We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Chronic Myeloid Leukemia

Letícia Antunes Muniz Ferreira

Abstract

Chronic myelogenous leukemia (CML) is a chronic clonal myeloproliferative disease characterized by left leukocytosis, splenomegaly, and the presence of the Philadelphia (Ph) chromosome, which results from the reciprocal and balanced translocation between the long arms of chromosomes 9q34 and 22q11, generating the hybrid protein BCR-ABL, with increased tyrosine kinase activity. The BCR-ABL protein is present in all patients with CML, and its hyperactivity triggers the release of effectors of cell proliferation and inhibitors of apoptosis, and its activity is responsible for the initial oncogenesis of CML. This chapter will review CML from its discovery, molecular and epigenetic mechanisms of disease progression to current treatments.

Keywords: chronic myeloid leukemia, hematologic malignancy, hematopoietic neoplasm, myeloproliferative disorder, Philadelphia chromosome

1. Introduction

Chronic myeloid leukemia (CML) is a neoplasm characterized by clonal expansion of hematopoietic stem cells, resulting in increase of peripheral blood myeloid, erythroid, and platelet cells, with bone marrow (BM) myeloid hyperplasia [1, 2]. Typical symptoms of CML include fatigue, anorexia, and weight loss. However, about 40% of patients are asymptomatic, and in these patients the diagnosis is based on an abnormal blood count [1].

CML is categorized into three phases: chronic, accelerated, and blast crisis. At the beginning of the chronic phase (CP), some patients are asymptomatic, but others have fatigue, weakness, headaches, irritability, fever, night sweats, and weight loss. The accelerated phase (AP) comes after a variable period of diagnosis from a few months to several years, and it is characterized by increased bone marrow and peripheral blood blasts, peripheral blood leukocytosis and basophilia, anemia and thrombocytopenia unrelated to treatment, or the development of cytogenetic evolution. Subsequently, the disease progresses to the blast phase (BP), defined hematologically by the increase of leukemic blasts in the peripheral blood and/or bone marrow (more than 20%). At this stage of the disease, many patients die within 3–6 months. The progression to AP and BP seems to be associated mainly with genomic instability, which predisposes to the appearance of other molecular abnormalities [3].

The average diagnosis of CML is 64 years. However, all age groups, including children, are affected. About 15% of all leukemias are CML. It is estimated for the USA that 1 out of 526 people will have CML in their lifetime. The American Cancer Society estimates for CML in the USA by 2019: about 8990 new cases will be diagnosed with CML (5250 in men and 3740 in women) and about 1140 CML deaths (660 men and 480 women) [4].

1.1 Discovery of leukemias

The first case of leukemia was described in 1827 by Alfred Velpeau. Velpeau observed in a 63-year-old patient an enlarged spleen and liver associated with fever, weakness, and the presence of blood pus [5]. Later, Alfred Donné described the autopsy of a patient who had an enlarged spleen and semi-purulent blood under a microscope [6].

However, the first description of leukemia was credited to John Hughes Bennett in 1845. Bennett gave a more complete and scientific description of a 28-year-old patient who had postmortem examination with massive enlargement of the liver, spleen, and lymph nodes, in addition to the presence of purulent blood [7]. In the same year, Rudolf Virchow described the autopsy of a 50-year-old female patient with splenomegaly and pus in her blood vessels [8].

In 1852, Bennett described 37 cases of leucocythemia [9]. Later, in 1856, Virchow noted that cases of splenomegaly leukemia had some granular blood cells with irregular or divided nuclei, while patients with lymphadenopathy already had smooth nucleus cells [10]. Virchow proposed two main varieties of chronic leukemia, splenic and lymphatic, which today are identified as leukemia and lymphoma, respectively [11].

The introduction of blood cell staining techniques in 1878 by Paul Ehrlich revolutionized hematology, allowing a differentiation of different types of leukocytes [12]. With this, Ehrlich distinguished lymphoid and myeloid leukemias [13].

1.2 Discovery of Philadelphia chromosome

The improvement of cytogenetic techniques allowed the study of chromosomal arrangements in various pathological conditions. Thus, specific human disorders were found to be associated with specific chromosomal abnormalities (e.g., Down syndrome, associated with an extra copy of chromosome 21) [14].

In 1960, Peter Nowell and David Hungerford identified a small chromosome in two CML patients. This chromosome was called the Philadelphia (Ph) chromosome, according to the chromosome standardization committee, which suggested that abnormal chromosomes be designated by the name of the city in which they were discovered [11, 14, 15]. The discovery of this chromosome was a very important step in understanding the pathophysiology of CML.

Chromosome banding techniques revolutionized the cytogenetic approach. Thanks to this advance in 1973, Janet Rowley demonstrated that the Ph chromosome was not a simple deletion but a reciprocal and balanced translocation between the long arms of chromosomes 9 and 22 [16]. Still in the 1970s, Herbert Abelson and Louise Rabstein identified the *ABL* gene, located on chromosome 9, position 9q34 [11]. Protein tyrosine kinase *ABL* is related to the processes of regulation of cell proliferation, survival, cell adhesion, and migration [17].

