Revista Ibero- Americana de Humanidades, Ciências e Educação- REASE

OPEN ACCESS

doi.org/10.51891/rease.v6i12.11342

CHRONIC MYELOID LEUKEMIA: A LITERARY REVIEW

LEUCEMIA MIELOIDE CRÔNICA: UMA REVISÃO LITERARIA

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RESUMO: A LMC (Leucemia Mieloide Crônica) é caracterizada pela presença do cromossoma Filadélfia, devido à sua translocação. Na leucemia, formam-se células sanguíneas doentes (cancro) que perturbam a produção de células saudáveis da medula óssea, diminuindo o seu número normal.Os doentes com LMC têm uma produção excessiva de glóbulos brancos e, normalmente, apresentam uma evolução lenta do crescimento das células doentes ao longo do tempo. Uma estimativa aproximada de casos na população é de cerca de 15% nos adultos, tendo em conta que existem outros tipos de leucemia, esta percentagem tem um peso muito maior, mas nas crianças a incidência é considerada rara, correspondendo a cerca de 10% de todos os casos de LMC.

Palavras-chave: Cromossomo. Células. Superprodução. Incidência.

ABSTRACT: CML is characterized by the presence of the Philadelphia chromosome, due to chromosome translocation, where a fusion will occur between a portion of oneof the genes on chromosome 22 and another part of one of the genes on chromosome 9. In leukemia, diseased (cancer) blood cells form and disrupt the production of healthy bone marrow cells, decreasing their normalnumbers. Patients with CML have an overproduction of white blood cells and normally have a slow evolution in the growth of diseased cells over time, an approximate estimate of cases in the population, which is around 15% in adults, considering that there are other types of leukemia, this percentage receives a much greater weight, but in children the incidence is considered rare, corresponding to about 10% of all cases of CML.

Keywords: Chromosome. Cells. Overproduction. Incidence.

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1. INTRODUCTION

CML is classified by the World Health Organization (WHO) as a "myelo-proliferative neoplasm" (when the bone marrow overproduces blood cells). (ABRALE;2023) It is a cancer that begins in the stem cells of the bone marrow where it affects the white cells (the body's defense cells), directly affecting hematopoiesis in the bone marrow.(INSTITUTO CAMALEÃO;2021) This type of leukemia is where a fusion occurs between a part of one of the genes on chromosome 22 and another part of one of the genes on chromosome 9.(CIÊNCIA NEWS;2015)

2. OBJECTIVES

2.1 GENERAL

The aim of this study was to carry out a literature review using scientific databases on Chronic Myeloid Leukemia.

2.2 SPECIFIC

Conceptualize Chronic Myeloid Leukemia; Correlating CML with the Philadelphia Chromosome; Comment on the prognostic factors of CML; Comment on the clinical symptoms of the disease; Report on the stages of CML; Report on the tests that are essential for diagnosing CML; Comment on the therapeutic options: medication and bone marrow transplant.

3. MATERIALS AND METHODS

3.1 TYPE OF STUDY

This work is based on a review of the scientific literature on Chronic Myeloid Leukemia

3.2 OBTAINING THE DATA

To write this article on Chronic Myeloid Leukemia, research was carried out on scientific databases such as Scielo, oncoguia, abrace, gov.com.br. Using key words in Portuguese and English.

The following descriptors were used in English: chronic myeloid, leukemia, chromosome, cells, overproduction, incidence. In Portuguese, the following words were used: chronic myeloid leukemia, chromosome, over production and incidence. To carry out a rich

and accurate review, the data survey sought out the most recent information on CML, always prioritizing the most up-to-date articles. Articles in both Portuguese and English were evaluated, with the main approach being chronic myeloid leukemia and its various related issues, so correlating the most relevant information in this bibliographic survey was of paramount importance for the development of this article.

4. RESULTS AND DISCUSSION

4.1 Chronic Myeloid Leukemia (CML)

Leukemia has been studied for many years, specifically CML, which is not a modern disease, since the first descriptions of cases occurred in 1845. With further studies and investigations into the uniqueness of CML, in 1960 for the first time there was a relationship between a chromosome irregularity and an oncological disease, where the Ph (Philadelphia chromosome) was described, aiming to see how the translocation of genes occurs, resulting in a gene considered a hybrid called BCR- ABL. After these discoveries, research progressed to find out more about the particularities of the disease for a more effective diagnosis and treatment.

