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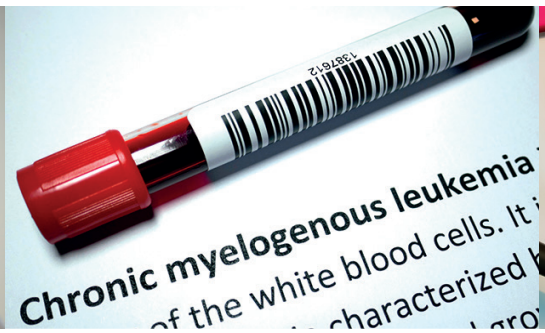
Haematology Nurses & Healthcare Professionals Group



Haematology Nurses and Healthcare Professionals (HNHCP)

Chronic myeloid leukemia (CML) & Chronic lymphocytic leukemia (CLL):

A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that the Haematology Nurses and Healthcare Professionals (HNHCP) group presents the learning program „Chronic Leukemias: A Resource for Healthcare Professionals".

A faculty of specialist nurses working in the field of haematology/oncology, haematologists, and patient advocates have collaborated to develop this comprehensive program dedicated to chronic Leukemia.

This program features topics relevant to the multidisciplinary team approach to caring for patients with chronic Leukemia and their caregivers. Nurses, other allied healthcare professionals and patient organisations play an important role in this process and the HNHCP is excited to share with you the most current information and up-to-date recommendations for addressing the unique aspects of addressing the patient's needs throughout the disease continuum.

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On behalf of the Haematology Nurses and Healthcare Professionals Group and the faculty who worked on this initiative, we hope that the Chronic Leukemia Resource will be of value to you in your care of patients with Chronic Leukemia.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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Chronic Leukemia: A Resource for Healthcare Professionals is also available online at

www.hemcare.org

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Contents

Quick Facts

1. Leukemias are cancers of the blood-forming tissues, predominantly the bone marrow.
2. Chronic lymphocytic leukemia (CLL), which most commonly affects older adults, is a cancer of a sub-type of white blood cell, B-lymphocytes.
3. Chronic myeloid leukemia (CML) is an uncommon malignancy originating in hematopoietic stem cells in the chronic phase of the disease that invade the peripheral blood system.
4. CLL results from one or more acquired mutations to the genetic material of a single bone marrow cell, in this case, CD5+ B cells.
5. The mutation status of immunoglobulin heavy-chain variable (IGHV) genes influences the natural history of CLL; mutated cells remain stable or grow more slowly than unmutated cells.
6. CML is associated with a well-defined genotypic anomaly, the Philadelphia chromosome (Ph), which is formed by a translocation between parts of chromosomes 9 and 22. The leukemia-causing oncogene, BCR-ABL1, is unstable and prone to develop multiple and heterogeneous genomic abnormalities.
7. The ABL1 gene signals cells to produce tyrosine kinase, which controls cell growth; an over-production of tyrosine kinase results in an over-production of granulocytes. The granulocytes have the BCR-ABL1 oncogene that causes CML and are referred to as leukemia or CML cells.

Module I: Understanding Chronic Leukemia

A. Epidemiology and Pathophysiology of Chronic Lymphocytic Leukemia (CLL)
    a. Epidemiology
    b. Pathophysiology
        i. Causes and risk factors
    c. Types
B. Epidemiology and Pathophysiology of Chronic Myelogenous Leukemia (CML)
    a. Epidemiology
    b. Pathophysiology
        i. Causes and risk factors
References

Introduction

Leukemias are cancers of the blood-forming tissues, predominantly the bone marrow. Abnormal blood cells can usually first be detected in the blood but may involve other sites such as the spleen, lymph nodes and other sites. The cancerous cells do not function normally and can lead to complications such as infections and bleeding.

Leukemia may be lymphocytic or myeloid depending on which bone marrow cells of origin are affected.

Chronic lymphocytic leukemia (CLL), also known as lymphoid or lymphocytic leukemia and small lymphocytic lymphoma (SLL), is a cancer of a sub-type of white blood cell, B-lymphocytes. In CLL there is a progressive accumulation of mature lymphocytes, which are usually monoclonal or genetically identical. CLL is a chronic or indolent cancer that presents as a progressive accumulation of incompetent mature B-lymphocytes, it is the most common hematologic cancer.

Chronic myeloid leukemia (CML) is a malignancy originating in hematopoietic stem cells in the chronic phase of the disease that invade the peripheral blood system. CML is also referred to as chronic myelogenous or myelocytic leukemia. CML is a type of myeloproliferative neoplasm characterized by high white blood cell counts, splenomegaly and/or other forms of extramedullary disease. CML accounts for about 15% of adult leukemias.

Greater understanding of the genetic transformations that occur in CLL and CML and how these transformations affect prognosis and treatment has been gained over the last few decades. Treatment advances, including many approved therapies and new therapy combinations have resulted in improved remission rates and progression-free survival, better quality of life, and longer survival for patients. New therapies are in the development pipeline and being evaluated in clinical trials.

Epidemiology and Pathophysiology of Chronic Lymphocytic Leukemia (CLL)

Epidemiology

According to estimates for CLL in the US for 2022,

- about 20,160 new cases will be diagnosed
- about 4410 people will die of CLL (Siegel 2022).

CLL is the most common type of leukemia in the Western world and mainly affects the elderly population; the average age of a patient with CLL is 70 years. More males than females are diagnosed with CLL and overall, approximately 0.6% of people will develop CLL during their lifetime. CLL rarely occurs in people under age 40 and is extremely rare in children. In addition to being a hallmark of the disease, CLL-associated immune dysfunctions strongly impact the immune surveillance, facilitate tumor progression, and eventually affect the disease course. Lastly, although the incidence of CLL has remained stable over the past 20 years, CLL-related mortality has decreased with survival in 2021 estimated to be 87.2% (Sant 2020). While incidence in Europe is similar to that in the US, in Asian populations the incidence of CLL is lower than that in the US (Bassig 2016).

Pathophysiology

CLL results from one or more acquired mutations to the genetic material of a single bone marrow cell that would otherwise develop into a healthy lymphocyte. In CLL, CD5+ B cells undergo malignant transformation. The B cells become continuously activated by acquisition of mutations that lead to monoclonal B-cell lymphocytosis. Further accumulation of genetic abnormalities and subsequent oncogenic transformation of monoclonal B cells leads to CLL (Kikushige 2020). The progressive accumulation of phenotypically mature malignant B- lymphocytes causes an initial accumulation of these cells in the bone marrow with eventual spread to lymph nodes and other lymphoid tissues, causing splenomegaly, hepatomegaly and systemic symptoms such as fatigue, fever, night sweats, early satiety and unintentional weight loss. Secondary lymphoid organs are the primary site for CLL cell proliferation.

As CLL progresses, abnormal hematopoiesis results in anemia, neutropenia, thrombocytopenia, and decreased immunoglobulin production. Hypogammaglobulinemia can develop in up to two thirds of patients, increasing risk for infectious complications. Patients have increased susceptibility to autoimmune hemolytic anemia (with a positive direct antiglobulin test) and autoimmune thrombocytopenia.

CLL is a lymphoproliferative disease typically characterized by a wide spectrum of immune alterations affecting both innate and adaptive immunity.

CLL can evolve into B-cell prolymphocytic leukemia and can transform to a higher-grade non-Hodgkin lymphoma. About 2% to 10% of CLL cases develop into diffuse large B-cell lymphoma referred to as Richter's transformation.

IGHV mutation

The mutation status of immunoglobulin heavy-chain variable (IGHV) genes influences the natural history of

CLL. Analysis of IGHV mutation distinguishes patients whose CLL cells express mutated IGHV with 2% or greater deviation from the IGHV germline sequence (these patients generally have indolent disease) from patients with unmutated CLL with less than 2% deviation (these patients generally present with more active and treatment-resistant disease). Mutated IGHV cells remain stable or grow at a slower rate than unmutated cells. While unmutated IGHV was previously a marker for a worse prognosis, this is no longer the case due to treatment with targeted agents (i.e., frontline ibrutinib) where targeted agents are available as first-line treatment (Burger 2020) [see Module 4 for detailed information on treatment of CLL].

Causes and risk factors

There are few known risk factors for CLL. Those that are known include:

- Age: the risk of getting CLL increase with increasing age
- Gender: CLL is slightly more common in males than females
- Exposure to certain chemicals such as certain herbicides (i.e., Agent Orange)
- Family history of CLL or family member with a history of a hematological disorder
- Race/ethnicity: CLL is more common in North America and Europe than in Asia; Asian people living in the US do not have a higher risk than those living in Asia making a higher risk more likely related to genetics rather than environmental factors.

Types of CLL

As mentioned, in CLL a significant number of abnormal lymphocytes are found in circulating blood and in bone marrow and lymphoid tissue. In SLL the bulk of disease is found in lymph nodes, bone marrow and in other lymphoid tissues and there are few abnormal cells in the circulating blood system. Hence, CLL and SLL are essentially different manifestations of the same disease and are managed in much the same way (Wierda 2022).

Prolymphocytic leukemia (PLL) shares some features with CLL. Prolymphocytes are immature forms of B lymphocytes or T lymphocytes. Both B- and T- prolymphocytic leukemias spread more quickly than is the case in CLL and PLL usually responds to treatment although relapses are common. PLL may develop in patients who have had CLL.

Overview: Epidemiology and Pathophysiology of Chronic Myeloid Leukemia (CML)

CML is a malignancy originating in hematopoietic stem cells in the chronic phase of the disease and characterized by myeloid cells of various maturation stages in peripheral blood and bone marrow. CML is known to be caused by the oncoprotein BCR-ABL1, a dysregulated tyrosine kinase.

Since the introduction of tyrosine kinase inhibitor (TKI) therapy in 2001, CML has been transformed from a life-threatening disease to a manageable chronic condition for most patients [see Module 4 for detailed information on treatment of CML]. TKI therapy has improved survival and patients taking this therapy generally experience fewer treatment side effects compared with traditional chemotherapy.

Epidemiology

According to estimates for CML in the US for 2022,

- about 8,860 new cases will be diagnosed
- about 1,200 people will die of CML (Siegel 2022).

CML is a relatively rare disease with incidence rates ranging between 1 and 1.5 cases per 100,000 persons/year without any major geographic or ethnic differences. The median age at diagnosis ranges between 60 and 65 years in Europe but is lower in countries with a younger population (Hochhaus 2017). Patients older than 70 years make up more than 20% of people with CML and children and adolescents < 5%. The incidence per year per 100,000 population varies by age and ranges between 1 and 2 depending on the age of the respective populations (Hehlmann 2020). Patient age is an important variable in making treatment decisions because overall survival (OS), comorbidities and the development of complications are all age-related (Hochhaus 2020).

There are 3 known risk factors for CML:

- Radiation exposure: exposure to high-dose radiation as occurs following an atomic bomb blast or nuclear reactor accident,
- Age: the risk of getting CML increase with increasing age,
- Gender: CML is slightly more common in males than females.

Pathophysiology

CML occurs when an abnormal pluripotent hematopoietic progenitor cell initiates excessive production of all myeloid lineage cells, primarily in the bone marrow but also in extramedullary sites (spleen and liver). Although granulocyte production predominates, the neoplastic clone includes red blood cells, megakaryocytes, monocytes and some T and B cells. Normal stem cells are retained and can appear after drug suppression of the CML clone (Kikushige 2020).