In 1984, Groffen et al., through the cloning of genomic DNA from CML patients, identified chromosome breaks within a limited region on chromosome 22, which they called the breakpoint cluster region (BCR) [18, 19]. Thus, the highly specific presence of the BCR chromosome breakpoint in patients with Ph-positive CML strongly suggested the involvement of this gene in leukemia.

In the formation of the Ph chromosome, the *ABL1* proto-oncogene (Abelson leukemia 1) is translocated from chromosome 9 to the *BCR* gene on chromosome 22 at position 22q11. This process gives rise to the chimeric *BCR-ABL1* gene, which encodes a constitutively active protein tyrosine kinase, considered central in the mechanism involved in chronic phase-chronic myeloid leukemia (CP-CML) [20–22]. Identification of this anomaly is extremely important for the diagnosis of the disease and for treatment purposes.

1.3 Variants of Ph chromosome

The Ph is detected by G-band karyotyping in around 90% of CML patients among whom 5–10% may have variant chromosome types [23–25]. Variants of Ph chromosome are characterized by the involvement of another chromosome in addition to chromosomes 9 and 22. Variant rearrangements can be simple or complex. Simple-type variants involve another chromosome, for example, t (9; 22; 6). Complex variants participate in the translocation of two or more chromosomes, besides chromosomes 9 and 22 [26, 27].

Variant Ph breakpoints occur in hotspots across the genome, usually in the G-light bands, within the cytosine and guanine (CG) richest parts of the genome [28]. CG content correlates with chromatin condensation and transcription activity; that is, open chromatin is transcriptionally active and relatively likely to undergo breakage and repair with a consequent tendency to illegitimate recombination and translocation [24].

Variant Ph chromosomes are distinguished from additional chromosomal abnormalities or clonal evolution that drives disease progression. The clonal evolution is a reflection of a genetic instability that characterizes the transition to advanced phase [29]. However, the mechanism of variant Ph generation and the molecular bases of biological differences between classic Ph and variant Ph chromosomes are not fully understood [30].

In atypical CML (aCML), patients are Ph-negative. This leukemia presents initial characteristics and clinical course similar to those of Ph-positive patients. However, Ph-negative patients have more heterogeneous characteristics, often more aggressive disease progresses with worse prognosis [31].

2. Molecular characterization of CML

The *BCR-ABL* fusion protein with strong tyrosine kinase activity is one of the molecular biological bases of leukemia [32]. The Ph chromosome is generated by the translocation t (9; 22) (q34; q11). The normal *c-ABL* gene is located on chromosome 9 and has 11 exons (1b, 1a, a2–a11). During chromosomal translocation, *c-ABL* gene breakdown can occur at three points: upstream of 1b, between 1b and 1a, and between 1a and a2. Regardless of the breakpoint, the first two alternative exons (1b and 1a) are always separated [21].

The normal *BCR* gene is located on chromosome 22 and consists of 23 exons (e1–e23). In generation of the *BCR-ABL* fusion gene, there are three breakpoints that can occur in the *BCR* gene: major (*M-BCR*), minor (*m-BCR*), and micro (*μ-BCR*). The M-*BCR* break can generate junctions e14a2, e13a2, e14a3, and e13a3; m-BCR breakdown can induce junctions e1a2 and e1a3; and the breakdown in μ-BCR can give rise to e19a2 junction [21].

Despite the many junctions that exist, in Ph-positive hematological neoplasms, the junctions e14a2 and e13a2 are the most frequent. These two junctions generate the same transcript encoding the p210 BCR-ABL protein. The junction e19a2 produces a transcript encoding the p230 BCR-ABL protein. And junction e1a2 creates a transcript that encodes p190 BCR-ABL [21, 29].

All domains of c-ABL protein—SRC-homology-2 (SH2) domain, SH3 domain, tyrosine kinase domain, nuclear localization signal (NLS), nuclear export signal (NES), DNA-binding domain (DBD), and actin-binding domain (ABD)—are present in the three BCR-ABL proteins. However, the three BCR-ABL proteins have different BCR domains [33].

The SH2 and SH3 regulatory domains mediate protein-protein interactions and control activation of transduction signals. The SH3 domain is known as a negative

regulator of kinase activity, acting as a counterpoint to the SH2 domain, inactivating its tyrosine kinase-activating and receptor potential [34]. In BCR-ABL products, a partial or complete deletion of the SH3 domain occurs, losing negative control. In contrast, the SH2 domain is eventually activated by the presence of a tyrosine kinase-activating component [35].

The BCR-ABL fusion protein acts as an oncoprotein by activating several signaling pathways that lead to transformation. Myc, Ras, c-Rafn MAP/ERK, SAPK/JNK, STAT, NFKB, PI-3kinase, and c-Jun are included as signal cascade molecules. Many signaling proteins have been shown to interact with BCR-ABL through various functional domains and/or to become phosphorylated in BCR-ABL-expressing cells. In brief, BCR-ABL activates the main signal pathways, such as RAS/MAPK, PI-3kinase, c-ABL pathways and CRKL pathways, and JAK-STAT, and the Src pathway to play a major role in transformation and proliferation. Inhibition of apoptosis is thought to result from activation of the PI-3 kinase and RAS pathways with induction through AKT of Myc and BCL-2 [36].

