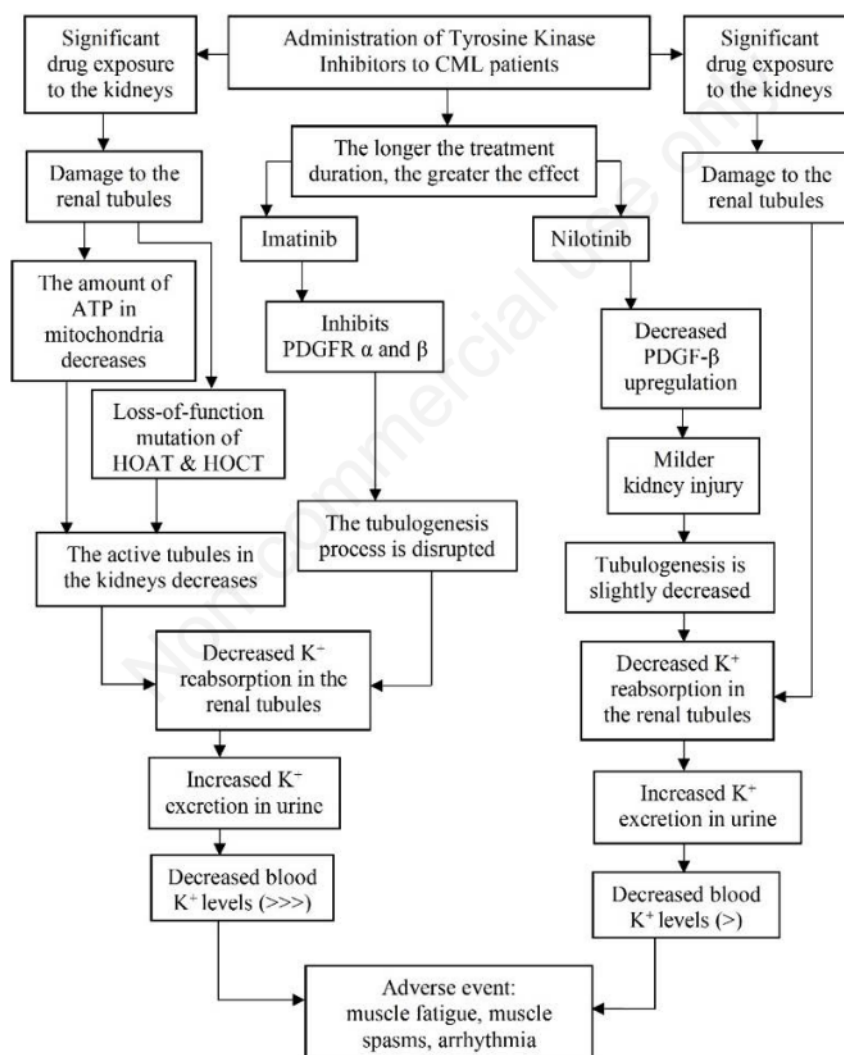


Figure 1. Mechanism of tyrosine kinase inhibitors' effect on blood potassium level. ATP, adenosine triphosphate; CML, chronic myeloid leukemia; HOAT, human organic anion transporter; HOCT, human organic cation transporter; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor.



levels were not necessarily caused by nilotinib itself, because the patients had previously been treated with imatinib for quite a long time, namely 9 months. In addition, the small number of patients is a limitation to this study. Furthermore, the duration of treatment might affect the patient's blood calcium levels, as demonstrated by Matti *et al.* study in which a longer duration of imatinib treatment led to larger changes in calcium levels.<sup>34-36</sup>

Some studies suggest that decreased blood calcium levels may be related to the effect of imatinib on PDGFR and colony-stimulating factor 1 receptor (CSF-1 receptor). PDGF, which is a chemotactic and mitogenic agent for cells derived from mesenchymal tissue, divides into PDGF-A which binds to PDGFR- $\alpha$  and PDGF-B with PDGFR- $\beta$ . PDGFR- $\alpha$  expression in mice osteoblast cultures showed a direct effect on the proliferation and differentiation processes of osteoblasts. When imatinib inhibits the PDGF-A/PDGFR- $\alpha$  axis, there is an inhibition in osteoblast proliferation, but increased activity in osteoblast differentiation from a preexisting pool of osteoblast precursor, thus the bone formation increases. However, this process will decrease as the treatment progresses because the pool of osteoblast precursors is depleted by the anti-proliferative and pro-apoptotic effects of imatinib.<sup>33,35</sup>

The activity between osteoblasts and osteoclasts is closely

related because of the interaction of the receptor activator of nuclear factor  $\kappa$ B (RANK) ligand on osteoblasts with its receptor RANK on osteoclast precursors. The presence of macrophage colony-stimulating factor (M-CSF) which is secreted by stromal cells and osteoblasts which bind to the colony-stimulating factor 1 receptor (C-FMS) on macrophages are required for macrophages to mature into osteoclasts. While on imatinib treatment, activation of C-FMS by M-CSF is inhibited, thus interfering with the development of macrophages into mature osteoclasts. This suggests an indirect effect of imatinib on osteoclasts via PDGFR- $\alpha$  inhibition in osteoblasts. Imatinib also directly inhibits osteoclasts through PDGFR- $\beta$ , hence the osteoclast development and bone resorption process decrease.<sup>33,35</sup> Those effects will result in decreased calcium dissolution from hydroxyapatite and decreased blood calcium levels in patients.

