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BCR-ABL TARGETED THERAPIES ASSOCIATED WITH LEUKEMIA CHRONIC MYELOID

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Abstract: Chronic myeloid leukemia (CML) occurs when the pluripotent stem cell undergoes a mutation that leads to clonal myelo-proliferation, generating an overproduction of mature and immature granulocytes. In 90% of CML cases, patients have the Ph+ Philadelphia chromosome, which represents a reciprocal translocation between chromosomes 9 and 22. Treatment for the comorbidity is performed with TKI tyrosine kinase inhibitors such as imatinib, nilotinib, bosutinib and ponatinib significantly improve response and prolong patient survival. This work is an integrative literature review developed according to the construction of the guiding question, literature search, data collection, categorization of selected studies, analysis, interpretation and discussion of results. In general, tyrosine kinase inhibitors have a similar principle of action, competing for the binding sites of the *BCR-ABL* enzyme with ATP, preventing prooncogenic activities; however, despite their promise, these drugs have hematological and non-hematological side effects. In view of this, challenges such as more accurate prognoses, safe dosage options and facing cases of multidrug resistance to standard therapy drugs. From the investigation of genetic characteristics combined with the use of sequencing technologies, such as predicting the course of the disease, they will have a greater probability of success.
Keywords: Chromosomal alteration. Chronic myeloid leukemia. Philadelphia chromosome.

INTRODUCTION

Formerly known as "white blood", the discovery of Chronic Myeloid Leukemia (CML) can be dated back to 1845, and is characterized by the clonal expansion of hematopoietic cells resulting in an increase in circulating granulocytic lineage cells. John Bennett and Rudolf Virchow published cases in which patients had hepatosplenomegaly accompanied by leukocytosis. Subsequently, Neumann identified leukemia as a disease of medullary origin. It was only in 1960 that Peter Nowell and David Hungerford, using karyotyping analyses, visualized a small chromosome in relation to the others in CML patients, which was later called the Philadelphia which represents a translocation between chromosome 9 and 22. This was the first correlation between cancer and chromosomal alterations. CML accounts for 15% of all leukemias affecting adults and is more common in men. The most frequent age of diagnosis is between 40- 60 years. Most CML patients (85-90%) are diagnosed in the chronic phase. There is a slight male predominance, but the clinical course is similar in both sexes [1,21].

The disease is initially asymptomatic and the progression of chronic myeloid leukemia is insidious, with a non-specific "benign" stage (weakness, anorexia, weight loss), eventually opening up the path to an accelerated or blastic phase with more dangerous signs such as splenomegaly and pallor, bruising, bleeding, fever, lymphadenopathy and skin changes. The peripheral blood smear, bone marrow puncture and the identification of the Philadelphia chromosome are important for diagnosis. O treatment is carried out with tyrosine kinase inhibitors (TKI) such as imatinib, nilotinib, bosutinib and ponatinib that significantly improve the response and prolong the survival of the affected patient 21,40. Myelosuppressive drugs (e.g. hydroxyurea), stem cell transplantation and interferon-alpha (IFN- α) can also be used [6].

In CML, the abnormal myeloid cells produce progenitors that lose the ability to self-produce. differentiate, but retain the ability to proliferate. The peripheral blood contains a variety of myeloid lineage, including immature cells with left shift up to blasts (Figure 1).

CML is characterized by 3 phases of the disease: Chronic Phase, Accelerated Phase and Blastic Phase or Crisis blastic. The blastic phase is characterized by uncontrolled growth of the lymphoid, myeloid or mixed, with myeloid blast crisis being the most common. According to the World Health Organization (WHO) the accelerated phase is characterized by the presence of 10-19% of blasts in the peripheral blood and most of the patients in the chronic phase, if left untreated, progress to the accelerated phase and then the blastic phase. The symptoms are nonspecific and may include fever, fatigue and weight loss, often as a result of anemia and splenomegaly. As the blastic crisis progresses, the symptoms can become more severe including bone fracture, pain and bleeding [1,2,21]. However, those in the chronic phase are asymptomatic and can be diagnosed after routine examinations.