Activation of these signaling pathways leads to deregulation of cellular processes such as proliferation, differentiation, DNA repair, decreased adhesion of leukemic cells to bone marrow stroma, and reduced apoptotic response to mutagenic stimulation, leading to uncontrolled clonal proliferation [37].

3. Diagnostic of CML

Approximately 40% of patients are asymptomatic, and the diagnosis is made with a blood count [1], performed by any clinical situation, preoperatively or even at a checkup. Several methodologies may be employed for the diagnosis of CML patients, including microscopic examination of peripheral blood and bone marrow, cytogenetics, and molecular biology.

3.1 Blood count

In peripheral blood of patients with CML, there is a leukocytosis of approximately 225,000/mm^3 ranging from 20,000 to 600,000/mm^3 and an intense increase in circulation granulocytes. Granulocytosis is characterized by a small proportion of leukemic blasts and promyelocytes and predominance of intermediate forms (such as myelocytes and metamyelocytes), in addition to maturing and fully mature neutrophils (rods and segmented). Differential leukocyte count shows staggered left shift from mature neutrophils to myeloblasts. Fifteen to 20% proportions of basophils may be found [1, 37].

The presence of mild anemia and thrombocytosis are also common in CML. There is a small correlation between hemoglobin concentration and the total number of white blood cells (hemoglobin values range from 9.7 g/dL ranging from 5.4 to 14.4 g/dL). Depending on the stage of the disease, the number of platelets ranges from 485,000/mm^3, ranging from 25,000 to 1,400,000/mm^3. Basophilia and eosinophilia are common findings. Leukocyte alkaline phosphatase is generally low and can be used to distinguish CML from other myeloproliferative diseases [1, 37, 38].

3.2 Myelogram

Analysis of bone marrow (BM) through myelogram reveals granulocytic hyperplasia, leading to a leukoerythroblastic ratio of 20:1. The differentiation sequence is maintained, however with a predominance of younger cells such as promyelocytes

and myelocytes. The number of megakaryocytes is increased. Other nonspecific biopsy findings include reticulin fibrosis and vascularization [1, 37].

3.3 Cytogenetics

The cytogenetic picture of CML provides unique and crucial information for diagnosis. Cytogenetic analysis of bone marrow or peripheral blood cells allows the identification of the Ph translocation and other chromosome changes that are associated with the leukemic process. Diagnostic assays at baseline for CML patients are based on the standard banding cytogenetics (chromosome banding analysis or CBA) and fluorescence in situ hybridization (FISH) [39].

Cytogenetic examination is preferably performed on bone marrow cells. The t (9; 22) (q34; q11) is easily recognized when the cell cycle of leukemic cells is disrupted in the metaphase. Identification of translocation 9; 22 requires analysis of at least 20 metaphases [40].

The FISH technique is used when the result is urgent. Fast and specific, this technique allows detection of *BCR-ABL* rearrangement through the use of molecular probes [37].

3.4 Molecular biology

The most modern and effective methods for detecting BCR-ABL transcripts are based on molecular biology techniques. Polymerase chain reaction (PCR) testing of peripheral blood RNA is highly sensitive: it can detect 1 Ph-positive cell expressing the BCR-ABL fusion transcript in 10^5–10^6 normal cells [1].

Real-time PCR is a great ally of clinical oncologist seeking better therapeutic outcomes because it helps in defining treatment, which can be more or less aggressive according to each patient's response [41]. Importantly, molecular methods, although extremely sensitive, do not allow observation of concomitant gene or chromosomal alterations.

4. Treatment of CML

Therapy for treatment of CML developed very slowly. Heinrich Lissauer, in 1865, described the use of arsenic in two leukemia patients [42], nothing new in view of the fact that the use of arsenic for cancer therapy had been described in the Indian Ramayana more than 2000 years earlier [43].

In the 1920s, radiotherapy entered clinical practice, and it was soon used for the treatment of CML, and for over 50 years, radiotherapy was considered the standard treatment. Radiation was usually directed to the spleen for symptomatic relief [43–45].

After the Second World War, there was the rapid development of alkylating agents. Thus, busulfan largely replaced radiotherapy in the 1960s. Later, hydroxyurea (hydroxycarbamide) was introduced in the USA (United States of America). Prospective studies showed that patients treated with hydroxyurea survived longer than those treated with busulfan. However, it was not clear whether this was due to the beneficial effect of hydroxyurea or a mitogenic effect of busulfan [44].

In the early 1980s, interferon-α (IFN-α) was introduced for the treatment of CP-CML. Few patients achieved any level of Ph-negative hematopoiesis, and others achieved a complete and lasting Ph-negative hematopoiesis. In rare cases, IFN-α may be discontinued without subsequent relapse. Thus, IFN-α replaced busulfan

and hydroxyurea in the treatment of CP-CML if the patient was not eligible for allogeneic BM transplantation [46].

In 1979, Fefer and colleagues treated four CP-CML patients with high doses of chemoradiotherapy, followed by transfusion of stem cells from their genetically identical twins [47]. At follow-up intervals of 22–31 months, these patients remained well absent of Ph-positive metaphases in their marrow. The previously fatal leukemia brought the possibility of treatment and cure through BM transplantation [45].