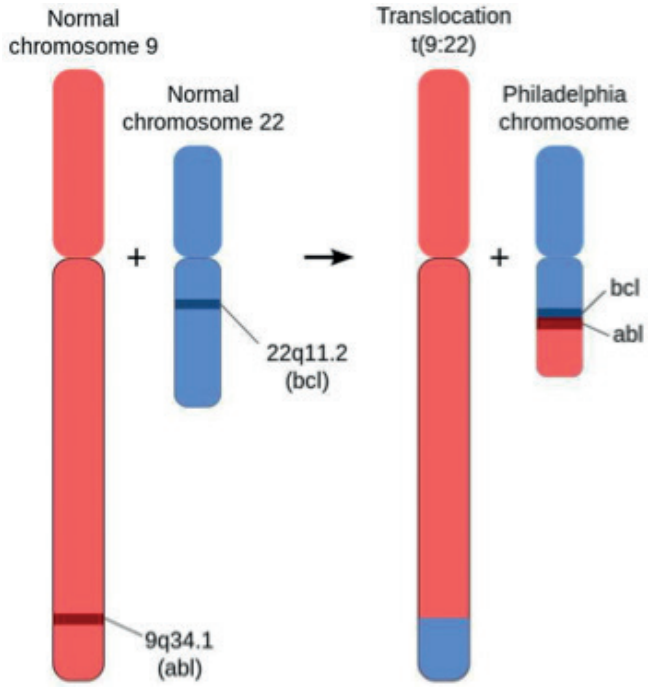

Figure 1. Formation of the BCR-ABL1 oncogene A portion of the ABL1 gene from chromosome 9 translocates and fuses with the remaining portion of the BCR gene on chromosome 22. The translocated piece of chromosome 9 results in an oncogene, BCRABL1 (Philadelphia chromosome). The BCR-ABL1 oncogene directs the production of an abnormal (mutant) protein, BCR-ABL1 tyrosine kinase. This abnormal enzyme protein is the principal factor in converting stem cells from normal into leukemic cells.

CML was the first neoplastic disease associated with a well-defined genotypic anomaly -- the Philadelphia chromosome. The Philadelphia (Ph) chromosome is formed by a translocation between parts of chromosomes 9 and 22 (**Figure 1**). In this translocation, the ABL gene breaks off from chromosome 9 and the BCR (breakpoint cluster region) gene breaks from chromosome 22 resulting in a fusion gene, BCR-ABL1, which is also referred to as t(9;22). The leukemia-causing fusion gene, or oncogene, BCR-ABL1, is not found in normal cells and it is unstable and prone to develop multiple and heterogeneous genomic abnormalities. BCR-ABL1 produces a new protein that leads to uncontrolled cell growth; hence, BCR-ABL1 is a central player in the pathogenesis of CML (Shah 2022).

More than 95% of CML patients have the Ph chromosome and, in these cases, the disease is referred to as Ph positive (Ph+) CML. A small proportion of patients with CML have the BCR-ABL1 gene but no detectable Ph chromosome; this is called Ph-negative (Ph-) CML. The prognosis is the same for Ph+ and Ph- CML patients. Some people have very low levels of BCR-ABL1 but do not have CML, as demonstrated in a seminal study in which very small quantities of BCR-ABL was found in blood cells of otherwise healthy individuals (Biernaux 1995).

The ABL1 gene signals cells to make a protein called tyrosine kinase, which sends signals to instruct cells when to grow and divide. The abnormal BCR-ABL1 gene produces an abnormal protein called BCR-ABL1 tyrosine kinase, which when over-produced, signals hematopoietic stem cells to accelerate the production of granulocytes. The granulocytes have the BCR-ABL1 oncogene that causes CML and are therefore referred to as leukemia cells or CML cells. An overproduction of granulocytes causes elevated white blood cell counts (WBC) and an enlarged spleen.

Over time, additional mutations occur in some CML stem cells, which prevent maturation into normal WBCs. These immature cells, blasts, crowd out healthy red blood cells (RBCs), WBCs and platelets resulting in disease-related complications such as anemia, infection or bleeding.

CML stem cells express the markers CD26, interleukin-1 receptor accessory protein (IL1RAP) and CD93 and are the cause of disease relapse and progression to blast crisis (Kumar 2021). The identification of different subgroups of leukemia stem cells may allow predictions as to which patients will develop treatment resistance or progress to the blast phase (Minciacchi 2021).

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Quick Facts

1. The diagnosis of CLL, requires the presence of ≥ 5 x 10^9/L B lymphocytes in the peripheral blood, sustained for at least 3 months (International Workshop on Chronic Lymphocytic Leukemia)
2. Because CLL is diagnosed mainly in older adults, comorbidities are frequently present. Multiple comorbidities (≥ 2) is an independent predictor of clinical outcome, independent of age or disease stage; hence, performance status assessment should be performed
3. There are two staging systems commonly used in CLL. The Rai system is based on lymphocytosis and the Binet system stratifies patients based on the number of involved areas and the level of hemoglobin and platelets.
4. Prognostic markers for CLL include cytogenetic abnormalities such as depletion of 13q [del(13q)], del(17p), trisomy 12 and del(11q), as well as the mutation status of immunoglobulin heavy-chain variable (IGHV) genes of the B-cell receptor
5. IGHV mutation status is an important predictor of survival outcomes: unmutated IGHV is associated with poor prognosis and significantly decreased survival compared with mutated IGHV. IGHV is a stable marker, i.e., it does not tend to change over time/after treatment.
6. Adverse prognostic factors in CLL include: diffuse pattern of bone marrow involvement; lymph node involvement (size, site(s) of involvement); advanced age; lymphocyte doubling time (the time it takes for the lymphocyte count to double) of less than 1 year; increased fraction of prolymphocytes (an early form of the lymphocyte) in the blood.

Module II: CLL: Diagnosis, Staging and Risk Assessment

Establishing a Diagnosis of Chronic Lymphocytic Leukemia (CLL) as the Basis for Treatment

Introduction

The identification of prognostic and predictive biomarkers is relevant, not only for patient counseling but also for planning follow-up or selecting treatment (see Module 4 and 5). Prognostic biomarkers separate groups of patients with different outcomes regardless of treatment. Predictive biomarkers provide information about the possible benefit of a specific treatment and can be used in the clinical decision-making process (Montserrat 2019).

Prognostic biomarkers in chronic lymphocytic leukemia (CLL) include clinical stage, IGHV mutational status, genetic abnormalities and lymphocytes doubling time.

Observation without treatment is the standard of care for asymptomatic patients without anemia, neutropenia, or thrombocytopenia; therefore, most patients do not require treatment at the time of diagnosis (Shadman 2023). In this regard, a key challenge at the time of diagnosis is determining if, and consequently when, early stage/asymptomatic patients will require treatment, and hence the focus on identifying robust prognostic factors on which to base time-to-first-treatment (HYPERLINK „https://haematologica.org/article/view/8779#author-1“Baliakas 2019b). Staging of the disease as well as testing for specific genetic and cytogenetic abnormalities and imaging procedures are not recommended during a watch-and-wait period but rather at the onset of clinical symptoms (Eichhorst 2021).

Diagnosis

Initial workup

A purpose of performing diagnostic testing in patients suspected of having CLL is to verify the disease and rule out other lymphoproliferative disease that can mimic CLL (**Box 1**). Approximately 70% of patients are diagnosed based on an unexplained lymphocytosis discovered incidentally and have no symptoms at the time of diagnosis. Flow cytometry of peripheral blood with immunophenotyping using cell surface markers is adequate for the diagnosis of CLL and bone marrow biopsy is generally not required (Wierda 2022; Burger 2020). The diagnosis of CLL, as established by the iwCLL (International Workshop on Chronic Lymphocytic Leukemia), requires the presence of ≥ 5 x 10^9/L B lymphocytes in the peripheral blood, sustained for at least 3 months (Hallek 2018). While CLL may be suspected in patients with < 5 x 10^9/L B lymphocytes in the blood, in the absence of lymphadenopathy or organomegaly (as detected by physical examination or imaging studies), or of disease-related cytopenias or clinical symptoms, this abnormality is defined as monoclonal B lymphocytosis (MBL) (Hallek 2018). In small numbers of cases, MBL progresses to CLL. It is now generally accepted that if peripheral B lymphocytes are < 5 x 10^9/L and lymphadenopathy and/or splenomegaly is present, small lymphocytic lymphoma (SLL) instead of CLL is diagnosed (Eichhorst 2021).

Flow cytometry of peripheral blood with immunophenotyping using cell surface markers is adequate for the diagnosis of CLL and bone marrow biopsy is generally not required (Wierda 2022; Burger 2020).

Other tests are recommended to be performed to either help predict prognosis, assess tumor burden or support

Box 1. Baseline Evaluation of Patients with CLL

Tests to establish a diagnosis
- CBC, differential count
- Immunophenotyping of peripheral blood lymphocytes

Assessment before treatment
- History and physical exam with attention to node-bearing areas and the size of liver and spleen
- Performance status
- CBC, differential count
- Serum chemistry, serum immunoglobulin, direct antiglobulin test
- Chest radiograph
- Infectious disease status
- Marrow aspirate/biopsy (if clinically indicated)

Additional tests for prognostic and/or treatment determination
- Molecular cytogenetics (FISH) to detect +12; del(11q); del(13q); del(17p)
- IGHV mutation status
- TP53 mutation
- Conventional karyotyping in peripheral blood lymphocytes[1] (if indicated)
- Serum β_2-microglobulin
- CT scan of neck, chest, abdomen, pelvis
- MRI, PET scans
- Lymph node biopsy/excision (rarely used in CLL)
- Abdominal ultrasound[2]

CBC, complete blood count; CT, computer tomography; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain; MRI, magnetic resonance imaging; PET, positron emission tomography

[1] Conventional karyotyping in peripheral blood lymphocytes may be useful before therapy if available

[2] Used in some countries to monitor lymphadenopathy and organomegaly

Adapted from: Hallek 2018; Wierda 2022

treatment decisions. Indication for treatment does not depend on the results of these tests, but rather on the patient's clinical stage and symptoms (Hallek 2018) (see Clinical Staging below).

Patient presentation

History and physical exam including measurement of size of liver and spleen and palpable lymph nodes should be performed. The patient's performance status should be assessed. Because CLL is diagnosed mainly in older adults, comorbidities are frequently present and the presence of multiple comorbidities (≥ 2) was shown to be an independent predictor of clinical outcome, independent of age or disease stage (Goede 2014).

Presenting symptoms are most commonly related to lymphoadenopathy. Approximately 20% to 50% present with symptoms from hepatosplenomegaly, and approximately 5% to 10% with unintentional weight loss of 10% or more body weight within a 6-month period (Shadman 2023). Fatigue, when present, may be reported as severe. The presence of "B" symptoms may signal more active disease and may be indicative of the need to initiate treatment. "B" symptoms include:

- Unexplained weight loss > 10% of body weight in the previous 6 months
- Severe fatigue (unable to work or perform activities of daily living
- Fevers > 38°C for at least 2 weeks without evidence of infection
- Drenching night sweats for more than a month without evidence of infection

Painless, enlarged lymph nodes are commonly found in more than half of new CLL patients. Nodes may become painful or may grow together to form large masses of lymphoid tissue. Enlarged nodes may be present even in the absence of an elevated white blood cell count. The number and size of enlarged lymph nodes is considered into the diagnosis and management. The term "generalized lymphadenopathy" refers to enlarged lymph nodes throughout the body.

Differential diagnosis

It is important to verify that the patient has CLL and not another lymphoproliferative disease that can masquerade as CLL. Other lymphoma entities to be differentiated from CLL are

- Hairy cell leukemia: a rare cancer of the lymphocytes that tends to progress slowly. The cancer cells are a type of B lymphocyte but different from those seen in CLL. Lymphocytes have fine projections on their surface making them appear "hairy"
- Large granular lymphocyte leukemia (LGL): cancer cells are large and have features of either T lymphocytes or natural killer (NK) cells. Most LGL leukemias are slow growing, but a small number are more aggressive
- Leukemic manifestations of mantle cell lymphoma
- Leukemic marginal zone lymphoma
- Splenic marginal zone lymphoma with circulating villous lymphocytes
- Follicular lymphoma
- Lymphoplasmacytic lymphoma (Eichhorst 2021; Hallek 2018)

Clinical Staging

There are two staging systems commonly used in CLL: the Rai system and the Binet system. The Rai system is based on lymphocytosis. That is, the patient must have a high number of lymphocytes in their blood and bone marrow that cannot be linked to any other cause such as infection.