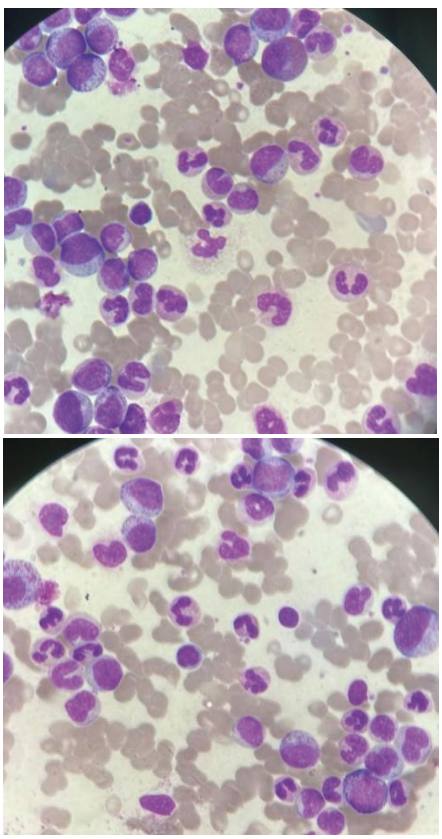


Figure1. Slide of patient diagnosed with Chronic Myeloid Leukemia

Source: Author's image.

For several years, the only possible treatment for patients was a stem cell transplant hematopoietic. Today, the emergence of cytogenetics has provided a new perspective for the more precise and effective treatment of CML. According to studies, in almost 90% of CML cases patients have the Philadelphia chromosome (Ph+). The Philadelphia chromosome or Philadelphia translocation is a chromosomal abnormality that corresponds to a reciprocal translocation t(9;22)(q11;q34), i.e, a translocation of region 1, band 1 of the long arm of chromosome 9 with region 3, band 4 of arm chromosome 22 (Figure 2). As a result of this abnormality, a chimeric gene is produced *BCR-ABL* (*Abelson Leukemia Gene*, named after Herbert Abelson, the scientist who discovered this gene) that is translated into a chimeric *BCR-ABL* protein (*breakpoint cluster* region). breakpoint), a constitutively activated tyrosine kinase. The main cellular dysfunctions resulting from abnormal kinase activity include increased proliferation and reduced apoptosis [2,22].

Since the identification of the molecular pathogenesis of CML, efforts have been made to identify the signaling pathways that influence the activity of *BCR-ABL* tyrosine kinases, linking these pathways to the change's characteristic of CML. These changes include: increased cell proliferation (activation of the RAS pathway), decreased apoptosis (STAT5 pathway, hyperactivation of the anti-apoptotic molecule BCLxl, inactivation of the pro-apoptotic molecule BAD via AKT, deregulation of cellular cytoadhering, happening to premature release of immature myeloid cells into the circulation, changes in angiogenesis, and increased genetic instability responsible for the progression of the disease [22].

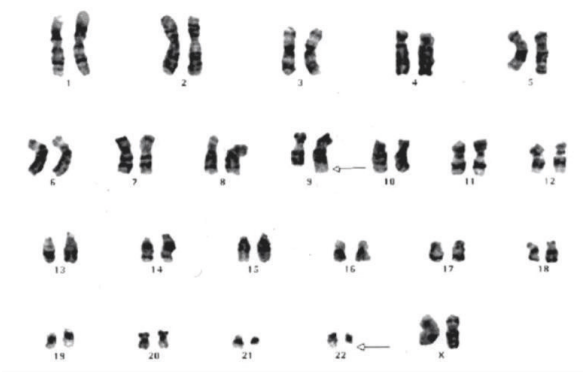


Figure 2. Representative karyotype of the positive Philadelphia chromosome.