Researchers began to treat CP-CML patients with allogeneic BM transplantation between identical HLA siblings. In the beginning, conditioning consisted of the use of cyclophosphamide and full body irradiation. However, years later, it was decided to use busulfan with cyclophosphamide [48]. According to the Center for International Blood & Marrow Transplant Research, allograft-associated transplant-related mortality for CP-CML patients is about 10–20% at 1 year, and the survival at 5 years is about 60% [49]. Most survivors have no evidence of leukemia, but occasional patients relapse early after transplantation [44].

Thus, from the 1990s, the treatment of choice for all relatively young CP-CML patients (under 50 years old) was an allogeneic stem cell transplant (SCT). In France, patients with CML who were not eligible for allograft were treated with IFN-α plus cytarabine [50], although more recent data from Italy cast doubt on this conclusion [51].

4.1 Tyrosine kinase inhibitors

Accumulated knowledge of action mechanism of BCR-ABL was sufficient to initiate experiments with target molecule designs to be used in the treatment of CML. From the knowledge that tyrosine kinase is the effective portion of oncoprotein, it was evident that its inhibition would be the most attractive target as a therapeutic strategy. The goal was to design a small chemical compound that would compete with ATP binding at the kinase domain site. Thus, with this site occupied by an "ATP-like" molecule, it would not be possible to provide any phosphate group for substrate transfer. With this, the tyrosine residues would remain in the "non-phosphorylated" form, and the protein substrate would not be able to change its conformation so that it could be associated with the effectors described above, resulting in the interruption of oncogenetic signals to the nucleus of cell.

This "ATP-like" molecule, known as imatinib, revolutionized the treatment in oncology and specifically of CML, opening the "era of targeted specific therapy." One of the first studies on the effectiveness of imabinib treatment (the International Randomized Study of Interferon and STI571 [IRIS] trial) estimated the rate of complete cytogenetic response (CCyR) at 12 months in the imatinib arm was 69%. Such responses are in relation to the standard treatment of the time (IFN-α and cytarabine) [52].

One of the last IRIS updates showed an estimated overall survival (OS) rate of 83% at 10 years (20.1% of patients had unknown survival status when data was analyzed). It should be mentioned that, despite these excellent results, 31 and 52% of patients assigned to imatinib discontinued treatment by 5 and 10 years of follow-up, respectively. The main cause of treatment discontinuation was the unsatisfactory therapeutic effect (11%), while only 4% of patients discontinued treatment due to side effects [53].

Treatment with imatinib induces a hematological response in 90% of patients diagnosed in the CP and a cytogenetic response in 80% of them, which made bone

marrow transplantation, the only curative treatment for CML, to be indicated only in those patients who develop imatinib resistance, observed in 20–25% of cases [52].

Known mechanisms of imatinib resistance include the presence of mutation point in the BCR-ABL tyrosine kinase domain, amplification of the BCR-ABL gene, overexpression of the multidrug resistance gene known as P-glycoprotein, and low expression of pickup transporters such as SLC22A1 (hOCT1) [54].

The second generation TKIs (2GTKIs), dasatinib, nilotinib, and bosutinib, were initially approved in CML patients who were resistant or intolerant to imatinib. Due to a more potent in vitro inhibition of the unmutated BCR-ABL kinase with a good safety profile, these second generation TKIs were later evaluated and approved in the first-line setting [55].

Dasatinib is an oral, second generation TKI that is 350 times more potent than imatinib in vitro. It also inhibits the Src family of kinases, which may be important in blunting critical cell signaling pathways [56]. Compared to the structure analog of imatinib, nilotinib's affinity for the ATP-binding site on BCR-ABL1 is 30–50 times more potent in vitro [57]. Like dasatinib, nilotinib initially demonstrated the ability to induce hematologic and cytogenetic responses in patients who had failed imatinib [56]. Bosutinib appeared to retain activity across most known mutations that confer imatinib resistance, except for T315I. Responses were independent of whether patients had resistance to or intolerance of imatinib [56].

A subset of patients with CML exhibited either primary or secondary resistance to imatinib. Primary resistance refers to patients never responding to imatinib, whereas secondary resistance occurs when a patient who had an initial response to imatinib eventually loses the response [36]. Although a significant proportion of patients respond to 2GTKI therapy after imatinib failure, most of them (70%, approximately) will eventually discontinue such treatment in the short term due to loss of response or toxicity [55].

There are many treatment mechanisms of resistance, and several of them, mostly in vitro or in selected patient samples, have been reported. However, their individual contribution to this phenomenon has not been completely defined. The most frequently identified mechanism of resistance is the development of mutations in the ABL tyrosine kinase domain [55].

A third generation TKI, ponatinib, is approved in CML patients with refractory CML or Ph-positive acute lymphoblastic leukemia (Ph + ALL) and those harboring the BCR-ABL1T315I mutant [58]. Clinical trials using the approved dose of 45 mg/day of ponatinib show the main concern with this drug is the increased incidence of cardiovascular complications [55]. **Table 1** shows the target recommendations for CML, according to the American Cancer Society.

First generation TKI	CML patients newly diagnosed
Second generation TKI	CML patients resistant or intolerant to imatinib
Third generation TKI	CML patients with refractory CML or Ph-positive acute lymphoblastic leukemia and those harboring the BCR-ABL1T315I mutant
Interferon or chemotherapy	CML patients who cannot take TKI or those who are not responding to treatment
Allogeneic stem cell transplantation	CML who have failed at least two TKIs and for all patients in advanced phase disease

Table 1.
Target recommendations for CML [4].