The Binet staging system stratifies patients into three prognostic groups based on the number of involved areas and the level of hemoglobin and platelets and, similar to the Rai staging system, provides meaningful correlation with clinical outcome. Both systems rely on physical evidence (i.e., presence of lymph node involvement, enlargement of spleen and/or liver) and blood parameters to assess the degree of tumor burden.

Early, asymptomatic stage disease, as determined by either of the staging systems in **Table 1**, does not require further risk assessment. Patients should be seen at 3-month intervals after the first year then followed every 3 to 12 months depending on the burden and dynamics of the disease (see Module 4).

Prognostic Factors

Prognostic biomarkers (**Box 2**) evaluate risk of disease progression and death and aid clinicians in aspects of patient counseling including determining frequency of follow-up and identifying those appropriate for risk-adapted early treatment (Cohen 2020). The most commonly defined cytogenetic abnormalities, and therefore prognostic markers for CLL include cytogenetic abnormalities such as depletion of 13q [del(13q)], del(17p), trisomy 12 and del(11q), as well as the mutation status of immunoglobulin heavy-chain variable (IGHV)

Table 1. Binet and Rai Staging Systems for CLL		
Stage	**Definition**	
Binet system		
Binet A	Hb ≥ 100 g/L (6.21 mmol/L), platelets ≥ 100 x 10^9/L, < 3 involved lymphoid sites[1]	
Binet B	Hb ≥ 100 g/L (6.21 mmol/L), platelets ≥ 100 x 10^9/L, ≥ 3 involved lymphoid sites[1]	
Binet C	Hb < 100 g/L (6.21 mmol/L), platelets < 100 x 10^9/L	
Rai system		
Low risk	Rai 0	Lymphocytes > 5 x 10^9/L
Intermediate risk	Rai I Rai II	Lymphocytosis and lymphadenopathy Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy
High risk	Rai III	Lymphocytosis and Hb < 110 g/L (6.83 mmol/L) with/without lymphadenopathy/organomegaly
	Rai IV	Lymphocytosis and platelets < 100 x 10^9/L with/without lymphadenopathy/organomegaly

CLL, chronic lymphocytic leukemia; Hb, hemoglobin
[1] The Binet system takes into account five potential sites of involvement: cervical, axillary, inguinal lymphadenopathy (either uni- or bilateral), spleen and liver. Involvement is judged only by physical exam and does not take into consideration the results of imaging studies for staging purposes.
Adapted from Eichhorst 2021

genes of the B-cell receptor (Burger 2020). Patients with one or more high-risk markers (del(17p), del(11q) or unmutated IGHV, characteristically have a shorter time to starting initial treatment and shorter remissions after treatment than patients with the following markers for low-risk CLL: del(13q), trisomy 12 or mutated IGHV. Overall, the prognostic significance of prognostic markers may vary depending on the patient population, treatment regimens and clinical outcomes being evaluated (Wierda 2022). Many of the factors were generated during the time when chemotherapy or chemoimmunotherapy were being used; newer and more effective novel therapies may affect prognosis.

Box 2. Established prognostic biomarkers in CLL	
Stage	**Definition**
Host factors	Age, gender
Disease markers	Rai and Binet staging systems
Antigen expression	CD38, ZAP70, CD49d/VLA-4
Serology	Lactate dehydrogenase, beta-2-microglobulin, thymidine kinase
Genetics	del(17p), TP53 gene mutation
Immunogenetics	IGHV
Source: Cohen 2020	

International Prognostic Index for CLL (CLL-IPI)

In 2016, a new prognostic model was released that enabled a more targeted management of CLL (International CLL-IPI working group 2016). This index estimates the risk of progression and time to initial treatment in patients with early-stage disease and categorizes risk (low, intermediate, high, or very high) on the basis of weighted individual risk factors. It is currently the most important prognostic system in CLL (**Table 2**). The Rai and Binet staging systems are incorporated into this index but do not recognize the biological diversity of CLL or predict response to modern therapy.

The CLL-IPI combines genetic, biochemical and clinical parameters into a prognostic model, discriminating four prognostic subgroups. It allows a more targeted management of patients with CLL in clinical practice and in clinical trials (International CLL-IPI working group, 2016). The index emphasizes the importance of including IGHV

Table 2. Summary CLL-IPI Scoring and Prognostic Index of CLL		
Variable	**Adverse factor**	**Score**
TP53(17p)	Deleted and/or mutated	4
IGHV	Unmutated	2
β_2-microglobulin	> 3.5 mg/L	2
Clinical stage	Binet B/C or Rai I-IV	1
Age	> 65	1
Prognostic score		0-10
Risk group	**Score**	
Low (no treatment required)	0-1	
Intermediate (no treatment unless disease is highly symptomatic)	2-3	
High (treat unless the patient is asymptomatic)	4-6	
Very high (treat with novel agents or treatment in a	7-10	

mutation status in the baseline evaluation of patients with CLL as a requirement before treatment, awarding this variable a score of 4 in the CLL-IPI Index (Hallek 2018) (**Table 2**).

A note of caution: most prediction models were developed from individuals treated with chemoimmunotherapy and it should not be assumed that these predictors operate within the context of other therapies such as BTK inhibitors or BCL2 inhibitors (Montserrat 2019).

Cytogenetic abnormalities

Researchers have for many years studied the genetic aberrations associated with CLL to better understand disease development and evolution and to improve risk stratification. Evidence to date indicates that cytogenetic complexity, i.e., the presence of multiple chromosomal aberrations, could be used as a predictive marker for prognosis and treatment response (**Table 3**).

Approximately 80% of patients with untreated CLL have cytogenetic abnormalities, which are detected by fluorescence in situ hybridization (FISH) (Wierda 2022). CLL FISH studies cannot be used to diagnose CLL because the anomalies can be seen in other lymphoproliferative disorders.

Several studies have indicated that a variety of genomic aberrations, particularly del(17p) and TP53 mutation status have the strongest relation to clinical outcome and their assessment before starting therapy is recommended for every CLL patient (Tausch 2020; Hallek 2018). The del(17p) abnormality is more frequently observed in patients with previously treated CLL, suggesting that acquisition and/or expansion of CLL clones with del(17p) may occur during the course of treatment.

Tumor markers for prognostic assessment pertain to the genomic background of the malignant clone, more particularly the TP53 gene (also referred to as tumor protein TP53, cellular tumor antigen TP53) and the somatic hypermutation status of the rearranged IGHV gene expressed by the clonotypic B-cell receptor immunoglobulin. There is not, however, a specific cytogenetic abnormality in CLL. TP53 mutation is seen in about 10% to 15% of patients at diagnosis and is common in patients with del(17p): prognosis is less favorable if both abnormalities are present.

IGHV mutation status is an important predictor of survival outcomes. Unmutated IGHV is associated with poor prognosis and significantly decreased survival compared with mutated IGHV, irrespective of the stage of disease (Hamblin 1999). IGHV is a stable marker, i.e., it does not tend to change over time, so testing is normally performed once. Testing for IGHV mutational status is necessary for treatment planning when considering chemoimmunotherapy.

Notch1 is involved in many physiologic processes of normal cells in which it regulates growth, apoptosis and differentiation. NOTCH1 mutations, which occur in about 5% to 12% of patients at diagnosis, are primarily found in the more aggressive IGHV nonmutated form of CLL and often correlate with trisomy 12 (Tardivon 2021).

The mutation frequency appears to increase with disease progression, reaching up to 31% in patients subsequently diagnosed with Richter syndrome (a transformation to diffuse large B-cell lymphoma) and in 21% of patients who are chemorefractory (is associated with increased risk of (known as Richter transformation).

SF3B1 gene mutations results in the dysfunctional processing of proteins. If present, this mutation may cause an accelerated disease progression and is associated with a less favorable outcome.

Complex karyotype is present when there are three or more structural and/or numeral aberrations on the chromosomes in a given sample. Patients with five or more aberrations had a shorter overall survival than those with three or four, independent of other factors according to one study (Baliakas 2019a). However, this study also found that patients with complex karyotype in combination with specific numerical aberrations, such as extra copies of chromosomes 12 and 19, had an indolent disease course (Baliakas 2019a). The authors conclude that complex karyotype defined as the presence of ≥ 3 numerical and/or structural abnormalities detected by conventional banding analysis (CBA) should not be generally accepted as unfavorable in CLL because of the heterogeneous nature of this disease: while high complex karyotype (≥ 5 aberrations) is prognostically adverse, low and intermediate complex karyotype are clinically relevant only if coexisting with TP53abs (Baliakas 2019a).

Immune alterations

CLL is characterized by complex immune alterations, which eventually manifest in clinically relevant immune dysfunctions including autoimmune phenomena and increased risk of infections. Autoimmune manifestations of CLL can include autoimmune cytopenias, immune thrombocytopenia, pure red cell aplasia and autoimmune granulocytopenia. An increased risk of infection is dependent on the underlying CLL-related immune dysfunctions; considering the current pandemic scenario, it should be mentioned that patients with CLL can be severely affected by SARS-CoV-2 infection and especially older patients seem to be at increased risk of infection.

Table 3. Cytogenetic and Other Abnormalities and their Prognostic Relevance[1]

Abnormality	Associated Risk/Outcomes
del(13q)	Approx. 55% at diagnosis; if no other abnormality is present, it indicates favorable outcome, indolent disease progression
del(17p)	< 10% at diagnosis, ≤ 30% in relapsed/refractory disease; often in conjunction with other abnormalities; unfavorable/high-risk
del(11q)	10% of patients with early-stage disease, 25% of untreated patients with advanced-stage; high risk/aggressive disease
Trisomy +12	In 10%-20% of patients; intermediate risk (if only cytogenetic abnormality), higher risk (if in conjunction with other abnormalities)
NOTCH1 gene mutations	10%-15% have mutation, more aggressive disease progression, unfavorable outcomes
TP53 gene mutation/ disruption	10%-15% at diagnosis, commonly in conjunction with del(17p); wild-type has favorable outcomes; if mutated then faster disease progression, identifies unfavorable/high-risk disease; indicates poor response to CIT or early relapse
SF3B1 gene mutations	10%-15% have mutation; faster disease progression, less favorable outcomes
IGHV	40% unmutated at diagnosis, identifies unfavorable/high-risk; 60% mutated at diagnosis, favorable outcomes
Complex karyotype (CK)[2]	≥ 3 unrelated clonal chromosome abnormalities in more than one cell on karyotype; unfavorable/high-risk
Blood lymphocyte doubling	Doubling within 1 year associated with higher risk, close monitoring required
CD38	Expression of CD38 is an indicator of higher risk
Beta-2 microglobulin	Associated with greater extent of disease
CD49d	Expression of CD49 is an indicator of higher-risk disease
ZAP-70	Increased expression may be associated with higher- risk disease

[1] This table provides useful prognostic information for survival and time to progression in patients who received treatment
[2] Based on results of metaphase karyotyping of CpG-stimulated CLL cells
CD, cluster designation; CIT, chemoimmunotherapy; del, deleted; ZAP, zeta-chain = associated protein kinase 70
Adapted from: Hallek 2019; Wierda 2022

Immune dysregulation also leads to an increased risk of second malignancies (Vitale 2021). CLL-related factors, such as the loss of immune surveillance together with older age contribute to the occurrence of second malignancies.

Cell surface markers

There is an elevation of CD4+ and CD8+ T lymphocytes in CLL, which have been investigated as having a prognostic impact on the disease. The ratio of T cells: malignant monoclonal B cells (MBC) has been identified as an independent predictor of time-to-first treatment in early stage CLL, with higher CD4: MBC and CD8: MBC ratios predicting longer overall survival. A reduced (or inverted) CD4:CD8 ratio has been associated with several disadvantageous situations including advanced disease stages, a predictor of recurrent respiratory infections, and shorter time-to-first-treatment, progression-free survival and overall survival (Vitale 2021).

Other risk factors

Beta-2 microglobulin is a protein that is released by different types of cells including CLL cells. High levels are associated with earlier progression of CLL. ZAP-70 is a protein expressed near the surface membrane of T cells; it plays a key role in T-cell signaling. A high level of lactate dehydrogenase (LDH), a protein present in most cells, indicates cell damage and may be a sign of disease progression.