Source: Baba et al., 2015

Regarding the molecular mechanism involving the *BCR-ABL* kinase, the formation of dimers occurs leading to autophosphorylation at BCR tyrosine 177. This process serves as an anchor for the GRB2/GAB2/SOS responsible for the activation of multiple signaling pathways such as PI3K/AKT, which favors protein synthesis by inducing cell proliferation. In addition, autophosphorylation of key residues in the *BCR-ABL* kinase also activate the JAK/STAT pathway (Figure 3). In resistance scenarios, the JAK/STAT pathways are used to support the growing cells. Another characteristic that contributed to complexity of treatments for the disease is the fact that leukemic stem cells can depend on exclusively on Beta-catenin and SMO signaling to survive in the event of kinase inhibition *BCR-ABL* by some medication [4].

Based on the structure of *BCR-ABL*, many molecules have been designed with the aim of inhibiting the kinase activity and five of them have already been brought into the clinic for the treatment of Ph+ CML patients. Good results were obtained in terms of remission rates and patients' quality of life. Some important problems, however, were observed. Firstly, a significant proportion of patients develop resistance to the drugs. Secondly, the drugs affect the majority of leukemia cells, but they do not eliminate leukemic stem cells.

The introduction of imatinib (DCB), for example, a tyrosine kinase inhibitor, revolutionized the therapy for CML, transforming it from a fatal disease into a chronic illness. However, some patients have a primary resistance to DCB, others acquire this resistance in the course of therapy. Therefore, a small number of leukemic stem cells retain the capacity for self-renewal under treatment of CBD. Thus, important challenges related to CML still need to be solved [3,4].

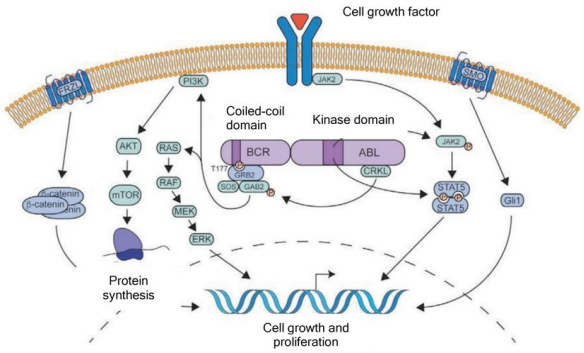


Figure 3 - Activation of the BCR-ABL1 Molecular Pathway

Source: Adapted from Braun etal.,2020

MATERIALS AND METHODS

The study is an integrative literature review, whose methodological path was developed according to with the following steps: construction of the guiding question; search of the literature (definition of the criteria for inclusion and exclusion, descriptors and combinations); data collection; categorization of studies analysis, interpretation and discussion of the results.

- **1ª stage:** construction of the guiding question

The review was based on the following question: "What are the drugs that have been developed? for the treatment of CML, what are its benefits and harms?".

- **2ª stage**: literature search

The bibliographic survey was carried out in

the following electronic databases: *Scientific Electronic Library online* (https://scielo.org/pt/), *US National Library of Medicine* (https://pubmed.ncbi.nlm.nih.gov/), *Medical Literature Analysis and Retrieval System online* (https://bvsms.saude.gov.br/minibanners/medline/) and Latin American and Caribbean Literature in Health Sciences (https://lilacs.bvsalud.org/). These databases were chosen because they had a greater number of indexed studies. The keywords and descriptors identified in the Health Sciences Descriptors (DeCS) for the search of articles were: Myeloid Leukemia, *BCR-ABL* Positive Chronic Myeloid Leukemia, Atypical Chronic Myeloid Leukemia *BCR- ABL* Negative, Philadelphia Chromosome and Leukemia. The query was made by combining the terms with the operator boolean "*AND*" as follows: "*Cancer therapy AND chronic myelogenous leukemia*", "*Chronic Myeloid Leukemia AND Chromosomal Alteration*", "*Chronic Myeloid Leukemia AND Philadelphia chromosome*" and "*Chronic Myelogenous Leukemia AND pathogenicity*" (Flowchart 1).

The inclusion criteria for the integrative review were original articles on the subject, published in Portuguese and English between 2013 and 2023, which is the time interval This was set at 10 years in order to cover numerous and up-to-date publications. Exclusion criteria were monographs, theses, dissertations and manuals.