4.1.1 Definition of therapeutic response

The quality of response to TKI treatment is categorized according to the laboratory method used. Patients are monitored by hematological, cytogenetic, and molecular response, and their terminology has been standardized by the European Leukemia Net [59].

Hematologic response is defined by the presence of platelets <450 × 10^9L, without differential immature granulocytes and <5% basophils, and a non-palpable spleen. Cytogenetic response (CyR) is defined according to the proportion of positive Philadelphia chromosome (Ph +) in bone marrow cells. The association between CyR and improved survival made the cytogenetic response the gold standard of CML therapy [36]. **Table 2** shows the cytogenetic response definition.

The IRIS study, conducted in 2003, defined two types of molecular response assessed by real-time PCR: major molecular remission (MMR) and complete molecular remission (CMR). Major molecular remission is defined as a three-log drop of the initial load of BCR-ABL at the time of diagnosis; this value is equal to or less than 0.1%. Complete molecular remission is defined when the BCR-ABL transcript is undetectable [60].

Response to treatment is monitored during the first 3 months through clinical evaluation, blood count, and biochemical exams every 2 weeks. After the third month, cytogenetics is recommended every 6 months until complete CCyR is achieved. From the moment the patient reaches CCyR (Ph + 0%), monitoring is performed through real-time PCR quarterly to detect minimal residual disease [61].

4.2 Allogeneic stem cell transplantation

For patients who fail frontline therapy, the second-line options include second and third generation TKIs. Even though second and third generation TKIs are potent and selective TKIs, some patients still do not respond to treatment. Allogeneic stem cell transplantation (allo-SCT) remains an important therapeutic option for patients with CML-CP who have failed at least two TKIs and for all patients in advanced phase disease [56].

Patients exposed primarily to TKI treatment do not respond negatively to allo-SCT. Conversely, if patients referred for transplant have the lower CML burden, they may respond better to allo-SCT [62].

Allo-SCT is the only treatment with healing potential. However, it remains associated with substantial risks of morbidity and mortality. For appropriate counselling of patients, a rapid and simple way to assess risk is needed [63]. Pre-allo-SCT risk factors for CML are donor type, disease stage, recipient age, recipient-donor gender combination, and, lastly, time between diagnosis and allo-SCT. **Table 3** presents the risk factors for allo-STC [63–67].

Complete cytogenetic response (CCyR)	0% Ph-positive metaphases
Partial cytogenetic response (PCyR)	1–35% Ph-positive metaphases
Minor cytogenetic response (mCyR)	36–65% Ph-positive metaphases
Minimal cytogenetic response (min CyR)	66–95% Ph-positive metaphases
No response (NR)	>95% Ph-positive metaphases

Table 2.
Cytogenetic response definition [59].

Prognostic factors	Score
Donor type	0—related identical human leukocyte antigen (HLA)
	1—unrelated identical HLA
Disease stage	0—chronic phase (CP)
	1—accelerated phase (AP)
	2—blast phase (BP)
Receiver age	0—< 20 age
	1—20–40 age
	2—> 40 age
Gender donor/receiver	1—female/male
	0—male/female
Time from diagnosis to transplant	0—< 12 months
	1—> 12 months

Table 3.
Risk factors for allo-STC [63–67].

In the era of TKIs, there is no doubt for the first-line treatment for CML patients. But when allo-SCT is indicated, this scoring system is still of great value in estimating overall disease-free survival and procedure-related mortality.

When considering allo-SCT for CML patients, it is important to know that a poor response to one or more TKIs does not predict a negative transplant response. TKIs pharmacologically block BCR-ABL activity, while allo-SCT depends on graft-versus-leukemia (GVL) effect [68].

The challenge of allo-SCT for treatment of leukemia and other malignancies of the hematopoietic system is the prevention of graft-versus-host disease (GVHD) without losing the GVL effect. Depletion of T cells abrogates GVHD and GVL effects. Delayed transfusion of donor lymphocytes into chimeras after T-cell-depleted stem cell transplantation produces a GVL effect without necessarily producing GVHD [69].

Allo-SCT should not be seen as a last resort but as a treatment strategy to be considered viable at the beginning of treatment for patients who have suboptimal responses to TKIs. The key issues for HSCT in CML are those of patient selection, risk stratification, and outcome optimization by means of regimen selection and improved supportive care [68].

5. Conclusions

CML is a myeloproliferative disease, resulting from clonal expansion of hematopoietic progenitor stem cells, characterized by *BCR-ABL* fusion gene, resulting from reciprocal translocation t (9; 22) (q34; q11) that gives rise to Ph chromosome. All the accumulated knowledge about action mechanisms of BCR-ABL1 has enabled the development of very efficient target-specific drugs, as well as molecular methods for disease monitoring.

Allo-SCT is a possible cure for CML; however, it is associated with mortality and morbidity increased due to complications in the pre- and posttransplantation periods, such as GVHD, immunosuppression, and multiple organ toxicity.

Although great progress has been made for the improvement in clinical treatment during the past decades, it is common for patients to develop resistance to treatments. Therefore, further exploring the novel therapeutic strategies is still crucial for improving disease outcome.

