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Study of correlation between imatinib mesylate plasma levels and hematological profile of patients undergoing treatment for chronic myeloid leukemia

Estudo da correlação entre os níveis plasmáticos de mesilato de imatinibe e o perfil hematológico de pacientes com leucemia mieloide crônica em tratamento

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ABSTRACT

Introduction: Chronic myeloid leukemia (CML) is a genetic disorder of hematopoietic stem cells, resulting in a myeloproliferative expansion of blood cells. CML is associated with the presence of the Philadelphia chromosome (Ph), generating an oncogene (*BCR-ABL*). The current treatment of choice is imatinib mesylate (IM). **Objective:** To correlate serum levels of MI with hematological parameters in patients with CML. **Method:** A retrospective cross-sectional study in patients treated for CML. Serum level of IM was determined by a high-performance liquid chromatography with diode array detector (HPLC-DAD), and statistical analysis was performed using SPSS version 20.0 software. **Results:** We studied 55 CML patients – 24 men (43.6%) and 31 women (56.4 %) – with a mean age of 54 years, who used IM. Among these, 45 patients were in the chronic phase (81.6 %); seven, in the accelerated phase (13.1%); and three, in the blast crisis (5.2%). Patients received a mean IM dose of 434 mg/day. Serum levels of the patients presented an average of 1,092 ± 617 ng/ml, and, in all, 47 patients (85.4%) had hematologic response (HR). **Conclusion:** There was no correlation between the number of leukocytes, platelets and hemoglobin and the serum level of IM, although there is a trend with respect to hemoglobin ($p = 0.062$).

Key words: chronic myeloid leukemia; imatinib mesylate; tyrosine kinase inhibitor; treatment outcome.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal malignant disease of hematopoietic stem cells. It causes a myeloproliferative expansion of blood cells and a marked bone marrow (BM) hyperplasia. This disorder is directly associated with the presence of Philadelphia (Ph) chromosome, which is the basis of diagnosis[1]. CML affects individuals of a mean age of 45-55 years, with one-third of patients older than 60 years. Typical symptoms are fatigue, anorexia, and weight loss; however, approximately 40% of patients are asymptomatic, in whose case diagnosis is based only on the abnormal peripheral blood cell count[2].

The disease basically has a course comprising three clinical phases. In the initial phase – or chronic phase –, patients still have cells with normal functions and may not display marked symptoms. In the subsequent phase – the accelerated phase –, peripheral blood presents more immature cells, patients suffer with more frequent symptoms, such as splenomegaly, sudoresis, purpura and leukocytosis, and respond with more difficulty to treatment. Lastly, the blast crisis is generally fatal and characterized by the presence of more than 30% of blasts in peripheral blood or bone marrow of patients, who are febrile, and in most cases, resistant to treatment[2].

The Ph chromosome is the result of a reciprocal translocation between chromosomes 9 and 22, termed t(9,22), which fuse and generate an oncogene called *BCR-ABL*. As a result of this oncogene, fusion proteins are formed (p210 and p185 – the former is responsible for 95% of the cases of patients diagnosed with CML) with the function of tyrosine kinase (PTK), that is, dysregulated function of proliferation and cell differentiation[3, 4]. Based on this, a targeted therapy was provided through direct inhibition of PTK generated by the *BCR-ABL* oncogene. In 2001, the Food

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and Drug Administration (FDA) established imatinib mesylate (IM) as a safe and efficient treatment for patients with this type of leukemia. The treatment with this drug begins as soon as the disease is diagnosed[5].

IM is a first-line drug for treatment of CML patients and it is marketed by Novartis as Glivec® or Gleevec®. It is a compound of the 2-phenylaminopyrimidine class and it is known principally by its function of specific inhibitor of ABL tyrosine kinase, competing for the ATP-binding site of the protein, thus inhibiting its function. This inhibition process decreases exacerbated cell proliferation and induces apoptosis in Ph+ malignant cells and, consequently, in hematological neoplasms, such as CML[5, 6]. The drug is responsible mainly for inhibiting the expression of the *BCR-ABL* gene, and, consequently, inhibiting the process of proliferation, which this gene is capable of, without any damage to patients' normal cells[6, 7]. However, the main effects provoked by IM were verified to be cytopenias, especially neutropenia and thrombocytopenia. A phase-I study of the drug found this adverse effect to clearly depend on the disease stage, and it was less frequent in recently-diagnosed patients[8, 9].

Thus, the objective of this work was to establish a correlation between plasma concentration of IM in patients being treated for CML and hematological data, so as to evaluate the myelosuppressive effect of the drug and enable better comprehension of its benefits.