- **3rd stage**: data collection

In order to select the studies, we carefully read the titles of the papers published and in progress. The adequacy of the inclusion criteria defined for the study was then checked. Next, the abstracts were read in detail and those that matched the objective were selected proposed by this study. The next step was to read the articles in their entirety in order to verify compatibility with the topic and ability to answer the objectives proposed for this review.

-**4th stage**: categorization of the selected studies

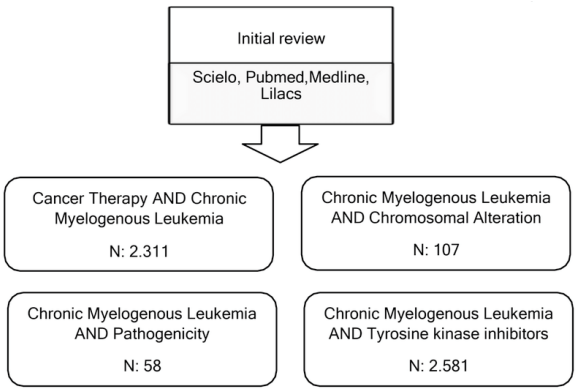
In order to extract the information from the included articles, the synthesis matrix tool was used. A matrix contains information on the therapeutic compound used for the treatment of CML, composition, mechanism of action, benefits found and adverse effects and references. The information was condensed into tables to make it easier to read and identify the relevance of the data obtained. from the literature.

- **5th stage**: critical analysis of the selected studies

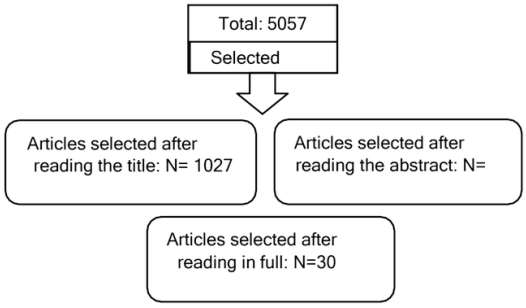
After categorizing the data, a critical analysis was carried out in order to characterize the studies selected. The data was discussed in accordance with the literature.

RESULTS AND DISCUSSION

The results of the database searches yielded a total of 5057 publications (Flowchart 1). After reading the titles and applying the inclusion and exclusion criteria, the following were selected 1027 articles were selected. Of these, the abstracts were read and duplicate articles were removed, 305 were filtered out. After reading these articles in full, 275 did not respond to the objective of this review and were excluded from the analysis. In the end, 30 publications remained for data collection (Flowchart 2).



Flowchart 1 - Total number of studies screened in the databases over the last 10 years.



Flowchart 2: Selection of studies included in the integrative review.

Interferons (IFN) are natural cell signaling glycoproteins that belong to the class cytokines. They participate in cell control and replication, and are modifiers of the response with antiviral, antiproliferative and immunomodulatory effects. In the 1980s, IFN-α was elected the drug of choice for the treatment of patients with CML, as it helped control proliferation, adherence and apoptosis of Ph+ cells. The first phase studies with Imatinib began in 1998 in patients with CML resistant or intolerant to IFN- α 5,6. Imatinib mesylate is a potent and specific inhibitor of all GLA-related kinases, competing for the binding sites of the enzyme BCR- ABL tyrosine kinase with ATP, which leads to inhibition tyrosine phosphorylation of proteins involved in BCR- ABL signal transduction 5,24. This substance shows a high degree of specificity for *BCR-ABL*; for the platelet growth factor receptor and the C-Kit tyrosine kinase receptor, which promotes the proliferation of stromal tumor cells gastrointestinal stromal cell (GIST), promoting growth arrest and apoptosis in the hematopoietic cells which express *BCR-ABL*, but does not affect normal cells. It is indicated for the treatment of patients with CML in blast crisis, accelerated phase, or chronic phase in case of resistance or intolerance to use of IFN-α. It is also indicated for the treatment of malignant gastrointestinal stromal tumors 6,32,40. With the introduction of Imatinib as a line of treatment, a revolution took place in CML therapy, transforming a fatal disease into a manageable chronic illness. A study international randomized trial compared the administration of 400 mg of Imatinib with an administration combined IFN-α and cytarabine (chemotherapy drug) and found a cytogenetic response (CCR) of 73.8% while patients treated with IFN-α together with cytarabine achieved a CCR of 8.5% 5,23. Despite the results presented and the fact that it is considered the first-line treatment for CML, side effects such as cramps, nausea and long-term mucocutaneous effects can occur [8].