Other adverse prognostic factors:

- Diffuse pattern of bone marrow involvement (more widespread replacement of normal marrow by leukemia)
- Lymph node involvement (size, site(s) of involvement)
- Advanced age
- Lymphocyte doubling time (the time it takes for the lymphocyte count to double) of less than 1 year
- Increased fraction of prolymphocytes (an early form of the lymphocyte) in the blood

Future Perspectives on Diagnosing Chronic Lymphocytic Leukemia

Progress in predicting outcomes in CLL has been modest, while progress in treatment has been exceptional. Mutations in NOTCH1, SF3B1 and BIRC3, among others, and complex karyotype might add important information to prognostic models but require standardization and harmonization, validation and further study (Montserrat 2019). Specific studies in patients with IGHV-mutated and IGHV-unmuted CLL and other genetic subgroups, as well as in areas such as drug resistance, clonal selection, transformation risk and adverse events are needed to build on what is now known about predicting outcomes in these patients (Montserrat 2019). In the era of targeted therapy, new predictive biomarkers such as BCR and BCL-2 pathway mutations to identify patients with relapsed/refractory disease who should be considered for treatment in new clinical trials will require further investigation (Cohen 2020).

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Notes

Quick Facts

1. CML has 3 phases: chronic, accelerated and blast. The phases are based on the number of immature blasts found in the blood and bone marrow.
2. Diagnostic workup should include: physical examination, electrocardiogram, biochemical profile, complete blood cell count (CBC) and differential, bone marrow aspirate for morphology and cytogenetics and the detection of BCR-ABL1 transcript using reverse transcriptase-polymerase chain reaction (RT-PCR), or of the Ph chromosome using fluorescence in situ hybridization (FISH).
3. Several systems are used to define advanced phase CML, which are based on percentage of blasts in peripheral blood and/or bone marrow, platelet count, and presence of splenomegaly.
4. Factors associated with a less favorable prognosis at initial diagnosis include: advanced stage, age ≥ 60 years, splenomegaly, very high/very low platelet count, ↑ blast count and ↑ basophil count in peripheral blood.
5. Since the introduction of tyrosine kinase inhibitors, most patients now die from causes other than leukemia while still in remission.

Establishing a Diagnosis of CML

Introduction

In patients who are asymptomatic, CML is often discovered during a routine medical appointment or while analyzing routine blood tests (Jabbour 2020). The absence of symptoms is more common in the chronic phase and most patients, approximately 85%, are diagnosed during this phase (Apperley 2015). Progression of disease is generally from the chronic to the accelerated to the blast phase, although some patients do progress directly from the chronic to the blast phase, without displaying any typical manifestations of the accelerated phase (Jabbour 2020).

Classification and phases

CML can be classified into 3 phases: chronic, accelerated and blast. The phases are based on the number of immature blasts found in the blood and bone marrow (**Table 1**).

CML progresses very slowly in the chronic phase, and it may take months to several years for the disease to progress to the next phase. Untreated chronic phase disease will eventually progress to accelerated or blast phase in 3 to 5 years on average (Sawyers 1999). In the accelerated phase, there is an increase in the number of immature myeloid blast cells and often new chromosomal changes, or other mutations occur, in addition to the Philadelphia (Ph) chromosome.

Progression from chronic to blast phase is relevant for prognosis and treatment, although the clinical and morphological boundaries between these stages are sometimes vague. Tests, such as immunocytology by flow cytometry and histochemistry, allow accurate assessment of immature cells and distinction between myeloid and lymphoid blast crisis (Hochhaus 2017a). The blast phase (or blast crisis) can mimic signs and symptoms of acute myeloid leukemia.

Additional chromosomal abnormalities in Ph+ cells (ACA/Ph+) refer to cytogenetic aberrations causing clonal evolution. In patients who are found to have additional chromosomal abnormalities in Ph+ cells, the presence of major route ACA/Ph+ (e.g., trisomy 8, isochromosome 17q, second Ph and trisomy 19) at diagnosis may have a negative prognostic impact on survival and disease progression to accelerated or blast phase

The overall incidence of accelerated and blast phase CML at diagnosis is 3.5% and 2.2%, respectively (Hoffmann 2015), but with the introduction of TKIs, the number has decreased significantly. In a long-term follow-up study, the cumulative progression to accelerated or blast phase CML after 10 years was 6.9% (Hochhaus 2017b). Progression rates are now lower thanks to improvements in managing patients with chronic phase CML who had an inadequate response to treatment.

Diagnostics

Patient presentation

Approximately 50% of patients with CML diagnosed in Europe and 30% to 50% of those in the US are asymptomatic at presentation (Hochhaus 2017a). At the time of diagnosis, most patients (90%-95%) are in the chronic phase (Jabbour 2020), rarely are patients diagnosed in the blast phase. In asymptomatic patients, the onset of nonspecific symptoms is subtle, but obvious enough

Table 1. Characteristics of the Chronic, Accelerated and Blast Phases of CML

	Clinical and hematological	Additional chromosomal alterations
Chronic phase	< 10% blasts; Patient may/may not exhibit symptoms; Slow progression; Good response to treatment	Second Ph, trisomy 8, isochromosome 17q, trisomy 19, complex karyotype or abnormalities of 3q26.2
Accelerated phase	**PB or BM blasts 15% - 29%**; PB blasts + promyelocytes ≥ 30%; PB basophils ≥ 20%; **platelets ≤ 100 x 10^9/L (unrelated to therapy)**; anemia; persisting/increasing splenomegaly unresponsive to therapy	**Cytogenetic evolution on treatment** (i.e., abnormalities in Ph+ cells)
Blast phase	**PB or BM blasts ≥ 30%; extramedullary blast proliferation**; high WBC; wide range of symptoms	

Clinical and hematological criteria in **bold** are European LeukemiaNet criteria for the definition of accelerated and blast phase CML. There are several classifications systems including those from MD Anderson Cancer Center and the World Health Organization (WHO).
BM, bone marrow; PB, peripheral blood
Adapted from: How 2021; Hochhaus 2020

Table 2. Signs and Symptoms of CML	
Common signs and symptoms at diagnosis	**Rare signs and symptoms at diagnosis**
• Fatigue • Weight loss • Malaise • Left upper quadrant fullness or pain due to splenomegaly, which is present in up to 60% of patients	• Bleeding (associated with low platelet count and/or platelet dysfunction) • Thrombosis (associated with thrombocytosis and/or marked leukocytosis) • Gouty arthritis (due to elevated uric acid levels) • Retinal hemorrhages • Upper gastrointestinal ulceration (from elevated histamine levels due to basophilia)
Adapted from: Jabbour 2020; Thompson 2015	

to prompt medical evaluation. Signs and symptoms of CML chronic phase result from anemia and splenomegaly (found in 50% to 60% of cases) (**Table 2**).

Initial workup

The diagnostic workup for CML should include physical examination with emphasis on the presence of hepatomegaly or splenomegaly, electrocardiogram, biochemical profile, complete blood cell count (CBC) and differential count, bone marrow aspirate for morphology and cytogenetics and the detection of the BCR-ABL1 transcript by reverse transcriptase-polymerase chain reaction (RT-PCR), or of the Philadelphia (Ph) chromosome by fluorescence in situ hybridization (FISH) (Shah 2022; Hochhaus 2020). Molecular testing is becoming widely available, replacing cytogenetic monitoring. RT-PCR is also used for following response to treatment by the assessment of molecular response (MR), which is defined as the ratio of BCR-ABL1 to ABL1 transcripts according to the International Scale (IS) (see Module 4) (Minciacchi 2021). Bone marrow aspiration is mandatory for all patients in whom CML is suspected, as it will confirm the diagnosis (e.g. by cytogenetic analysis) and provide information needed for staging in terms of the blast and basophil percentages (Hochhaus 2017a). Aspirate can provide important information, which allows for confirmation of the diagnosis and determination of disease stage based on the percentages of blasts and basophils (Jabbour 2020).

Advanced stage workup

The recognition of disease progression from chronic to blast phase is relevant for prognosis and treatment, although the clinical and morphological boundaries between these stages are sometimes vague (Hochhaus 2020).

The patient may present with more severe symptoms in advanced phases of CML. These can include shortness of breath, bone pain, skin infiltrate, lymphadenopathy and worsening of anemia as well as fever, arthralgia and abdominal pain as caused by splenic infarction (Jabbour 2014). Central nervous system (CNS) involvement has been described in blast phase (Shah 2022). CML is most frequently suspected based on an abnormal CBC obtained incidentally or during evaluation of splenomegaly. The granulocyte count is elevated, usually ≤ 50 x 10^9/L in asymptomatic patients and 200 x 10^9/L to 1000 x 10^9/L in symptomatic patients. Neutrophilia (a left-shifted white blood cell differential), basophilia and eosinophilia are common. Reduced phagocytic activity of granulocytes is typical of CML and differentiates the disease from other chronic myeloproliferative disorders.

Bone marrow composition undergoes rapid changes during therapy, usually initiated in the chronic phase. Changes include, for example, reduction of granulocytic cellularity, normalization of megakaryopoiesis and normalization of erythropoiesis.

Advanced phase classification systems

Different classification systems are used to define advanced phase (accelerated and blast phases) CML. One major difference between these systems, developed by the International Blood and Marrow Transplant Registry (IBMTR), MD Anderson Cancer Center (MDACC), European LeukemiaNet and the World Health Organization (WHO), is the threshold blast percentage used to distinguish chronic-, accelerated- and blast-phases, with the WHO defining blast phase as a blast percentage of more than 20% and all other systems using a threshold of more than 30% (How 2021). The varying classification systems and their definitions of advanced CML must be considered when interpreting and applying trial results to individual patients. The MDACC and IBMTR criteria are also frequently used as eligibility criteria in clinical trials (**Table 3**).

Differential diagnosis

CML should be differentiated from leukemoid reactions, which usually produce white blood cell counts < 50 x 10^9/L and other blood abnormalities. CML may be difficult to differentiate from other myeloproliferative or myelodysplastic syndromes (Jabbour 2020). The most

Table 3. MDACC and IBMTR Classification Systems for Advanced Chronic Myeloid Leukemia	
MD	**IBMTR**
Accelerated phase	
PB blasts 15% - 29%	PB or BM blasts 10% - 29%
PB blasts + promyelocytes ≥ 30%	PB blasts + promyelocytes ≥ 20%
PB basophils ≥ 20%	PB basophils ≥ 20%
Platelets ≤ 100 x 10^9/L (unrelated to therapy)	Platelets ≤ 100 x 10^9/L (unrelated to therapy) or > 1000 x 10^9/L (unresponsive to therapy)
Splenomegaly (unresponsive to therapy)	Splenomegaly (unresponsive to therapy)
Cytogenetic evolution on treatment	Anemia Hb < 8g/dL (unresponsive to therapy)
Blast phase	
PB or BM blasts ≥ 30%	
Extramedullary blast proliferation	

BM, bone marrow; IBMTR, International Blood and Marrow Transplant Registry; MDACC, MD Anderson Cancer Center; PB, peripheral blood
Source: How 2021

difficult diagnosis is to confirm CML in patients who have splenomegaly and leukocytosis but who do not have the Ph chromosome. Patients who are Ph negative and BCR-ABL1 negative are considered to have Ph-negative CML or chronic myelomonocytic leukemia.

Prognostic Factors

Chronic phase

Since the advent of tyrosine kinase inhibitor (TKI) therapy, progression from chronic to advanced stage CML is much less common making it more difficult to identify the prognostic significance of additional cytogenetic abnormalities present at initial diagnosis. The BCR-ABL1 transcript type plays a major role in influencing response to treatment, outcome of treatment and treatment-free remission (TFR) (Castagnetti 2017). (The type of transcript refers to the translocation of the proto-oncogene ABL and the region of the breakpoint cluster [BCR] gene.) Several atypical cytogenetic abnormalities detected either at diagnosis or evolving over time are associated with a poorer prognosis/treatment response, independently of risk stratification scoring (see below) (Clark 2021) (**Box 1**). Cytogenetic studies may reveal more than one variant in a patient's cells.