METHOD

This is a retrospective cross-sectional study in patients undergoing IM treatment for CML. The correlation of IM levels with hematological parameters of each patient was carried out. Blood counts were performed on automated cell counter Sysmex KX-21. IM concentration was determined directly in the plasma by a system of high-performance liquid chromatography with diode array detector (HPLC-DAD)[10].

The current study was approved by the Research Ethics Committee under number 03048712.5.0000.5327. A free informed consent was prepared for patients and was previously signed according to resolution no. 466/12 of Conselho Nacional de Saúde.

The population sample of the study was $n = 55$ patients. The mean and median ages of the population were, respectively, 54 and 55 years (21-87). Among the total, 43.6% (24) were men; 56.4% (31), women. Forty-seven patients (85.4%) presented hematological response (HR), which is defined basically by those patients with normal hematological parameters, according to recommendations updated by the European LeukemiaNet (ELN)[11].

At the moment of diagnosis, 45 patients were in the chronic phase (81.6%); seven, in the accelerated phase (13.1%); and three, in the blast crisis (5.2%).

Statistical analysis

Serum levels of imatinib, as well as hematological parameters, were expressed as mean and standard deviation, followed by Pearson's correlation. Statistical Package for the Social Sciences (SPSS) version 20.0 was used, and $p < 0.05$ was considered statistically significant.

RESULTS

After analysis of each patient's blood count, we found an average of leukocytes of 6,000 ± 2,100/µl; an average of hemoglobin (Hb) of 12.2 ± 1.4 g/dl; and an average of platelets of 220 ± 58 × 10^3/µl (**Table**).

Among the total of patients, five (9.09%) presented altered leukocytes. Among them, four (7.3%) presented leukopenia; and one (1.8%), leukocytosis. Among the total of men, 25% (six) presented Hb < 13 g/dl; and among the total of women, 71% (21), Hb < 12 g/dl.

TABLE – Profile of patients with CML receiving IM treatment

Profile of the study participants	
n **(participants)**	**55**
Men	24 (43.6%)
Women	31 (56.4%)
Age (mean)	54 years
Age (median)	55 years (21-87)
Leukemic phase	
Chronic phase	31 (56.4%)
Accelerated phase	7 (13.1%)
Blast crisis	3 (5.2%)
Hematological parameters	
Leukocytes (× 10^3 µl) (mean ± SD)	6,000 ± 2,100
Hemoglobin (g/dl) (mean ± SD)	12.2 ± 1.4
Platelets (× 10^6 µl) (mean ± SD)	220 ± 58
Serum level of IM	
Mean ± SD (ng/dl)	1,092 ± 617
< 1,002 ng/dl (%)	29 (52.7%)
≥ 1,002 ng/dl (%)	26 (47.3%)
Dose of IM	
mg/day (mean)	434

CML: chronic myeloid leukemia; IM: imatinib mesylate; SD: standard deviation.

Concerning platelets, just three (5.4%) from the total of 55 patients presented thrombocytopenia (platelets < 140 × 10^3/µl).

Patients' serum levels presented an average of 1,092 ± 617 ng/ml. Among the total of patients, 52.7% (29) presented plasma levels < 1,002 ng/ml, and, among these, 89.6% (26) presented HR. Patients that presented imatinib level ≥ 1,002 ng/ml were observed; 26 (47.3%) fitted, and among them, 21 (80.8%) presented HR (Table).

Figures 1, **2** and **3** presented Pearson's correlation of the IM serum level with the number of leukocytes, platelets and hemoglobin.

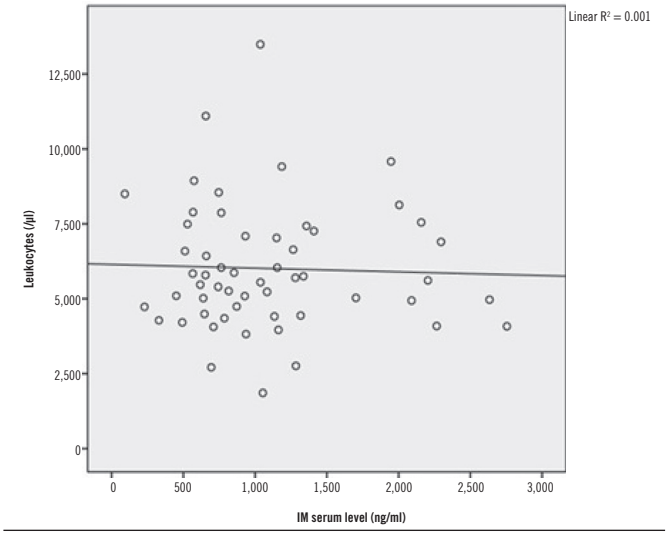

FIGURE 1 – *Pearson's correlation of the serum level of IM with leukocyte number (*p = *0.792)*

IM: imatinib mesylate.