Keshava Murthy Vinay and collaborators carried out a study in an outpatient clinic in India with consenting adult patients over the age of 18 and taking imatinib for a minimum period of 250 days. They observed mucocutaneous adverse effects, specifically skin hyperpigmentation, edema periorbital and vesiculobullous eruptions in patients on long-term imatinib treatment. In addition observed that female gender and younger age are risk factors for developing skin hyperpigmentation [8].

Resistance or intolerance to imatinib, defined as failure in hematological, cytogenetic

or molecular and the presence of side effects after drug administration, respectively, were observed, especially in patients in advanced stages of the disease 4,5,8,28. As a result, the

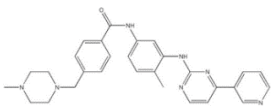
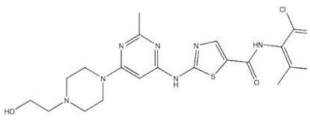
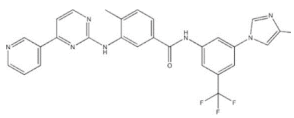
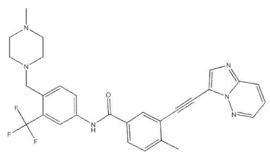
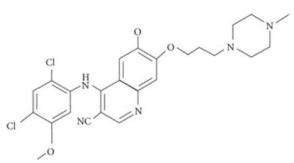
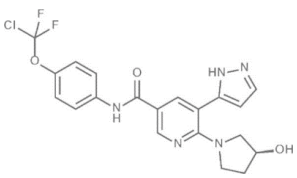
Compound therapeutic	Structural formula	Mechanism action	Benefits	Effectsadverse	References
IMATINIBE		It is up to binding sites of the BCR- ABL enzyme with ATP.	They prevent growth and induces apoptosis in hematopoietic cells expressing BCR- ABL.	Adverse effects long-term mucocutaneous pain; muscle cramps; pain; nausea; vomiting, fatigue and abdominal pain.	*Vinay K; etal (2017), Cortes; et al (2016); Iqbal, Z et al (2013), *Hehlmann R; et al (2017), *Hoachhous A; et al (2017).
DASATINIBE		Inhibits autophosphorylation of kinases.	Prevents oncogenic activities.	Diarrhea, Edema peripheral, headache, hypocalcemia and myelosuppression.	*Santos-Macías,et al (2016), *Maiti N; et al (2016), *Imagawa J; et al (2015), *Huhtan J; et al (2022), *Santoleni F; et al (2013).
NILOTINIBE		Inhibitor ATP-competitive of BCR-ABL.	Prevents a activation of the BCR-ABL-dependent mitogenic and antiapoptotic pathways.	Risk of illness arterial occlusion.	*Fossard; et al (2015), *Mahon F.X; et al (2018), *Rea D; et al (2017), *Wang J; et al (2015), *Contreras O; et al (2018).
PONATINIBE		Inhibitor ATP-competitive of BCR-ABL.	Effective against M3ISI mutation that has resistance against the other TKIs	Events arteriovascula-occlusive.	*Heiblig; et al (2018), * Cortes; et al (2013), *Eide C.A; et al (2019), *Deiningin M.W; et al (2016), *Lipton J.H; et al (2014).
BOSUTINIBE		Inhibitor SRC/ABL kinase.	Resistance most of t h e of mutants of BCR-ABL.	Disorders gastrointestinal and hepatic.	*Gambacorti- Passerini; et al (2018) *Cuts; et al (2018), Cortes; et al (2016), *Rea D; et al (2021), Gambacorti; et al (2014).
ASCIMINIBE		Inhibitor allosteric targeting myristoyl of BCR/ABL1.	Low toxicity, high selectivity and increases the effect of other TKIs.	Tiredness, nausea, diarrhea, pain joint r a s h and upper respiratory tract infection. infection	*Eide; et al (2019), *Kantarjian; et al (2013), *Manley; et al (2020), *Hughes; et al (2019), *Wylie A; et al (2017).