The effect of nilotinib is similar to that of imatinib, the difference is that c-ABL and PDGFR inhibition can have a neutral or inhibition effect on osteoblast differentiation, depending on the dosage that has been administered. At a lower dose, c-ABL inhibition is more dominant, resulting in an inhibitory effect on osteoblast differentiation; whereas, at a higher dose, c-ABL inhibition is balanced by PDGFR inhibition resulting in a neutral effect

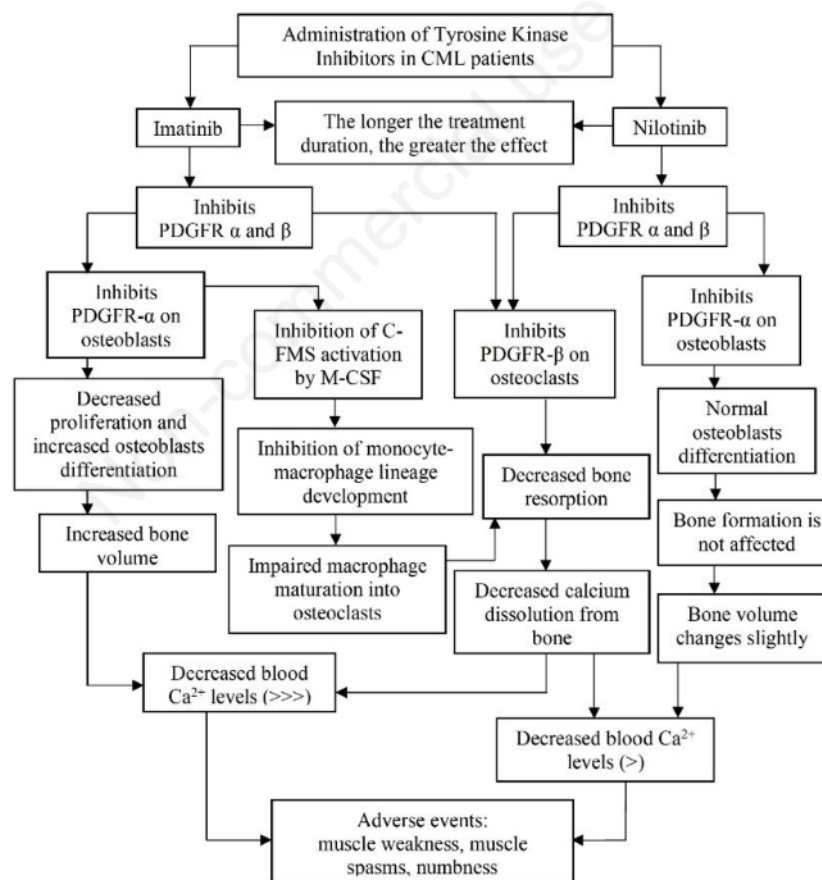


Figure 2. Mechanism of tyrosine kinase inhibitors' effect on blood calcium level. C-FMS, colony-stimulating factor 1 receptor; CML, chronic myeloid leukemia; M-CSF, macrophage colony-stimulating factor; PDGFR, platelet-derived growth factor receptor.



**Table 3. Literature related to the effects of tyrosine kinase inhibitors on blood calcium level in patients with chronic myeloid leukemia.**