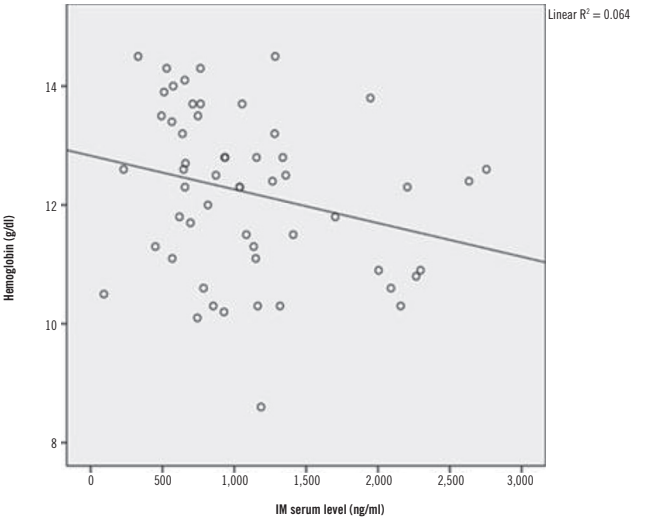

FIGURE 2 – *Pearson's correlation of the serum level of IM with hemoglobin measurement (*p = *0.062)*

IM: imatinib mesylate.

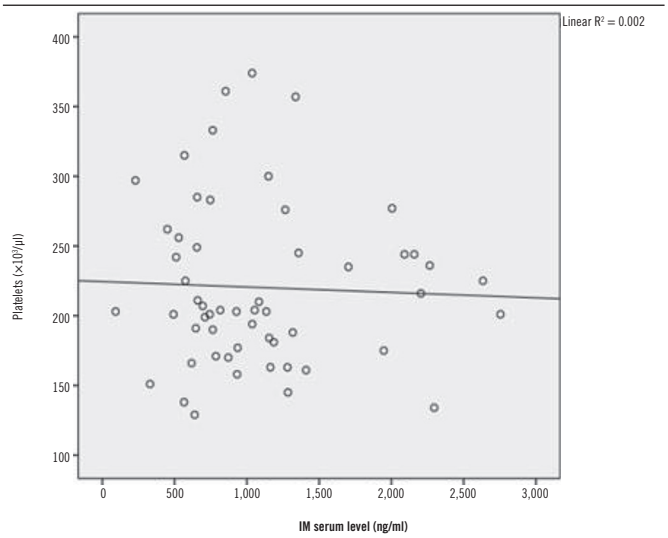

FIGURE 3 – *Pearson's correlation of the serum level of IM with platelet number (*p = *0.767)*

IM: imatinib mesylate.

DISCUSSION

Among the total of patients in this study, five (9.1%) presented leukocyte alteration – four (7.3%) with leucopenia and one (1.8%) with leukocytosis. Regarding platelets, just three (5.4%) of the 55 patients presented thrombocytopenia (platelets < 140 × 10^3/µl). These results presented values below the expected, when compared with other already reported studies, which cite leukopenia in 17%-35% of patients, and thrombocytopenia in 9%-20%[12, 13].

Among the men, 25% (six) presented Hb < 13 g/dl; among women, 71% (21) presented Hb < 12 g/dl, characterizing a picture compatible with that of anemia, according to the World Health Organization (WHO)[14]. Such values are above those found in some studies that indicate the presence of anemia in around 4%-7% of patients[12, 13]. These effects significantly impair patients' habitual activities and can put their lives into risk. When studied, neutropenia was present in 17% of patients, thrombocytopenia in 9%, anemia in 4%, high liver enzymes in 5%, and 17% presented other adverse events related to the drug[9, 12].

IM induces durable HR in nearly all CML patients in the chronic phase, with minimal toxic effects. Studies demonstrate that the sooner in the chronic phase IM is administered, the higher will be the rate of cytogenetic response, as well as the higher will be the rate of disease-free progression[13, 15, 16]. Quick response is also a characteristic of this treatment[17, 18].

Patients received a mean therapeutic dose of 434 mg/day; among the total, 81.6% (45) received doses of 400 mg/day; and the others, doses varying from 300-800 mg/day (Table). Although there is a recommendation for a standard initial IM dose, studies point out a relationship between plasma levels of the drug and its therapeutic effect[19-21]. At a conducted study, maintenance of IM plasma levels equal to or greater than 1,000 ng/ml, measured after the first month of treatment with the standard dose 400 mg/day, was shown to help yield a better response to treatment[22, 23]. Several other studies confirm this relationship and use the same threshold of 1,000 ng/ml as a target for therapeutic monitoring of the drug[24, 25]. The great variability between IM plasma levels from patient to patient is also confirmed. Even with the same daily dose, patients may present different levels among each other, and this variability is directly associated with differences in metabolism, genetic polymorphisms, low adherence to daily oral therapy, absorption factors or even food-drug interaction[21, 24, 26].