Box 1. Additional cytogenetic abnormalities at initial diagnosis possibly associated with a poorer prognosis	
BCR-ABL1 transcript variants	e13a2, e14a2 (two most common subtypes); e1a2, e19a2 (less common subtypes)
Ph+	Trisomy 8, isochromosome 17q, second Ph, trisomy 19[1]

[1] Some evidence suggests that disease progression may not be as rapid in patients with this abnormality treated with second-generation tyrosine kinase inhibitors
Sources: Hochhaus 2020; Johansson 2002

Table 4. Prognostic Scoring Systems to determine Risk Profile	
Sokal scoring system	Based on patient age, spleen size, platelet count and percentage of blast cells in peripheral blood
Hasford scoring system	Based on patient age, spleen size, platelet count, percentage of blast cells, eosinophils and basophils in peripheral blood
European Treatment and Outcome Study for CML (EUTOS) Long-Term Survival scoring system (ELTS)	Based on patient age, spleen size, platelet count and percentage of blast cells in peripheral blood to determine long-term survival
Calculation of relative risk based on Sokal or Hasford (EURO) score available at: https://www.leukemia-net.org/content/leukemias/cml/euro_and_sokal_score/index_eng.html Calculation for risk of death using the ELTS core is available at: https://www.leukemia-net.org/content/leukemias/cml//elts_score/index_eng.html	

Factors associated with a less favorable prognosis at the time of initial diagnosis include:

- Phase of CML – less favorable prognosis if advanced stage at initial diagnosis
- Age – ≥ 60 years
- Splenomegaly
- Very high or very low platelet count
- ↑ blast count, ↑ basophil count in peripheral blood

Three prognostic scoring systems are used to determine the risk profile of patients with chronic phase CML at the time of diagnosis (**Table 4**). All three systems categorize risk as low, intermediate and high. Calculation of risk score at diagnosis remains an important component of the diagnostic workup, as this information has prognostic and therapeutic implications. The risk of progression to an advanced phase is higher in patients with intermediate or high-risk scores compared to those with a low-risk score at diagnosis. Therefore, determination of risk score should be performed prior to initiation of tyrosine kinase inhibitor therapy in patients diagnosed with chronic phase CML (Pfirrmann 2016).

Since most patients now die from causes other than leukemia while still in remission, the new EUTOS Long Term Survival (ELTS) score has been developed to predict the probability of dying from CML (i.e., leukemia-related death). The ELTS is based on TKI-treated patients. In this system, age has a negative prognostic value since it has less impact in TKI-treated patients than in patients treated with conventional chemotherapy (as in the Sokal system) (Hochhaus 2020). It is the most useful predictor of CML-related death in patients treated with first-line imatinib (Pfirrmann 2016).

Advanced disease

As previously stated, few patients initially present in an advanced (accelerated or blast) phase of CML and few patients now progress to this stage due to the efficacy of TKIs. Of course, a prognostic negative factor is a poor response or disease refractory to first-line treatment administered during the chronic phase (**Table 5**).

Table 5. Prognostic Scoring Systems to determine Risk Profile	
Characteristic	**Poor risk factors**
Clinical	Older age Anemia Thrombocytopenia Basophil% Prior TKI Myeloid immunophenotype
Chromosomal	+8, Ph+, i(17q), +17, +19, +21, 3q26.2, 11q23, -7/7q, complex, del17p, hyperdiploidy, chromosome 15 abnormalities
Molecular	TP53 ASXL1 Acquisition of new mutations during TKI treatment (ABL1 kinase mutations, TP53, KMT2D, TET2)
TKI, tyrosine kinase inhibitor Adapted from: How 2021	

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Notes

Quick Facts

1. Novel agents are the "preferred choice" for all lines of treatment of chronic lymphocytic leukemia (CLL) after their superiority over conventional chemoimmunotherapy was demonstrated in clinical trials.
2. Novel targeted agents (i.e., ibrutinib + rituximab) have shown greater efficacy with fewer and less serious adverse events and better tolerability in treating CLL than chemoimmunotherapy.
3. Achievement of a complete response with undetectable measurable residual disease at the end of treatment is the strongest predictor of improved survival in patients with newly diagnosed or relapsed/refractory CLL
4. TKIs (a type of targeted therapy taken orally), including the newest STAMP inhibitor, asciminib, now provide patients with CML an average life expectancy near that of the general population.
5. Treatment in advanced CML is often intensive combination chemotherapy with a TKI to revert to a chronic phase/remission in preparation for alloHCT; TKI selection is affected by patient comorbidity, costs, prior treatment and BCR-ABL1 mutational status.
6. Mutations in the BCR-ABL1 gene alter the shape of the BCR-ABL1 protein, which can affect the inhibition action of TKI agents on BCR-ABL1.
7. TKI treatment can be discontinued in some patients with CML after achieving treatment-free remission. However, approximately 50% of patients will relapse indicating the need to carefully select and monitor patients.

Module IV: Treatment Strategies in Chronic Leukemias

A. Novel Therapies in Chronic Leukemia

B. Chronic Lymphocytic Leukemia

- a. Goals of treatment
- b. Chemotherapy versus novel treatment
- c. Patient assessment before initiating treatment
  - i. Evaluation of level of fitness
- d. Early-stage, asymptomatic disease
- e. Relapsed/refractory disease
- f. Allogeneic stem cell transplantation
- g. Evaluation of treatment response
- h. Treatment of relapsed/refractory disease
- i. Limitations of currently available treatments

C. Chronic Myelocytic Leukemia

- a. Chronic phase: first line
- b. Chronic phase: second line and beyond
- c. Treatment-resistant BCR-ABL1 mutations
- d. Advanced phase
- e. Allogeneic stem cell transplantation
- f. Evaluation of treatment response
  - i. Treatment response milestones
- g. Treatment during pregnancy
- h. Treatment-free remission

D. Future Perspectives on Treating Chronic Leukemias

References

Novel Therapies in Chronic Leukemia

In 2019, novel agents were upgraded from being a "great treatment option" to the "preferred choice" for all lines of treatment of chronic lymphocytic leukemia (CLL) after their superiority over conventional chemoimmunotherapy (CIT) was demonstrated in clinical trials (Iovino 2020). These therapies include inhibitors of Bruton tyrosine kinase [BTK (ibrutinib)], apoptosis regulator B-cell leukemia/lymphoma 2 [BCL-2 (venetoclax)] and phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta [PI3Kδ (idelalisib)]). Select novel agents can be used as monotherapy or in combination with other types of therapies such as anti-CD20 monoclonal antibodies (e.g., rituximab, ofatumumab or obinutuzumab); a combination that is highly efficacious in CLL (How 2021). Several next-generation molecules are in clinical trials and are showing a more favorable safety profile and improved efficacy.

The introduction of the first-generation tyrosine kinase inhibitors (TKIs) dramatically changed the management of CML and provided remarkable overall survival (OS) rates (Canet 2021). For example, treatment with the first-generation TKI imatinib has improved the 8-year OS from 20% to 87% (Kantarjian 2012). With five TKIs (first-generation imatinib; second-generation dasatinib, bosutinib and nilotinib; and third-generation ponatinib) targeting BCR ABL approved in most countries, and with the approval of the first-in-class TKI specifically targeting the ABL myristoyl pocket (STAMP inhibitor), asciminib, now approved in the US, treatment decisions are complex and require assessment of patient-specific factors (Garcia-Gutierrez 2022). In refractory disease, the TKI asciminib has shown advantage over bosutinib in highly refractory CML patients, especially those with T315I mutation (Hochhaus 2020a). These agents now provide patients with CML an average life expectancy near that of the general population (Bower 2016; Sasaki 2015).

Chronic Lymphocytic Leukemia

Treatment of CLL is only required if active disease is documented, according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria (**Box 1**), and in general practice, patients with asymptomatic early-stage disease (Rai 0, Binet A), should be monitored without therapy (Hallek 2018). Response to treatment is highly variable and now can be more accurately predicted thanks to discoveries on the relationship between biomarkers and clinical outcomes (see Module 2). Early treatment with chemotherapeutic agents, signaling inhibitors or BCL2 antagonists alone or in combination with monoclonal antibodies, does not translate into a survival advantage in patients with early-stage CLL (Eichhorst 2021; Hallek 2018). None of the currently approved therapies are curative and chemoimmunotherapy no longer has a role in the treatment of refractory/relapsed CLL. Whenever possible, patients should be treated within a clinical trial for all lines of therapy.

Box 1. International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria indications for initial treatment[1]

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cutoff levels of Hb < 10 g/dL or platelet counts < 100 x 10^9/L are generally regarded as indication for treatment. In some patients, platelet counts < 100 x 10^9/L may remain stable over a long period and therapeutic intervention may not be necessary.
2. Massive (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. Progressive lymphocytosis with an increase of ≥ 50% over 2-months, or lymphocyte doubling time (LDT), < 6 months.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
   a. Unintentional weight loss ≥ 10% within the previous 6 months.
   b. Significant fatigue (i.e., ECOG performance scale 2 or worse; unable to work or perform usual activities). Fevers ≥ 100.5°F or 38.0°C for ≥ 2 weeks without evidence of infection.
   c. Night sweats for ≥ 1 month without evidence of infection.

[1] at least 1 of the criteria should be met as an indicator of the need for treatment
Source: Hallek 2018

Goals of treatment

Because CLL, in most cases, is an incurable disease, treatment should improve quality of life and prolong survival (Eichhorst 2020). Progression-free survival may be a more relevant treatment goal in younger patients and/or in fit patients than in older patients.

The goals of treatment for CLL include:

- Stop the multiplication of CLL cells
- Activate programmed cell death (apoptosis) in CLL cells
- Attain and maintain long periods of remission
- Improve survival
- Help patients and families to manage symptoms and complications

Chemoimmunotherapy vs novel treatment

In a phase 3 trial, patients 70 years of age or younger with previously untreated CLL were randomized to receive either ibrutinib and rituximab for 6 cycles (after a single cycle of ibrutinib alone), followed by ibrutinib until disease progression, or 6 cycles of chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab, the standard first-line therapy. At a median of 36 months, results for progression-free survival favored ibrutinib + rituximab over chemoimmunotherapy (89.4% vs 72.9%). Results of overall survival also favored ibrutinib + rituximab over chemoimmunotherapy (98.8% vs 91.5% at 3 years) (Shanafelt 2019). Results for progression-free survival in a subgroup of patients without immunoglobulin heavy-chain variable region (IGHV) mutation also favored ibrutinib + rituximab over chemoimmunotherapy. The incidence of adverse events of grade 3 or higher was similar in the two groups, although infectious complications were less common with ibrutinib + rituximab than with chemoimmunotherapy. Lastly, the combination regimens venetoclax + obinutuzumab and venetoclax + rituximab provided superior undetectable minimal residual disease in peripheral blood compared to chemoimmunotherapy in patients with a median age of 61, in advanced Binet stage and unmutated IGHV status (Eichhorst 2021).

Whereas novel targeted agents have been shown to significantly improve outcomes compared with chemoimmunotherapy, their advantage is largely attributed to the decreased incidence of adverse events and generally good tolerability (Awan 2020). Compared with venetoclax-plus-obinutuzumab, chemoimmunotherapies are associated with less health benefits at higher cost. Facit: targeted therapies achieve greater benefits at higher cost (Alrawashdh 2022). Chemoimmunotherapy can, however, be considered for young, fit patients with IGHV-mutated disease (Awan 2020).

Patient assessment before initiating treatment

Although it is important to identify prognostic and predictive biomarkers and more effective, safer therapies, relevant critical aspects affecting the outcome of an individual diagnosed with CLL, such as frailty, co-morbidity, and access to effective medical care, often are neglected. Interventions to address or correct these aspects has great potential to rapidly improve outcomes.

Treatment is highly recommended in patients with advanced or symptomatic stage CLL.