Author details

Letícia Antunes Muniz Ferreira
University Center of Jales—UNIJALES, Jales, SP, Brazil

*Address all correspondence to: leticiaamferreira@gmail.com

IntechOpen

References

[1] Sawyers CL. Chronic myeloid leukemia. The New England Journal of Medicine. 1999;**340**(17):1330-1340. DOI: 10.1056/NEJM199904293401706

[2] Ayala M, Ávila E, Domínguez J, Aquino X, Vela J. Diagnosis and treatment of chronic myeloid leukemia in the imatinib mesylate era: Report of the experience at "La Raza" Medical Center in Mexico. Clinical Lymphoma, Myeloma & Leukemia. 2016;**16**(2): 57-62. DOI: 10.1016/j.clml.2015.10.006

[3] Chen R, Chen B. The role of dasatinib in the management of chronic myeloid leukemia. Drug Design, Development and Therapy. 2015;**9**:773-779. DOI: 10.2147/DDDT.S80207

[4] American Cancer Society [Internet]. 2019. Available from: https://www.cancer.org/cancer/chronic-myeloid-leukemia.html [Accessed: 20 July 2019]

[5] Velpeau A. Sur la résorption du pus et sur l'altération du sang dans les maladies. Revue Médicale Suisse. 1827;**2**:216-240

[6] Donné A. Cours de microscopie complémentaire des études médicales. Paris: Ballière; 1844. p. 550

[7] Bennett J. Case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood. Edinburgh Medical and Surgical Journal. 1845;**165**:1-11

[8] Virchow R. Weisses Blut. Froiep's Notizen. 1845;**36**:151-156

[9] Bennett J. Leucocythaemia, or White Cell Blood in Relation to the Physiology and Pathology of the Lymphatic Glandular System. Sutherland and Knox: Edinburg; 1852

[10] Virchow R. Die Leukämie. Gesammelte Abhandlungen Zur Wissenschaftlichen Medizin. Meidinger: Frankfurt; 1856

[11] Gonon-Demoulian R, Goldman JM, Nicolini FE. History of chronic myeloid leukemia: A paradigm in the treatment of cancer. Bulletin du Cancer. 2014;**101**(1):56-67. DOI: 10.1684/bdc.2013.1876

[12] Ehrlich P. Über die specifischen granulationen des blutes. Archiv für Anatomie, Physiologie und Wissenschaftliche Medicin. 1879:571-579

[13] Ehrlich P. Farbenanalytische Untersuchungen Zur Histologie und Klinik Des Blutes. Berlin: Hirschwald; 1891

[14] Nowell PC. Discovery of the Philadelphia chromosome: A personal perspective. The Journal of Clinical Investigation. 2007;**117**(8):2033-2035. DOI: 10.1172/JCI31771

[15] Nowell P, Hungerford D. A minute chromosome in human chronic granulocytic leukemia. Science. 1960;**142**:1497

[16] Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature. 1973;**243**(5405):290-293. DOI: 10.1038/243290a0

[17] Pendergast AM. The Abl family kinases: Mechanisms of regulation and signaling. Advances in Cancer Research. 2002;**85**:51-100. DOI: 10.1016/S0065-230X(02)85003-5

[18] Groffen J, Stephenson JR, Heisterkamp N, de Klein A, Bartram CR, Grosveld G. Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. Cell. 1984;**36**(1):93-99. DOI: 10.1016/0092-8674(84)90077-1

[19] Chandra HS, Heisterkamp NC, Hungerford A, Morrissette JJ, Nowell PC, Rowley JD, et al. Philadelphia Chromosome Symposium: Commemoration of the 50th anniversary of the discovery of the Ph chromosome. Cancer Genetics. 2011;**204**(4):171-179. DOI: 10.1016/j.cancergen.2011.03.002

[20] Melo JV, Gordon DE, Cross NC, Goldman JM. The ABL-BCR fusion gene is expressed in chronic myeloid leukemia. Blood. 1993;**81**(1):158-165

[21] Melo JV. The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood. 1996;**88**(7):2375-2384

[22] Chauffaille MLLF, Bandeira ACA, Silva ASG. Diversity of breakpoints of variants Philadelphia chromosomes in chronic myeloid leukemia in Brazilian patients. Revista Brasileira de Hematologia e Hemoterapia. 2015;**37**:17-20. DOI: 10.1016/j.bjhh.2014.07.006

[23] Ishihara T, Minamihisamatsu M. The Philadelphia chromosome. Considerations based on studies of variant Ph translocations. Cancer Genetics and Cytogenetics. 1988;**32**(1):75-92. DOI: 10.1016/0165-4608(88)90026-x

[24] Fisher AM, Strike P, Scott C, Moorman AV. Breakpoints of variant 9;22 translocations in chronic myeloid leukemia locate preferentially in the CG-richest regions of the genome. Genes, Chromosomes & Cancer. 2005;**43**(4):383-389. DOI: 10.1002/gcc.20196

[25] Marzocchi G, Castagnetti F, Luatti S, Baldazzi C, Stacchini M, Gugliotta G, et al. Variant Philadelphia translocations: Molecular-cytogenetic characterization and prognostic influence on frontline imatinib therapy, a GIMEMA Working Party on CML analysis. Blood. 2011;**117**(25):6793-6800. DOI: 10.1182/blood-2011-01-328294