According to the figures of Pearson's correlation, leukocytes, platelets, and hemoglobin are not associated with the serum level of IM ($p > 0.05$), although a tendency is observed regarding hemoglobin ($p = 0.062$). The lack of statistical significance in these cases can be directly related to the absence of sampling n in this study.

Among the total of patients, 85.4% (47) presented HR with the use of the drug. In the literature, patients in the chronic phase presented a 98% rate of HR[18]. HR to treatment with IM was determined by reductions in the count of peripheral leukocytes and platelets[8]. This result is in agreement with the fact that IM efficacy varies according to the disease stage, and the sooner the treatment with the drug begins, the higher the probability of positive response will be[27-29]. Thus, the results of HR obtained in this research (85.4%) are compatible with the percentage of patients in the initial or chronic phase of this study (81.6%), previously cited.

In spite of the efficacy already confirmed of IM in the clinical treatment of CML patients, and of the high rate of patients with HR present in this study, there is still no guarantee of the time during which these positive responses to treatment are maintained, or if it is possible to offer patients an alternative to transplantation for long-term survival. This is reinforced principally by the fact that many patients do not respond to the drug or develop resistance to it[5, 23, 29].

Among the total of patients, 52.7% (29) presented plasma level < 1,002 ng/ml; and, among them, 89.6% (26) presented HR. These results disagree with what was revealed by another study, in which a threshold of IM concentration above 1,002 ng/ml was directly associated with efficacy in the treatment of patients who use this drug[21, 22, 27].

The serum level of IM presented an average of 1,092 ± 617 ng/ml. This variability among patients of the same group may have several causes, such as poor adherence to oral treatment, concomitant diseases, genetic polymorphisms, or even food-drug interaction[9, 13]. Such results suggest that monitoring plasma levels of this drug helps develop better treatment strategies for patients with CML and gain better understanding of clinical picture, treatment failure or success, and patients' response.

FINAL CONSIDERATIONS

In this study, correlation was not observed between patients' serum levels of IM and the levels of leukocytes, hemoglobin, and platelets. There is however, a tendency concerning hemoglobin ($p = 0.062$), which presents statistical difference close to that considered ideal.

Although the effectiveness of IM has already been confirmed by many researchers in patients with CML, and a high rate of HR (85.4%) was found in this study, there is still no guarantee of how long these favorable responses to treatment will last, or whether it is possible of offer patients an alternative to transplantation, for long-term survival. This confirms the fact that many patients do not respond to treatment with this form of therapy, or develop resistance to it. Because of that, it is justifiable to follow researches dedicated to the future development of other pharmaceutical compounds in this area, enabling an improvement in the quality of life of individuals affected by this disease.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

RESUMO

Introdução: *Leucemia mieloide crônica (LMC) é uma desordem genética de células-tronco hematopoiéticas, resultando em uma expansão mieloproliferativa das células sanguíneas. A LMC está associada à presença do cromossomo Philadelphia (Ph), o que gera um oncogene (*BCR-ABL*). Atualmente, o tratamento de primeira escolha é o mesilato de imatinibe (MI).* ***Objetivo:*** *Correlacionar os níveis séricos de MI com parâmetros hematológicos em pacientes com LMC.* ***Método:*** *Estudo transversal retrospectivo em pacientes com LMC em tratamento. O nível sérico de MI foi determinado por um sistema de cromatografia líquida de alta eficiência com detector de arranjo de diodos (CLAE-DAD), e a análise estatística foi realizada no programa SPSS versão 20.0.* ***Resultados:*** *Foram estudados 55 pacientes – 24 homens (43,6%) e 31 mulheres (56,4%) – com média de idade de 54 anos, portadores de LMC que utilizavam MI. Destes, 45 encontravam-se em fase crônica (81,6%); sete, em fase acelerada (13,1%) e três, em crise blástica (5,2%). Os pacientes em questão receberam uma média de dose do MI de 434 mg/dia. O nível sérico dos pacientes apresentou média de 1.092 ± 617 ng/ml e, ao todo, 47 pacientes (85,4%) apresentaram resposta hematológica (RH).* ***Conclusão:*** *Não houve correlação do número de leucócitos, plaquetas e hemoglobina com o nível sérico de MI, embora exista uma tendência observada com relação à hemoglobina (*p = *0,062).*

Unitermos: *leucemia mieloide crônica; mesilato de imatinibe; inibidor da tirosina quinase; resultado de tratamento.*

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