Table 1. Comparison of the main TKIs used as a line of treatment for CML

the need to study a second line of treatment. Dasatinib was initially studied in the second line after imatinib failure, consists of an orally administered 2nd generation tyrosine kinase inhibitor, and is indicated for the treatment of patients who have shown intolerance or resistance to therapy preview [19].

The chemical name of desatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-l-piperazinyl]-2- methyl-4-pyrimidyl]amino]-5-thiazolcarboxyamide, and its molecular formula C22H26CIN7O2S. H2O. Its mechanism of action consists of binding to kinases (*BCR-ABL*, SRC, LCK, YES, FYN, c-KIT), inhibiting their autophosphorylation with in order to prevent oncogenic activity. As a targeted therapy, desatinib has a high specificity and selectivity to avoid contact with processes and cells unrelated to the disease; however, it has

significant adverse effects 34,38. According to studies by Steinberg et al. of the adverse effects found were diarrhea, peripheral edema, headache, abnormalities in the liver function, hypocalcemia and an interruption in treatment due to myelosuppression [9,10].

Another drug produced as a 2nd generation tyrosine kinase inhibitor is Nilotinib, which had successful responses and tolerance in 50% of patients in the long term33. It is a drug analog to imatinib; however, the selectivity and binding affinity against the ABL kinase of nilotinib is substantially higher when compared to imatinib. Nilotinib interacts with Glu286 and Asp381 forming a molecule of AMN107, which is an ATP-competitive inhibitor of the activity of the tyrosine protein *BCR-ABL* kinase, preventing the activation of *BCR-ABL-dependent* mitogenic and antiapoptotic pathways, leading to the death of the *BCR-ABL* phenotype. This drug has recently been approved and has demonstrated responses in patients undergoing treatment for the chronic and accelerated phases of CML and who are resistant or intolerant to treatment with imatinib 33,35. However, some studies suggest a correlation between the use of of nilotinib and the increased risk of occlusive arterial disease in patients with cardiovascular risk factors possibly by inducing hyperglycemia and hypercholesterolemia [11,35,36].

One of the problems with the first and second generation TKIs is that they don't cover the *BCR-ABL* mutant T315I and ponatinib was designed to solve this specific problem. This mutation determines a sequence alteration that induces the exchange of the amino acid threonine (ACT) for isoleucine (ATT). In contrast Like imatinib, nilotinib and dasatinib, ponatinib bypasses isoleucine via a carbon-carbon triple bond. carbon40. It is considered the most potent TKI with a long half-life, however, this effectiveness comes at a cost of reduced selectivity, which can lead to the inhibition of multiple additional kinases, for example in the vascular system (vascular endothelial growth factor and vascular endothelial-derived growth factor receptors). platelets). Studies have also revealed the involvement of Van Willebrand factor in mediating adhesion platelets with dose-dependent secondary microvascular angiopathy [12,29].