[26] Sandberg AA. Chromosomes and causation of human cancer and leukemia: XL. The Ph1 and other translocations in CML. Cancer. 1980;**46**(10):2221-2226. DOI: 10.1002/1097-0142(19801115)46:10<2221::aid-cncr2820461019>3.0.co;2-8

[27] Heim S, Mittelman F. Cancer Cytogenetics: Chromosomal and Molecular Genetic Aberrations of Tumor Cells. 2nd ed. New York: Wiley Liss; 1995

[28] Jeffs AR, Benjes SM, Smith TL, Sowerby SJ, Morris CM. The BCR gene recombines preferentially with Alu elements in complex BCR-ABL translocations of chronic myeloid leukaemia. Human Molecular Genetics. 1998;**7**(5):767-776. DOI: 10.1093/hmg/7.5.767

[29] Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood. 2009;**113**(8):1619-1630. DOI: 10.1182/blood-2008-03-144790

[30] Chauffaille MLLF. Cytogenetics and FISH monitoring CML during tyrosine kinase inhibitors treatment. Revista Brasileira de Hematologia e Hemoterapia. 2008;**30**(1):13-139. DOI: 10.1590/S1516-84842008000700005

[31] Koldehoff M, Beelen DW, Trenschel R, Steckel NK, Peceny R, Ditschkowski M, et al. Outcome of hematopoietic stem cell transplantation in patients with atypical chronic myeloid leukemia. Bone Marrow Transplantation. 2004;**34**(12):1047-1050. DOI: 10.1038/sj.bmt.1704686

[32] Zhu HQ, Gao FH. Regulatory molecules and corresponding processes of BCR-ABL protein degradation. Journal of Cancer. 2019;**10**(11):2488-2500. DOI: 10.7150/jca.29528

[33] Zhou T, Medeiros LJ, Hu S. Chronic myeloid leukemia: Beyond BCR-ABL1. Current Hematologic Malignancy Reports. 2018;**13**(6):435-445. DOI: 10.1007/s11899-018-0474-6

[34] Marcucci G, Perrotti D, Caligiuri MA. Understanding the molecular basis of imatinib mesylate therapy in chronic myelogenous leukemia and the related mechanisms of resistance. Commentary re: A. N. Mohamed et al. The effect of imatinib mesylate on patients with Philadelphia chromosome-positive chronic myeloid leukemia with secondary chromosomal aberrations. Clin. Cancer Res., 9: 1333-1337, 2003. Clinical Cancer Research. 2003;**9**(4):1248-1252

[35] Di Bacco A, Keeshan K, McKenna SL, Cotter TG. Molecular abnormalities in chronic myeloid leukemia: Deregulation of cell growth and apoptosis. The Oncologist. 2000;**5**(5):405-415. DOI: 10.1634/theoncologist.5-5-405

[36] Bennour A, Saad A, Sennana H. Chronic myeloid leukemia: Relevance of cytogenetic and molecular assays. Critical Reviews in Oncology/Hematology. 2016;**97**:263-274. DOI: 10.1016/j.critrevonc.2015.08.020

[37] Dulley F, Hamerschlack N. Leucemia mielóide crônica. Associação Brasileira de Linfoma e Leucemia. 2004;**25**:11-12

[38] Jamur VR. Estudo citogenético de pacientes com Leucemia Mielóide Crônica tratados com o Mesilato de Imatinibe [dissertation]. Curitiba: Universidade Federal do Paraná; 2005

[39] Molica M, Massaro F, Breccia M. Diagnostic and prognostic cytogenetics of chronic myeloid leukaemia: An update. Expert Review of Molecular Diagnostics. 2017;**17**(11):1001-1008. DOI: 10.1080/14737159.2017.1383156

[40] Webber LM, Garson OM. Fluorodeoxyuridine synchronization of bone marrow cultures. Cancer Genetics and Cytogenetics. 1983;**8**(2):123-132. DOI: 10.1016/0165-4608(83)90044-4

[41] Anunciação SF, Elias LFQ, Guimarães DC, Neto Filho JL, Sadi VA. Aspectos diagnósticos da leucemia mieloide crônica e detecção de doença residual mínima. Estudos. 2008;**35**(11/12):1069-1083

[42] Lissauer H. Zwei Falle von Leucaemie. Berliner Klinische Wochenschrift. 1865;**2**:403-404

[43] Deininger MW. Chronic myeloid leukemia: An historical perspective. Hematology. American Society of Hematology. Education Program. 2008:418. DOI: 10.1182/asheducation-2008.1.418

[44] Goldman JM, Majhail NS, Klein JP, Wang Z, Sobocinski KA, Arora M, et al. Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. Journal of Clinical Oncology. 2010;**28**(11):1888-1895. DOI: 10.1200/JCO.2009.26.7757

[45] Goldman JM. Chronic myeloid leukemia: A historical perspective. Seminars in Hematology. 2010;**47**(4):302-311. DOI: 10.1053/j.seminhematol.2010.07.001