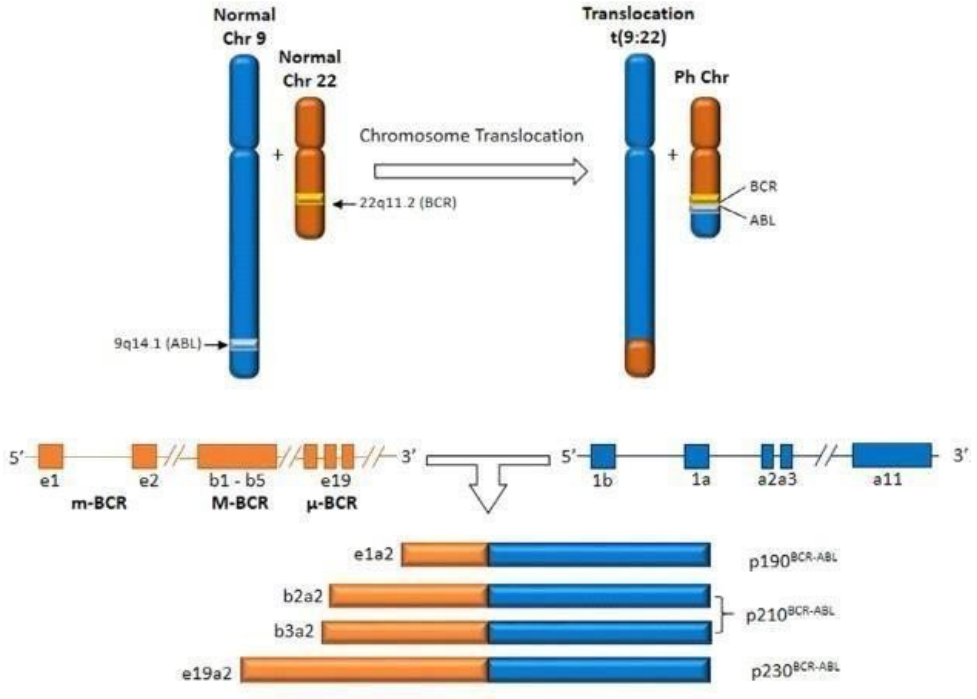

Figure 1- Translocation (9;22) and BCR-ABL transcription associated with CML, AML and ALL (SOURCE: AVELINO et al, 2017)

4.2 Symptoms of CML

In general, Chronic Myeloid Leukemia develops slowly and progressively. Therefore, in the early stages, it is common for the patient to be asymptomatic. But signs at this stage are:

Sensation of weakness;

Fatigue;
Excessive sweating and fever;
Bone pain;
Weight loss;
Bleeding;
Constant palor;
High fever.

After the introduction of tyrosine kinase inhibitor therapy, CML became a controlled disease for most patients, living normally and with fewer side effects. (PFZIER,2022)

4.3 Stages of Chronic Myeloid Leukemia

Leukemia can be classified as "acute" or "chronic" according to the speed of growth of its diseased cells and their functionality (ABRALE;2023). Thus, in acute leukemia there is a rapid progression of the disease, with immature cells developing in large numbers and not being able to perform their normal functions, while in chronic leukemia there is a slow progression with a greater number of mature cells than in acute leukemia.

In order to differentiate between leukemias, it is necessary to note that they are capable of differentiating into two lineages; Lymphoid and Myeloid. The classification of leukemia types is based on the progression and lineages of the disease.

The four main types of leukemia are:

Acute myeloid leukemia	(AML)
Chronic myeloid leukemia	(CML)
Acute lymphoid leukemia	(ALL)
Chronic lymphoid leukemia	(CLL)

4.4 Diagnoses of LMC

The diagnosis is usually made by clinical and hematological findings together. The following methods can be used to diagnose CML:

Measuring splenomegaly;
Complete blood count;

Myelogram;
Bone marrow karyotype;
PCR-qualitative (to identify the BCR-ABL transcript) etc.