No.	Author, Year	Research Topic	Research Subject	Research Result	Level of Evidence
1.	Berman <i>et al.</i> , 2006 <sup>33</sup>	Altered bone and mineral metabolism in imatinib-treated patients.	There are 77 patients who received imatinib treatment in this study, consisted of 63 CML patients, 13 GIST (Gastro-intestinal Stromal Tumor) patients, and 2 malignancy (sarcoma) patients. In addition, there were 14 people as a control group.	Patients in the low blood phosphate level group tended to have lower total calcium levels than patients in the normal blood phosphate level group. In addition, differences in total calcium levels were more pronounced in the low phosphate group than in the control group.	4B*
2.	O'Sullivan <i>et al.</i> , 2009 <sup>35</sup>	Effects of imatinib on bone markers and biochemistry serum in long-term treatment.	9 CML patients who received imatinib treatment.	There was a significant difference in blood calcium levels of patients treated with imatinib for 24 months ( $p < 0.05$ ) compared to the baseline examination before treatment. At baseline, blood calcium levels were $8.8 \pm 0.2$ mg/dL, while the calcium levels at the eighteenth month were lower by an average of $0.3$ mg/dL than baseline. However, this decrease did not occur between the 3 and 18 months.	2
3.	O'Sullivan <i>et al.</i> , 2011 <sup>36</sup>	Effects of nilotinib on bone in CML patients.	10 CML patients treated with nilotinib.	From biochemical serum examination, the blood calcium level was reported in the lower range of normal levels, namely $8.5 \pm 0.3$ mg/dL ( $p < 0.001$ ) after being treated with nilotinib for a range of 12-54 months.	4B*
4.	Wang <i>et al.</i> , 2015 <sup>22</sup>	Evaluation of the efficacy and safety of nilotinib as compared with imatinib in a Chinese population.	267 patients with CML in the chronic phase (CML-CP) were randomly assigned to one of two treatment groups: imatinib or nilotinib. 133 patients received imatinib treatment; whereas 134 patients received nilotinib treatment.	50.8% of patients treated with imatinib experienced hypocalcemia in all grades and as much as 0.8% among them experienced it in grade 3/4. Meanwhile, 34.6% of patients treated with nilotinib experienced hypocalcemia in all grades and as much as 0.8% among them experienced it in grade 3/4.	2
5.	Hasan <i>et al.</i> , 2015 <sup>24</sup>	Evaluation of electrolyte disturbances in Iraq CML patients receiving nilotinib.	30 CML patients treated with nilotinib, who had previously experienced resistance or no response to imatinib treatment, and 30 healthy people as a control group.	The results in patients treated with nilotinib (before, after) and the control group were ( $8.68 \pm 1.88$ , $8.1 \pm 1.72$ and $9.12 \pm 0.38$ ) mmol/L, respectively ( $p > 0.05$ ). There is a significant difference between the examination results after nilotinib treatment when compared to the control group ( $p = 0.004$ ).	2
6.	Maiti <i>et al.</i> , 2017 <sup>34</sup>	Evaluation of calcium and phosphate levels in CML patients receiving TKI treatment with different doses.	95 CML patients were divided into three groups, namely the imatinib 400 mg group consisted of 55 patients, the imatinib 600-800 mg group consisted of 8 patients, and the nilotinib 800 mg group consisted of 32 patients.	There was a significant decrease in blood calcium levels of patients receiving imatinib and nilotinib treatment ( $p = 0.05$ ) with results of $1.85 \pm 0.16$ and $1.90 \pm 0.18$ mmol/L, respectively. Patients who received imatinib treatment with different doses (400 mg and 600-800 mg) also experienced a decrease in blood calcium levels that is $1.85 \pm 0.16$ and $1.78 \pm 0.19$ mmol/L, respectively, but the results were not significant ( $p = 0.411$ ).	4B*

Not using \*: Howick *et al.*, 2011<sup>17</sup>. Using \*: Joanna Briggs Institute, 2014<sup>48</sup>. CML, chronic myeloid leukemia; CML-CP, chronic myeloid leukemia in chronic phase; GIST, gastro-intestinal stromal tumor; TKI, tyrosine kinase inhibitor.

in the form of increased osteoblast differentiation.<sup>36</sup> Therefore, the difference in the decrease of blood calcium levels between imatinib and nilotinib treatment is not that great.

Decreased blood calcium levels have a variety of clinical manifestations that range from a small decrease, which may only be seen through laboratory tests and without signs and symptoms, to a large decrease that has symptoms such as fatigue, muscle spasm, and QT prolongation.<sup>37</sup> Other factors that may affect the blood calcium levels of CML patients include a history of diabetes mellitus, hypertension, and kidney disorders.<sup>22,34,38-40</sup> Figure 2 depicts the summary of the mechanism of the role of TKI influence on the blood calcium level.

## Conclusions and discussion

It can be concluded that the changes in blood potassium levels of CML patients are in the form of an increase and a decrease; meanwhile, changes in blood calcium levels range from the lower normal values to below normal values (hypocalcemia). This effect occurs because imatinib and nilotinib act on PDGFR. Changes that occur vary from the abnormality in laboratory test results to the symptomatic toxicities such as muscle spasm and QT prolongation. Overall, grade 1/2 adverse events were common and could affect the patient's quality of life.

In daily practice, CML patients who are treated with imatinib or nilotinib should routinely check their blood electrolyte levels, both before and during treatment. In addition, when the patient comes for a consultation, it is necessary to ask about the clinical complaints experienced during the treatment. If the complaints are very disturbing and supported by the abnormal values in the blood electrolyte tests, the clinician should change the treatment used by the patient. In terms of scientific development, this literature review can serve as the basis for further research on damage to the kidneys that affects blood potassium levels in CML patients taking imatinib or nilotinib, and the possible interactions between TKIs and drugs that might affect blood potassium and calcium levels in CML patients.

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