[46] Talpaz M, Kantarjian HM, McCredie K, Trujillo JM, Keating MJ, Gutterman JU. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha A in chronic myelogenous leukemia. The New England Journal of Medicine. 1986;**314**(17):1065-1069. DOI: 10.1056/NEJM198604243141701

[47] Fefer A, Cheever MA, Thomas ED, Boyd C, Ramberg R, Glucksberg H, et al. Disappearance of Ph1-positive

cells in four patients with chronic granulocytic leukemia after chemotherapy, irradiation and marrow transplantation from an identical twin. The New England Journal of Medicine. 1979;**300**(7):333-337. DOI: 10.1056/NEJM197902153000702

[48] Goldman JM, Baughan AS, McCarthy DM, Worsley AM, Hows JM, Gordon-Smith EC, et al. Marrow transplantation for patients in the chronic phase of chronic granulocytic leukaemia. Lancet. 1982;**2**(8299):623-625. DOI: 10.1016/s0140-6736(82)92736-2

[49] Horowitz MM, Rowlings PA, Passweg JR. Allogeneic bone marrow transplantation for CML: A report from the International Bone Marrow Transplant Registry. Bone Marrow Transplantation. 1996;**17**(Suppl 3):S5-S6

[50] Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. The New England Journal of Medicine. 1997;**337**(4):223-229. DOI: 10.1056/NEJM199707243370402

[51] Baccarani M, Rosti G, de Vivo A, Bonifazi F, Russo D, Martinelli G, et al. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. Blood. 2002;**99**(5):1527-1535. DOI: 10.1182/blood.v99.5.1527

[52] O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. The New England Journal of Medicine. 2003;**348**(11):994-1004. DOI: 10.1056/NEJMoa022457

[53] Gugliotta G, Castagnetti F, Breccia M, Levato L, D'Adda M, Stagno F, et al. Long-term outcome of a phase 2 trial with nilotinib 400 mg twice daily in first-line treatment of chronic myeloid leukemia. Haematologica. 2015;**100**(9):1146-1150. DOI: 10.3324/haematol.2015.129221

[54] Branford S, Rudzki Z, Walsh S, Parkinson I, Grigg A, Szer J, et al. Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood. 2003;**102**(1):276-283. DOI: 10.1182/blood-2002-09-2896

[55] García-Gutiérrez V, Hernández-Boluda JC. Tyrosine kinase inhibitors available for chronic myeloid leukemia: Efficacy and safety. Frontiers in Oncology. 2019;**9**:603. DOI: 10.3389/fonc.2019.00603

[56] Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. American Journal of Hematology. 2016;**91**(2):252-265. DOI: 10.1002/ajh.24275

[57] Weisberg E, Manley PW, Breitenstein W, Brüggen J, Cowan-Jacob SW, Ray A, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell. 2005;7(2):129-141. DOI: 10.1016/j.ccr.2005.01.007

[58] O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;**16**(5):401-412. DOI: 10.1016/j.ccr.2009.09.028

[59] Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: An update of concepts and management

recommendations of European LeukemiaNet. Journal of Clinical Oncology. 2009;**27**(35):6041-6051. DOI: 10.1200/JCO.2009.25.0779

[60] Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. The New England Journal of Medicine. 2003;**349**(15):1423-1432. DOI: 10.1056/NEJMoa030513

[61] Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006;**108**(6):1809-1820. DOI: 10.1182/blood-2006-02-005686

[62] Lee SJ, Kukreja M, Wang T, Giralt SA, Szer J, Arora M, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. Blood. 2008;**112**(8):3500-3507. DOI: 10.1182/blood-2008-02-141689

[63] Gratwohl A, Hermans J, Goldman JM, Arcese W, Carreras E, Devergie A, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet. 1998;**352**(9134):1087-1092. DOI: 10.1016/s0140-6736(98)03030-x

[64] Bittencourt H, Funke V, Fogliatto L, Magalhães S, Setubal D, Paz A, et al. Imatinib mesylate versus allogeneic BMT for patients with chronic myeloid leukemia in first chronic phase. Bone Marrow Transplantation. 2008;**42**(9):597-600. DOI: 10.1038/bmt.2008.218

[65] Gratwohl A, Brand R, Apperley J, Crawley C, Ruutu T, Corradini P, et al. Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: Transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Haematologica. 2006;**91**(4):513-521

[66] van Rhee F, Szydlo RM, Hermans J, Devergie A, Frassoni F, Arcese W, et al. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: A report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation. 1997;**20**(7):553-560. DOI: 10.1038/sj.bmt.1700933

[67] Devergie A, Apperley JF, Labopin M, Madrigal A, Jacobsen N, Carreras E, et al. European results of matched unrelated donor bone marrow transplantation for chronic myeloid leukemia. Impact of HLA class II matching. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplantation. 1997;**20**(1):11-19. DOI: 10.1038/sj.bmt.1700844

[68] Innes AJ, Milojkovic D, Apperley JF. Allogeneic transplantation for CML in the TKI era: Striking the right balance. Nature Reviews. Clinical Oncology. 2016;**13**(2):79-91. DOI: 10.1038/nrclinonc.2015.193

[69] Kolb HJ. Graft-versus-leukemia effects of transplantation and donor lymphocytes. Blood. 2008;**112**(12):4371-4383. DOI: 10.1182/blood-2008-03-077974