Work-up prior to treatment should include:

- History and physical examination including careful palpation of all lymph node areas, spleen and liver
- Complete blood cell count and differential count
- Serum chemistry including lactate dehydrogenase (LDH), bilirubin, serum Igs, direct antiglobulin test (DAT) and haptoglobin
- Tests for kidney and liver function
- History and status of relevant infections [i.e., hepatitis B (HBV) and C (HCV), cytomegalovirus (CMV), HIV]
- Cytogenetics (FISH) and molecular genetics for detection of deletion of the chromosome 17 [del(17p)] affecting the tumor protein p53 expression and, if del(17p) is absent, TP53 sequencing for detection of TP53 gene mutation. Genetic lesions may evolve throughout the disease and analyses should be carried out as close as possible (e.g., < 6 months) prior to initiation of therapy
- CpG-stimulated metaphase karyotype for complex karyotype
- Molecular analysis for detecting Ig heavy chain variable (IGHV) gene mutation status
- Chest imaging and other imaging tests as appropriate
- Other examinations to exclude reasons for existing anemia if necessary, such as bone marrow examination, extended FISH analysis to detect additional cytogenetic abnormalities, hepatitis E testing (if the patient is positive for HBV), serum β2-microglobulin (an important prognostic marker) (Wierda 2022; Eichhorst 2020; Hallek 2018)

Evaluation of level of fitness

A challenge facing both patients and clinicians is determining a level of fitness before the initiation of treatment, especially treatment with novel therapies. Before inclusion in a clinical trial, the performance status using the Eastern Cooperative Oncology Group (ECOG) should be determined. Geriatric assessment tools, which measure the ability to perform activities of daily living and social functioning, are often included in the routine diagnostic workup and are used to plan targeted interventions. Recently, the importance of assessing concomitant conditions that may affect vulnerability toward immunochemotherapy using tools such as the Cumulative Illness Rate Scale (CIRS) has been increasingly recognized and implemented in clinical practice (Frustaci 2022). In a real-world study, a CIRS score > 6 proved to be an informative tool for predicting outcome including progression-free survival, event-free survival and discontinuation or reduction of treatment (Frustaci 2022).

While older patients may present with an adequate performance status and insignificant comorbidities, they may in fact have subclinical impairments that would limit their ability to tolerate the stress of treatment. The normal

aging process reduces organ and vital system functions with the potential to compromise treatment benefit.

Early-stage, asymptomatic disease

For most patients, and in general practice, patients with early-stage disease should be monitored without therapy unless there is evidence of disease progression (Hallek 2018) or disease-related symptoms including night sweats, fatigue, weight loss, symptomatic or functional extranodal involvement (Awan 2022). Watch and wait, also referred to as active surveillance, is a standard of care applicable to these patients. Rather than active treatment with drugs or other therapies, patients are closely monitored to regularly assess the size of lymph nodes, spleen, etc., and results of routine blood tests; treatment may be provided in asymptomatic patients entered on a clinical trial. A rapidly increasing lymphocyte count in patients with no other symptoms may not be a reason to start treatment.

There are patients with intermediate-risk (stages I and II) and high-risk (stages III and IV) disease according to the modified Rai Classification or at Binet stage B or C who benefit from the initiation of treatment, although in some cases, these patients can be monitored without therapy until there is evidence for disease progression or symptoms of CLL become evident (also referred to as active disease).

Patients who do not receive treatment and are closely monitored may become anxious that their disease will progress and should be reassured that disease progression is very slow and the disease at its present state is not serious enough to warrant drug treatment. A small number of patients never require treatment. Summary points of clinical studies on early treatment in CLL are:

- No demonstrated benefit of early treatment with chemotherapeutic agents in terms of survival; results following novel agent administration are still being evaluated
- No clear survival benefit following early use of alkylating agents or aggressive chemotherapy
- Risks associated with early treatment, including potential side effects and treatment complications are considerable
- Drug resistance is possible with early treatment and may adversely affect later treatment options once disease progression occurs (Awan 2020)

Four factors primarily guide the decision for individualized treatment: TP53 mutation and/or deletion, age, the presence and level of comorbidities and immunoglobulin heavy chain variable region gene (IGHV) mutation status (Awan 2020) (**Figure 1**). Patient-related factors such as comedications, personal preferences, drug availability and potential of treatment adherence are also taken into consideration.

Monotherapy with ibrutinib or ibrutinib + CD20 antibodies has yielded a longer progression-free survival than fixed duration chemoimmunotherapy. First-line ibrutinib + venetoclax seems to provide deep and durable responses. Evaluation at year 2 in patients with previously untreated CLL who received ibrutinib + venetoclax showed a MRD negative rate of 65.4% in the bone marrow vs 0% with ibrutinib monotherapy (FLAIR study; Hillmen 2022). At year 3, patients enrolled in the CAPTIVATE study (fixed duration of ibrutinib + venetoclax in previously untreated patients) had a PFS rate of 88%, including rates of ≥ 80% in patients with del(17p)/mutated TP53 or unmutated IGHV (Wierda 2022).

In the GAIA/CL13 study, coprimary endpoints (MRD negativity at 15 months and median PFS) were met for both first-line venetoclax + obinutuzumab vs

Symptomatic early-stage CLL or advanced-stage CLL

IGHV-unmutated No TP53 mutation or del(17p)		IGHV-mutated No TP53 mutation or del(17p)		TP53 mutation or del(17p)
Fit patients ↓ Ibrutinib CIT1: FCR[2]	Unfit patients ↓ Venetoclax + obinutuzumab[3] Ibrutinib or acalabrutinib[4] CIT1: CLBO	Fit patients ↓ CIT1: FCR[2] Ibrutinib	Unfit patients ↓ Venetoclax + obinutuzumab[3] CIT: CLBO Ibrutinib or acalabrutinib[4]	All patients ↓ Ibrutinib or acalabrutinib[4] Venetoclax + obinutuzumab[3] Venetoclax Idelalisib + rituximab

BR, bendamustine + rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil + obinutuzumab; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.
[1] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability; [2] BR might be considered alternatively in patients > 65 years; [3] If available; [4] If approved and available
Source: Eichhorst 2020

Figure 1. Treatment recommendations for front-line therapy

chemoimmunotherapy and ibrutinib + venetoclax + obinutuzumb vs chemoimmunotherapy for fit patients with CLL (Eichhorst 2021).

Relapsed/refractory disease

Relapse is common with CLL. Molecular and cytogenetic testing is an important part of treatment planning for patients with relapsed/refractory (r/r) CLL. Although IGHV mutation status remains the same throughout the disease course and will be assessed at diagnosis or before first therapy, cytogenetic abnormalities like del(17p) and TP53 mutations can evolve over time and should be reevaluated before each line of therapy. The recommendation is to repeat TP53 mutation status testing and FISH for del(17p) before each line of therapy is initiated (Wierda 2022; Eichhorst 2020).

Second-line therapy does not have to be initiated immediately at the time of disease progression. Current guidelines include specific parameters to indicate the need for second-line therapy, including progressive anemia or thrombocytopenia, massive or progressive splenomegaly, massive (≥ 10 cm) or progressive lymphadenopathy and increasing disease-related symptoms. That is, treatment at relapse should only be started in symptomatic patients and not simply at the time of reappearance of the disease as many patients can be followed without therapy for a long period of time (Eichhorst 2020).

Multiple treatment options provide durable PFS in patients with r/r CLL, including BTK inhibitors and venetoclax (**Table 1**). Phosphoinositide 3-kinase inhibitors are also approved and can be considered for some patients. There is no role for chemoimmunotherapy in cases of r/r CLL and repeated administration of fludarabine, cyclophosphamide and rituximab is not recommended due to increased toxicity rates/risk of secondary myeloid neoplasm.

The decision about which treatment to provide should be discussed with the patient. The discussion should include the following points:

- Treatment duration (no termination versus fixed duration)
- Administration route (oral versus intravenous)
- Compliance issues
- Available clinical evidence
- Risk of complications
- Response to and side effects of prior therapies
- Number and complexity of follow-up appointments required to monitor response (Eichhorst 2020).

Allogeneic stem cell transplantation

Generally, autologous stem cell transplantation (alloHCT) is not useful in CLL, but should be considered in:

- Patients refractory to chemoimmunotherapy with TP53 mutation or del(17p), but fully responsive to novel inhibitor therapy. Risk of transplant-related adverse events should be low
- Patients refractory to chemoimmunotherapy and to novel inhibitor therapy, even those with a higher risk of non-relapse mortality
- Patients with Richter's transformation in remission after therapy

A modified form of alloHCT (reduced-intensity conditioning or nonmyeloablative) may be an option for patients who do not respond to other treatments. This type of transplant is often done in high-risk CLL patients with del(17p) or TP53 mutations identified early in the

Table 1. Treatment Recommendations for Relapsed Disease

Symptomatic relapsed CLL		
TP53 mutation or del(17p)	Short remission duration (< 36 months)	Long remission duration (> 36 months)
Ibrutinib or acalabrutinib Venetoclax + rituximab[1] Venetoclax alone[2] Idelalisib + rituximab Consider alloSCT in fit patients	Ibrutinib or acalabrutinib Venetoclax + rituximab[1] Venetoclax alone[2] Idelalisib + rituximab	Repeat front-line or Change to ibrutinib or acalabrutinib Venetoclax + rituximab[1] Idelalisib + rituximab CIT[3]

alloSCT, allogeneic stem cell transplantation; CIT, chemoimmunotherapy
[1] After prior ibrutinib, preferred therapy; [2] After prior CIT and B-cell receptor inhibitor; 3 Repetition of fludarabine, cyclophosphamide, rituximab not recommended; [4] If approved and available
Source: Eichhorst 2020

course of the disease trajectory. It may also be offered to patients with relapsed CLL who have received multiple prior therapies.

Evaluation of treatment response

The outcome in patients with CLL depends on the interaction of factors related to the patient, disease characteristics, therapy, response to therapy and environment. Assessment of MRD is a highly sensitive indicator of disease burden. MRD assessment can be performed using either blood or bone marrow.

Achievement of a complete response with undetectable measurable residual disease (uMRD; < 1 CLL cell per 10,000 leukocytes in blood or bone marrow) at the end of treatment is the strongest predictor of improved survival in patients with newly diagnosed as well as r/r CLL (Dimier 2018). There is, however, no "one" set of predictive biomarkers and these markers may change over the course of the disease and must therefore be determined before treatment decisions are made (Montserrat 2019).

In addition to MRD, assessment of treatment response should also include history and physical examination and CBC and differential count (Hallek 2018).

Chronic Myeloid Leukemia

The outcome of treatment of CML has changed dramatically in the last two decades with the discovery of the BCR-ABL1 fusion gene and the development of tyrosine kinase inhibitor (TKI) therapy. With current TKI therapies, most patients diagnosed with chronic phase CML can expect to have good quality of life for a normal life span. Hence, the use of TKIs has transformed CML from a potentially fatal disease to one that can be controlled. However, not all patients respond to TKIs and some patients develop resistance to these drugs.

Between 1970 and 2000, most patients with CML were treated with interferon and required a bone marrow transplantation, which was the only curative treatment strategy. Imatinib was the first TKI used and had better efficacy with fewer adverse events than interferon. Second-generation TKIs that were able to induce faster and deeper responses (dasatinib, nilotinib, bosutinib) became available between 2007 and about 2013. A third-generation TKI, ponatinib, subsequently became available.

TKIs are a type of targeted therapy taken orally. These agents identify and attack specific types of cancer cells while causing less damage to normal cells than conventional chemotherapy treatments. In CML, TKIs target abnormal BCR-ABL1 protein that causes uncontrolled CML cell growth and block this abnormal protein's ability to function thereby causing CML cell destruction. Because each TKI has a slightly different mode of action, patients may start with one drug and later switch to another if the first treatment choice is ineffective.

Goals of treatment in CML are to provide normal survival and good quality of life without life-long treatment (Shah 2022; Bower 2016) and to achieve treatment-free remission (TFR) after discontinuation of TKIs (Kumar 2021). Patients with chronic CML who have maintained a stable and deep molecular response (DMR) for at least two years are considered good candidates for discontinuation of TKI treatment and this is especially true for younger patients. Patients are often motivated to attempt TFR because of the possibility to discontinue taking TKIs, the economic savings, a decrease in drug adverse and off-target effects, and the likely improvement in quality-of-life off treatment. TFR periods may last from a few months to several years and many patients who need to restart treatment are able to obtain and maintain a major molecular response again. The concept of TFR is, however, relatively new and little is known about the molecular components regulating TFR (Minciacchi 2021).