Bosutinib, another 2nd generation drug, was approved in 2012 for patients previously treated with at least one TKI and for whom imatinib, nilotinib and dasatinib were not considered It has proven resistance to and most *BCR-ABL* mutants resistant to imatinib, except for T315I and V299L. In a phase I/II study, significant clinical improvement was reported with bosutinib in patients with CML resistant and/or intolerant to previous TKIs and in patients with disease advanced 14. However, gastrointestinal and liver disorders represent the hallmark of toxicity of bosutinib after studies revealed an increase in liver enzymes with the administration of bosutinib. medication for a while 13,14. Asciminib is an allosteric TKI drug (a non-competitive inhibitor that binds to enzyme other than in the active site) of experimental *BCR-ABL* that targets the myristoyl binding of BCR/ABL1, stabilizing it in an inactive kinase conformation. Studies with asciminib showed strong clinical activity in patients who have failed other therapies with TKIs. They reported low toxicity, high selectivity, suggesting that high doses can be tolerated in order to achieve a suppression in the *BCR-ABL1* activity. Asciminib stands out for its ability to potentiate the efficacy of TKIs, particularly ponatinib. These drug combinations may offer opportunities interesting for faster and deeper remission. Frequent side effects of asciminib include feeling tired, nausea, diarrhea, joint and muscle pain, skin rash and infection of the airways upper airways. It can also cause

changes in blood levels and kidney function [17,18].

In fact, each tyrosine kinase inhibitor has a specific pharmacological profile due to its different chemical structures. Asciminib was recently approved (2021) for patients resistant to other inhibitors because the binding site of this drug is different from others, therefore, effective against the T315I mutation of the *BCR-ABL* oncoprotein. Imatinib is the only TKI whose absorption depends on both influx transporters (OCT1 and OATP1A2) and efflux transporters (ABCB1 and ABCG2), while the others depend only on efflux transporters. The efflux of dasatinib is also regulated by the ABCC4 and ABCC6 transporters. A phenomenon common to all in the metabolic aspect is that the CYP3A4 isoform of CYP450 mainly metabolizes TKIs [19].

Not only CYP3A4, the flavin-containing monooxygenase 3 (FMO3) and uridine 5'-diphospho-glucuronosyltransferase (UGT) also metabolize dasatinib and, similarly, by the process of glucuronidation, asciminib is metabolized by the UGT enzymes (UGT1A3, UGT1A4, UGT2B7 and UGT2B17) [19]. Despite the studies carried out, the cellular and molecular mechanisms associated with the expression of *BCR-ABL* and impairment of apoptosis in CML leukemic cells have not been fully elucidated.

Current treatments for CML are hydroxyurea, bone marrow transplantation or tyrosine kinase inhibitors. kinase[7,40]. TKIs are highly effective in the treatment of CML, but they do not lead to a cure for patients with CML and cases of resistance to TK inhibitors have already been described. Therefore, in order to efficiently treat patients and destroy leukemic stem cells, it is necessary to identify new genes and pathways that play critical roles in the survival and self-renewal of CML leukemic stem cells.

CONCLUSION

Conventional therapies for the control of CML are chemotherapy with hydroxyurea, therapeutic drugs with IFN-α, busulfan or low-dose cytarabine, lymphocyte infusion and transplantation of medullary cells. Over time, the treatment of CML has advanced considerably based on the molecular therapy with tyrosine kinase inhibitors. Drugs that have drastically changed therapy showing promising results for patients with this disease. The complete hematological response that demonstrates successful therapy occurs when the patient presents after treatment: platelet count < 450,000/mm3, leukocyte count < 10,000/mm3, no immature granulocytes, basophils < 5% and no palpable spleen. The cytogenetic response is complete when the patient has no partial Ph+ cells when the patient has between 1% and 35% Ph+ cells, lowest when 36% to 65% Ph+ cells are present, lowest when 66% to 95% Ph+ cells are present. Ph+ cells and absent when >95% Ph+ cells are present.

As mentioned above, although promising for the treatment of CML, the TKIs have sometimes significant side effects that can be classified as hematological (thrombocytopenia, neutropenia, anemia and cardiac dysfunction) and non-hematological (diarrhea, nausea, vomiting, pleural effusion and rash). In view of this, a number of challenges remain, such as more accurate CML prognosis, safer dosage options for TKIs and multidrug resistance to therapy. Thus, as there are mutations It is necessary to continue investigating the genetic characteristics of somatic cells outside the *BCR-ABL* gene. and epigenetics with the use of sequencing technologies in order to improve predictions of disease course and treatments with a greater chance of success.

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