Based on the results achieved, it is possible to define the stage of the disease's progression and then continue with the steps to be taken. It is possible to quantify that an increasing number of patients are being diagnosed with CML through periodic blood tests, because they are still asymptomatic. Therefore, the CBC plays an important role in identifying CML, in line with the fact that an accurate interpretation is essential for directing the diagnosis. (RBAC;2023)

Based on the choice of material to be observed, i.e., which material will be used for analysis, according to the WHO, the diagnosis will give a different result at each stage of the disease. It can be found in:

Chronic phase: in this phase it is common for patients with CML to be diagnosed with the disease in the phase it is present, so there are often good responses to standard treatments. It is important to take care not to worsen into the accelerated phase.

Accelerated phase; in this phase it is usual to see other new mutations and an increase in immature cells (basophils). Failure to comply with treatment correctly will result in this phase progressing to the blastic phase.

Blastic phase; also called "blastic crisis" and is considered the most advanced phase of the disease. It presents itself in CML as the acute form of the disease where it will have very characteristic and noticeable symptoms.

It should be emphasized that if the patient is in Blastic Crisis, a bone marrow transplant is not indicated.

To find out which test will be carried out, you need to decide which sample will beused:

Peripheral blood

Bone marrow

Genetic or molecular samples, etc.

The diagnosis of CML is made by means of a number of tests that make it easier to arrive at anaccurate result, such as;

Blood count

Myelogram

Cytogenetics

Bone marrow biopsy

When a CBC is taken, it is possible to find similar results when the patient has the disease (CML). The following results are expected in a CBC test: leukocytosis with left shift, plateletosis, monocytosis, basophilia, enlarged cells, etc. It is important to carry out cytogenetictests to identify which chromosome is the abnormality in the disease, which in this case is the PH chromosome. Finally, a bone marrow aspiration (myelogram) and a bone marrow biopsy are carried out. The bone marrow aspiration will identify the abnormality found in the blood count results, identifying which cells are normal or abnormal, and the biopsy will show the exact location and quantity of the cells present in the bone marrow; extremely hypercellular.

Bone marrow with marked granulocytic hyperplasia and slight hypogranulation, megakaryocytic hyperplasia, presence of less than 5% Blasto, moderate medullary fibrosis, etc.

Figure 2 - Data table translated with data from - CBC profile in the different stages of chronic myeloid leukemia (SOURCE: SOSSELA, et al, 2017).

STAGES OF THE DISEASE	PARAMETER ANALYZED	VALUES FOUND
Chronic phase	Leucogram	
	leukocyte count	leukocytosis (>50,000 leukocytes /mm3). with left shift
	Differential	Predominance of neutrophils and myelocytes metamyelocyte count ↓ Rare promyelocytes Presence of up to 10% of basophilic and eosinophilic blasts ↑ Normocytic and normochromic anemia
	Erythrogram	Presence of erythroblasts Standard value or ↑
	Platelets	
Accelerated phase	Leucogram	
	Leukocyte count	Increasing leukocytosis (>100,000 leukocytes /mm³)
	Differential	Blasts (10 to 19%)
	Erythrogram	Basophils (≥20%)
	Platelets	Increasing anemia
		<100,000 or >1,000,00
Blastic crisis	Leucogram	
	Differential Blasts	(≥20%)

4.5 Treatment by CML Stages

It is possible to differentiate the stage the patient is at in the disease to better visualize how to proceed with the treatment of patients and what measures to take, given where the patient may be.

In the Blastic Phase

In the Transformation Phase

In the Chronic Phase

The treatment of CML for many people can be very difficult to cope with, considering that the side effects are one of the biggest obstacles for patients, who will have to live with the symptoms throughout their lives so as not to risk uncontrolled levels of BCR-ABL (Philadelphia chromosome gene). (WINNING CANCER ;2014)

Chronic phase: the patient should be treated with tyrosine kinase inhibitors such as niotinib, desatinib or bosutinib, in addition to imatinib, which is the most chosen, and the varieties and dosages of the medication should be adjusted based on the results of the follow-up with the patient.

Accelerated Phase: due to the high rate of leukemic cells, there is a certain difficulty in the effectiveness of the treatment, it depends on whether or not the result is successful in the chronic phase, the patient is usually medicated with the same drugs ordered in the chronic phase, but not imatinib, as it has no long-term effect in this phase of the disease.

Blastic phase: in this phase the symptoms are more severe, so the treatment must change. Patients are medicated with the same drugs, but there is the possibility of a bone marrow transplant.