Treatment should be managed in cooperation with a specialized referral center that provides rapid access to quality-controlled and reliable tests including chromosome banding analysis, fluorescence in situ hybridization (FISH) and quantitative reverse transcriptase polymerase chain reaction (qPCR) with mutation analysis (Hochhaus 2020a).

Chronic phase: First-line treatment

For many patients diagnosed with chronic phase CML there is no reason to choose a 2nd generation TKI over imatinib, which has a well-established safety profile with no life-threatening long-term side effects identified to date (**Table 2**) (Hochhaus 2017; Smith 2020). At 10-year follow-up, overall survival was 82% in patients receiving imatinib alone or in combination (Hehlmann 2017). Of note in this study is that risk group, major-route chromosomal aberrations, comorbidities, smoking and treatment center rather than any form of treatment optimization influenced survival significantly.

Some patients may benefit from 2nd generation TKIs provided as upfront therapy:

- Patients with higher/intermediate ELTS or Sokal scores for whom a reduction in disease progression has been established with 2nd generation TKIs
- Women of childbearing age who wish to become pregnant and for whom the more rapid molecular response achieved with a 2nd generation TKI may be desirable
- Younger patients (< 30 years) and children in good health who are candidates for stem cell transplantation if needed and who may have more aggressive disease at diagnosis (Shah 2022; Smith 2020).

Table 2. Tyrosine Kinase Inhibitors (TKI) for the Treatment of CML

Drug	Dose/Administration	Indication	Contraindications
Imatinib (1st gen.)	400 mg/day (standard dose) - 300 mg/day in CP if 400 mg not tolerable - 400 mg twice/day in AP Oral	Newly diagnosed adults/children in Ph+ in CP with low-risk score	None known; patients with low cardiac ejection fraction and low glomerular filtration require monitoring
Bosutinib (Bosulif) (2nd gen.)	400 mg/day newly diagnosed 500-600 mg/day previously treated Oral	Newly diagnosed adults Ph+ in CP with low/intermediate/high-risk score; adults resistant to/intolerant of prior therapy in CP, AP, BP	Mutations T315I, V299L, G250E, F317L Avoid concomitant histamine receptor antagonists[1]
Dasatinib (2nd gen.)	100 mg/day in CP 70 mg twice/day BP & AP Oral	Newly diagnosed adults Ph+ chronic phase with low/intermediate/high-risk score; adults resistant to/intolerant of prior therapy in chronic, accelerated or blast phase	Mutations T315I/A, F317L/V/I/C, V299L Avoid concomitant histamine 2 receptor antagonists[1]; caution in patients with respiratory failure and previous/concomitant pleuro-pulmonary or pericardial disease
Nilotinib (Tasigna) (2nd gen.)	300 mg twice/day Oral	Newly diagnosed adults/children (≥ 1 year) with Ph+ in CP with low/intermediate/high-risk score; adults resistant to/intolerant of prior therapy in CP, AP; children (≥ 1 year) resistant to/intolerant of prior therapy	Mutations T315I, Y253H, E255K/V, F359V/C/I Avoid concomitant histamine 2 receptor antagonists[1]; Avoid concomitant antidepressants if possible[2]; Avoid concomitant cardiovascular medications known to prolong QT interval & strong CYP3A4 inhibitors[3]; History of coronary heart disease, cerebrovascular accident, peripheral arterio-occlusive disease
Ponatinib (3rd gen.)	45 mg/day 30 mg – 15 mg/day if cardiovascular insufficiencies Oral	Adults in CP, AP, BP; adults with T315I-positive in CP, AP, BP	Not recommended for newly diagnosed CP
Asciminib (Allosteric inhibitor)	Ph+: 80mg/day Ph+ with T315I mutation: 200 mg twice/day Oral	Adults with Ph+ in CP, previously treated with ≥ 2 TKIs; Ph- disease in CP with T315I mutation	None known; Monitor for myelosuppression, pancreatic toxicity, hypertension, cardiovascular toxicity; Avoid concomitant use with strong CYP3A4 inhibitors

[1]Including famotidine, ranitidine, nizatidine; [2]Including fluoxetine, bupropion, citalopram; [3]Including amiodarone, diltiazem, verapamil
AP, accelerated phase; BP, blast phase; CP, chronic phase; gen, generation
Sources: Shah 2022; Hochhaus 2020a; Scemblix package insert (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215358s000Orig1lbl.pdf)

Assessments prior to initiation of therapy include:

> Electrocardiogram (ECG), lipid profile, fasting glucose or HbA1c, cardiovascular risk assessment (echocardiography and angiologic evaluation if nilotinib or ponatinib are planned, which carry higher risks of cardiovascular complications), screening for hepatitis B and C; assessment of co-morbidities; assessment of possible drug interactions; discussion with patient to determine treatment preferences.

Quality generics of some TKIs (i.e., imatinib) are now available and have an advantage in that the cost of therapy is often significantly reduced. Reduced cost and broader availability should help with compliance issues (see Module 5).

Chronic phase: Second line and beyond treatment

Treatment is often changed from the first line TKI for several reasons. A mandatory change is indicated in cases of treatment failure or resistance. In case of intolerance and treatment-related complications, the decision to change treatment is made in consultation with the patient and hematologist-oncologist while considering options for supportive care and the level of initial treatment response. While it may not be possible to completely eradicate leukemic stem cells, leukemic cells remaining after treatment are the cause of relapse and disease progression.

The criteria for the choice of second line TKI are almost entirely patient-related and depend on age, comorbidities, toxicity of first TKI and other factors (Hochhaus 2020b). If there are no alternatives, a TKI should be continued even among chronic phase CML patients who do not achieve cytogenetic response because TKI treatment confers a survival advantage for these patients although there is little evidence to support this observation (Hochhaus 2020b).

The evaluation of response (achievement of milestones) to second-line treatment should be the same as those used to evaluate first-line treatment.

There are no firm definitions of an acceptable response to third, fourth or fifth-line treatment. However, a BCR-ABL1 transcript level > 1% or a cytogenetic response less than complete (Ph+ > 0%) are insufficient for optimal survival. The choice of subsequent TKI should depend on the sensitivity profile of specific BCR-ABL1 mutations. If the response to two or more TKIs is suboptimal, an alloHCT should be considered.

Treatment-resistant BCR-ABL1 mutations

Imatinib resistance occurs in 10% to 15% of patients and to 2nd generation TKI in < 10% given as first line treatment (Hochhaus 2020b). Failure to respond to treatment may be due to the patient not being fully compliant with taking prescribed medication. Disease resistance may also be related to an inability of the TKI to inhibit protein production. Alternatively, resistance may be due to clonal evolution (additional chromosomal aberrations, additional chromosomal abnormalities) and the activation of BCR-ABL1 independent pathways.

Treatment options include ponatinib, asciminib or alloHCT.

Advanced phase

Fortunately, CML does not often progress to the accelerated or blast phase since the advent of TKI treatment. Not all patients dying of CML reach the blast-phase defining blast levels. Once blast phase has occurred, survival is generally < 1 year with death due to infection or bleeding (Hochhaus 2020a). However, as shown in the study by Chalandon and colleagues (2023), increasing numbers of patients present for transplantation due to progression to accelerated or blast phase disease while undergoing or showing a response to TKI treatment because monitoring is less intense in these situations. Patients transplanted in advanced phases (acute and blast phases and those in a second or subsequent chronic phase) seem to have lower survival than those transplanted under more favorable disease conditions (Chalandon 2023).

Treatment in advanced CML is often intensive combination chemotherapy generally with a TKI to revert to a chronic phase or a remission in preparation for an alloHCT if possible. Ultimately, selection of a TKI is affected by patient comorbidity, costs, prior treatment and BCR-ABL1 mutational status.

Robust responses to TKIs have been shown in patients presenting with de novo accelerated phase CML using both imatinib and 2nd generation TKIs. In patients showing resistance to a 2nd generation TKI without specific mutations, ponatinib is preferred over a change of 2nd generation TKI, unless cardiovascular risk factors are present (Shah 2022; Hochhaus2020a).

The use of chemotherapy based on acute myeloid leukemia in blast phase regimens may be attempted in patients in blast crisis. Induction chemotherapy is recommended in conjunction with TKI as response rates associated with TKI treatments alone are inadequate (How 2021). A palliative approach may be more appropriate for patients who cannot tolerate further intensive therapy.

Allogeneic stem cell transplantation

AlloHCT may present a potentially curative option for some patients with CML, thanks to ongoing advances in alternative donor sources, more accurate HLA testing and the use of reduced-intensity conditioning regimens.

Box 2. Explanation of International Scale for Standardization of BCR-ABL1 molecular response values in CML		
1-log reduction	BCR-ABL1 levels decreased to 10 times below standardized baseline	BCR-ABL 10%
2-log reduction	BCR-ABL1 levels decreased to 100 times below standardized baseline	BCR-ABL1 1%
3-log reduction	BCR-ABL1 levels decreased to approximately 1,000 times below standardized baseline	BCR-ABL1 0.1%
4.5-log reduction	Referred to as complete molecular response (CMR) or MR4.5; Indicates that approximately 0.0032% of cells have BCR-ABL1 gene	BCR-ABL1 ≤ 0.1%
Adapted from: Hochhaus 2020a		

Disease phase, HLA matching, age and sex of the donor and recipient, and time from diagnosis to transplant play a role in transplant risk factors (Gratwohl 1998). In first chronic phase, alloHCT is the preferred option in managing the small number of patients who show disease resistance or who are intolerant of TKIs. Similarly, a patient presenting in accelerated phase should become eligible for alloHCT if the response to treatment is not optimal, and patients progressing to accelerated phase during treatment should immediately be considered for alloHCT. Patients presenting in or progressing to blast phase should be offered alloHCT after initial control of their disease (Hochhaus 2020).

Imatinib is recommended in patients who relapse with chronic and advanced phase CML after alloHCT (Shah 2022). In patients who previously failed imatinib, dasatinib, nilotinib, bosutinib, ponatinib or omacetaxine may be more appropriate options, or the recently approved agent, asciminib, may be considered.

Evaluation of treatment response

Evidence suggests that the life expectancy of CML patients treated with TKIs is close to the life expectancy of the general population (Hochhaus 2020b). Off-target effects of TKIs, adverse events and the high costs associated with lifelong treatment with TKIs have led researchers to explore the possibility of discontinuing TKI treatment in patients who have achieved a deep molecular remission (BCR-ABL1 < 0.01) (Minciacchi 2021).

Assessment of treatment response by molecular monitoring from peripheral blood leucocytes or bone marrow using reverse transcriptase quantitative PCR (RT-qPCR) is a strong predictor of outcome and sequential monitoring and can detect inadequate responses and rising levels of disease indicative of developing resistance to TKI treatment (Smith 2020). Bone marrow aspirate, cytogenetic analysis and FISH are not required to monitor response but may be recommended in selected patients (Smith 2020).

Mutations in the BCR-ABL1 gene alter the shape of the BCR-ABL1 protein, which can affect the inhibition action of TKI agents on BCR-ABL1 that prevents further growth of leukemic cells. RT-PCR (reverse transcription-polymerase chain reaction) is used to follow treatment response by assessing molecular response (MR), which is defined as the ratio of BCR-ABL1 transcripts according to the International Scale. The IS was developed as a standardization tool for quantifying and interpreting molecular responses, allowing for comparisons of results between different testing sites (**Box 2**). The IS defines the standard baseline as BCR-ABL1 100%.