Leukemia affects all ethnic groups and regions, including immunosuppressed people and pregnant women, which can have a greater effect and require greater patient awareness. The combination of pregnancy and CML means that some care must be taken with treatments, for example, if the patient in question is in the first trimester of pregnancy, it is recommended that she undergoes leukocyte afferent sessions, as some treatments can cause damage to the baby. Symptoms include anemia, fatigue, infections, bleeding, and other problems. But some patients are completely asymptomatic, and the disease is discovered in a

common blood test. (HOSPITAL OSWALDO CRUZ;2020).

Women of childbearing age who are taking imatinib (a drug used to treat CML) should be advised not to become pregnant and to take appropriate contraceptive measures. Patients who become pregnant during the therapeutic phase with imatinib will be advised to stop treatment, as there is currently insufficient evidence to support the continuation of imatinib during pregnancy, and interferon- alpha is recommended as an alternative treatment. After pregnancy, reintroduction of imatinib may be considered. For men who wish to conceive children, sperm cryopreservation can be considered prior to treatment with imatinib. (GRUPO ONCO CLÍNICAS,2023)

4. 6 Bone Marrow Transplantation

Bone marrow transplantation consists of the intravenous infusion of hematopoietic progenitor cells with the aim of re-establishing bone marrow function (CASTRO JR et al, 2003) and can be of three different types: - *Allogeneic*, in which the bone marrow is taken from a donor previously selected by blood compatibility tests; - *Autologous*, where the progenitor cells used are from the patient themselves; and - *Syngeneic*, which is carried out between identical twins

Figure 3- Data table translated with data from - Types of bone marrow transplant (SOURCE: CASTRO JR, et al, 2011).

Types of transplants	**Source of hematopoietic progenitor cells**	**Donor**
Autogenic	Bone marrow Peripheral blood	Patient's own
Allogeneic	Bone marrow Peripheral blood Umbilical cord blood	Related: (Brother or other relative) Unrelated: Any person with no ties to the patient
Syngeneic	Bone marrow Peripheral blood	Identical twin Brother

4.7 Chronic Myeloid Leukemia X Tyrosine Kinase

A widely used drug is tyrosine kinase inhibitors, which help in all phases of the disease, but their best response is in the chronic phase of CML."Because of the discomfort, many patients decide on their own to take a break from the medication. As the positive results of the drugs don't take long to appear and the BCR-ABL indexes are almost zero within a year (in 3 months of treatment the indexes reach less than 10%, in 6 months, 1% and in a year, 0.1%), patients believe that they are cured." (Instituto Vencer o Câncer, 2023)

There is intense tyrosine kinase activity in the BCR-ABL gene and the drugs that aim to reach it are called tyrosine kinase inhibitors. These are drugs that really. Help a lot in the course of the disease, however, they should not be considered as a cure.

Examples of the drugs used for each disease and each individual case are:

Figure 4: - Data table translated with data from - (ABRALE;2023)

Name	Dosage	What it is for
Imatinib	400 mg once a day	first generation tyrosine kinase inhibitor.
Desatinib	100 mg once a day	second generation tyrosine kinase inhibitor
Nilotinib	300 mg twice a day	induces a faster molecular response. than the responses of Imatinib

4.8 patient rights

All citizens have the right to basic health conditions, and it is the duty of the state to guarantee this health for all who live in it, according to Article 196 of the Brazilian Federal

Constitution.

Therefore, if the CML patient is unable to afford treatment, tests, and medication, which are often expensive, it is the state's duty to guarantee this treatment in hospitals that it insures.

FINAL CONSIDERATION

The purpose of this study was to carry out a literature review on Chronic Myeloid Leukemia, with the aim of presenting the main characteristics that differentiate this type of leukemia from other existing types, as well as exposing the singularities of diagnosis, incidence, and treatment. It is important to highlight the other issues present, such as:

It is important to understand that there are certain stages of the disease and that, depending on the stage at which the patient receives the transplant, adversities may occur. However, it is also important to assimilate and differentiate the various and extremely individual forms of treatment for CML, to contextualize the particularity of each case and each patient.

The conclusion is that bone marrow transplantation is still the most effective treatment, but it does not guarantee a positive response for the patient. It can therefore be seen that this disease is not simple and requires various diagnostic tests and individual treatments, which is why it is important to know the specific nature of each disease.

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