Treatment response milestones

Treatment results are discussed in terms of achievable milestones. An early evaluation of molecular response to treatment allows patients at risk of poorer survival to be identified (**Tables 3 and 4**). Most commonly, monitoring of BCR-ABL1 transcript levels is performed at 3, 6 and 12 months to determine if the current treatment should be continued or changed. These treatment milestones expressed as BCR-ABL1 on the International Scale are:

- Early molecular response (EMR): BCR-ABL1 < 10% at 3 months and 6 months after start of treatment.
- Complete cytogenetic response (CCyR): the absence of Ph chromosome in bone marrow as measured by cytogenetic testing; BCR-ABL1 0.1% to 1%; ideally achieved within 12 to 18 months of starting treatment
- Major molecular response (MMR): BCR-ABL1 < 0.1%; can predict a CML-specific survival close to 100% as disease progression is uncommon once this level of cytoreduction has been achieved (Hochhaus 2020a)
- Complete molecular response (CMR) or deep molecular response (DMR): Molecularly undetectable leukemia, BCR-ABL1 ≤ 0.0032% (Hochhaus 2020a). If DMR is maintained for at least two years, patient may be considered a candidate for therapy discontinuation.

Table 3. Early Treatment Response Milestones in CML

BCR-ABL1 (IS)	3 months	6 months	12 months[1]
> 10%[2]			
> 1% - 10%			
> 0.1% - 1%			
≤ 0.1% DMR			

[1] BCR-ABL1 ≤ 0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (MR4)
which is a prerequisite for a trial of treatment-free remission (TFR). [2] Patients with BCR-ABL1 slightly > 10% at 3 months and/or with a steep decline from baseline may achieve < 10% at 6 months and have a favorable outcome; therefore, the value should be interpreted at 3 months before changing treatment strategy
DMR, deep molecular response; IS, International Scale
Red TKI-resistant disease; switch to alternate TKI and evaluate for allogeneic stem cell transplant
Yellow Possible TKI resistance; switch to alternate TKI or continue same (other than imatinib) or increase imatinib dose to max of 800 mg; consider evaluation for allogeneic stem cell transplant
Green TKI-sensitive; if optimal, continue same TKI; if not optimal, shared-decision with patient
Green TKI-sensitive; continue same TKI
Adapted from: Shah 2022

Table 4. Criteria for Response and Relapse in CML

Response/Relapse	Definition
Complete hematologic response (CHR)	Complete normalization of peripheral blood counts, leukocyte count < 10 x 10^9/L, platelet count < 450 x 10^9/L No immature cells (myelocytes, promyelocytes, blasts) in peripheral blood No signs/symptoms of disease, resolution of palpable splenomegaly
Cytogenetic response	Complete cytogenetic response: no Ph+ metaphases Major cytogenetic response: 0%-35% Ph+ metaphases Partial cytogenetic response: 1%-35% Ph+ metaphases Minor cytogenetic response: > 35% - 65% Ph+ metaphases
Molecular response	EMR: BCR-ABL1 ≤ 10% at 3 and 6 months MMR: BCR-ABL1 ≤ 0.1% or ≥ 3-log reduction in BCR-ABL1 transcripts from standardized baseline, if qPCR not available DMR/CMR: BCR-ABL1 ≤ 0.01% (MR4) or BCR-ABL1 ≤ 0.0032% (MR4.5)
Relapse	Any sign of loss of hematologic response Any sign of loss of CCyR or its molecular response correlate (↑ in BCR-ABL1 transcript to > 1%) 1-log increase in BCR-ABL1 transcript levels with loss of MMR

CCyR, complete cytogenetic response; CMR, complete molecular response; DMR, deep molecular response; EMR, early molecular response; MMR, major molecular response
Adapted from: Shah 2022

Treatment during pregnancy and parenting

According to available data, men planning fatherhood do not need to discontinue treatment with imatinib or second generation TKIs (Hochhaus 2020a). For women, management of CML occurring during pregnancy must be individualized.

TKI therapy, especially during the first trimester, should be avoided and has been associated with both a higher rate of miscarriage and fetal abnormalities. If TKI therapy is considered during pregnancy, the potential risks and benefits must be carefully evaluated in terms of maternal health and fetal risk on an individual basis prior to initiating TKI therapy. A prolonged washout period prior to pregnancy, prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy), and close monitoring should be considered. If treatment is needed during pregnancy, it is preferable to use interferons (interferon alfa-2a or peginterferon alfa-2a) (Hochhaus 2020a).

Birth control is strongly recommended while on active TKI therapy due to the risk of fetal abnormalities (Shah 2022). Prior to attempting pregnancy, patients of childbearing age and their partners should be counseled about the potential risks and benefits of discontinuation of TKI therapy and possible resumption of TKI therapy should CML recur during pregnancy. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy. Referral to a high-risk obstetrician is recommended.

Management of treatment- and disease-related side effects:

- Hydroxyurea is not recommended during pregnancy, especially in the first trimester.
- Leukapheresis can be used for an increased WBC, although data are lacking regarding at what level of WBC leukapheresis should be initiated
- Low-dose aspirin or low-molecular weight heparin can be considered for treating thrombocytosis
- Monthly monitoring with qPCR and initiating treatment if the BCR-ABL1 increases to > 1.0% is recommended

TKI therapy can be restarted after delivery, but patients should be advised not to breastfeed while on TKI therapy. Breastfeeding without TKI therapy may be safe with molecular monitoring, but preferably in patients with CML who have achieved durable DMR. Close molecular monitoring is recommended for patients who extend the treatment-free period for breastfeeding. However, if the loss of MMR after treatment cessation is confirmed, breast feeding should be terminated and TKI therapy should be restarted.

Should an unplanned pregnancy occur while taking TKI treatment, the agent should be discontinued immediately and fetal scans performed. Subsequent management of the pregnancy and the CML will be similar to that of women presenting with CML in pregnancy (Smith 2020).

Treatment-free remission

For some patients, discontinuation of TKIs is safe and associated with the successful achievement of treatment-free remission (TFR). TFR refers to having a stable deep molecular response without the need for ongoing TKI treatment. A deep molecular response (DMR) is defined as residual BCR-ABL1 transcript levels of at least MR4 on the international scale (Hochhaus 2021). This response is generally faster and the incidence of DMR at specific time points is higher with second-generation TKIs than with imatinib (Kantarjian 2021).

In a non-randomized study, for example, 61% of patients remained in treatment-free remission at 3 months. Furthermore, discontinuation of TKI was associated with improvements in patient-report outcomes such as a meaningful improvement in fatigue, depression, diarrhea, sleep disturbance and pain interference (Atallah 2021).

Approximately 50% of patients will relapse after treatment discontinuation, regardless of the TKI used (Shah 2022). Most relapses occur within the first 6 months of drug discontinuation. Treatment discontinuation is safe if eligible patients are carefully selected, and high-quality standardized quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) is used to detect BCR-ABL1 (**Box 3**).

Box 3. Criteria for TKI discontinuation

Age ≥ 18 years
Chronic phase CML, no prior history of accelerated or blast phase CML
On approved TKI therapy for at least 3 years
Prior evidence of quantifiable BCR-ABL1 transcript
Stable molecular response for ≥ 2 years as documented on at least 4 tests performed at least 3 months apart
Access to a reliable qPCR test
Monthly molecular monitoring for the first 6 months following discontinuation, every two months during months 7 – 12, and quarterly thereafter
Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months; resumption of TKI if MMR is not achieved after 3 months (Shah 2022)

The decision to stop treatment should be discussed with the patient. Many patients experience fear or anxiety during treatment discontinuation and withdrawal symptoms, such as musculoskeletal and/or joint pain, can occur a few weeks or months after TKI discontinuation. Symptoms of TKI withdrawal is likely based on a release of off-target effects of the TKI (Hochhaus 2021). In most

cases symptoms are mild and transient, but some patients may require temporary anti-inflammatory treatment. Therefore, patients should be closely monitored after TKI discontinuation.

Future Perspectives in Treating Chronic Leukemia

Early intervention may replace the more traditional "watch and wait" strategy for asymptomatic CLL patients if it continues to provide an overall survival benefit. Cellular immunotherapy with chimeric antigen receptor T-cells (CAR-T) may become available for high-risk CLL along with allogeneic stem cell transplant (allo-SCT) (Iovino 2020). The high financial burden accompanying treatment with novel agents, especially when used in combination, requires evaluation in coming years to avoid unnecessary overtreatment of patients. In this regard, efforts should be made to improve access to novel agents to patients around the world.

The expanding selection of BTK inhibitors in development (i.e., next generation agents such as zanubrutinib, orelabrutinib, LOXO-305 and ARQ 531) will possibly provide a viable treatment option that allows patients to switch to a different BTK inhibitor if resistance emerges because of acquired mutations (Patel 2021). Emerging targeted therapies, such as CD3/CD20 bispecific antibodies may provide options for high-risk patients.

In addition to expanding the number of agents that can be used in treating CLL, research is currently addressing optimal treatment sequence, safety and efficacy of combination therapies, and modifications of current treatment regimens such as intermittent sequence therapy to address some of the current unmet needs in CLL therapy (Patel 2021).

Results of recent trials have demonstrated that CAR T cell therapy can induce long-term, disease-free remissions in CLL patients and research in this area is on-going. Other drugs under investigation for treatment of CLL include: lenalidomide, PD-1 checkpoint inhibitors (i.e., nivolumab, pembrolizumab).

Treatment with tyrosine kinase inhibitors (TKI) is now providing patients with CML survival rates approaching those of the general population. However, co-payments by patients and healthcare costs for lifelong therapy with TKIs are significant.

One problem remains: what is the optimal initial TKI for a given patient who has her/his own clinical and biological features? Most treatment decisions are based on indirect comparisons of unrelated studies and personal preferences (Sasaki 2021). A machine-learning assisted approach may help with decision-making in complex clinical situations. For instance, better survival probability was obtained by selecting the optimal frontline TKI using a recently developed Leukemia Artificial Intelligence Program (LEAP) in chronic CML compared to conventional methods (Sasaki 2021).

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Notes

Quick Facts

1. Common disease- and treatment-related adverse events in chronic leukemia are anemia, myalgias, fatigue, risk of infection, dermatologic events and thrombocytopenia.
2. Because low-grade toxicities of BTK inhibitors may adversely affect quality of life, they should be identified and managed early to prevent drug discontinuation/non-adherence.
3. Cardiovascular toxicities of BTK inhibitors are potentially life-threatening; detailed baseline clinical evaluation of risk and close monitoring are therefore essential to prevent complications.
4. Common side effects of TKIs are cytopenias, nausea, diarrhea, fatigue, rash and liver damage, although some effects are drug specific. While side effects frequently occur, most can be managed with dose reductions or drug interruption.
5. Non-adherence to oral anti-cancer agents has many causes. Interventions to manage non-adherence center around providing education and support, switching to an alternative agent if side effects are the cause of non-adherence and including the patient/family in decision-making.

Module V: Management of the Patient with Chronic Leukemia

Introduction

A distinction should be made between hematologic and non-hematologic adverse events. Hematologic adverse events, such as neutropenia, thrombocytopenia and anemia, are usually limited to the first treatment period, may require temporary dose adaption or support with G-CSF, are rarely a cause of treatment change, and very rarely a cause of complications. Non-hematologic adverse events should be divided into side effects that affect treatment tolerability and quality of life and cause a change in treatment (i.e., fatigue, diarrhea, rash, cardiovascular changes). Some of these non-hematologic events may be serious enough to significantly affect patient health and have a potential to cause death.

Management of Disease- and Treatment-Side Effects common in Chronic Leukemias

Side effects of cancer treatment can impact many aspects of patient well-being. Side effects differ depending on the mechanism of action of the particular agent administered and the patient's tolerance of the agent, which will be different for each person. Co-morbidities, concomitant medications, age and previous cancer therapy will influence the type and severity of side effects. Common disease- and treatment-related side effects of agents used to treat chronic leukemias and their preventative and actual management are described in **Table 1**.

Table 1. Nursing Management of Common Disease- and Treatment-related Adverse Events

Problem	Causes	Clinical presentation	Management
Anemia	BTKs, Chemotherapy, Chronic leukemia	Fatigue; shortness of breath; chest pain on exertion; heart palpitations; pallor of skin/ mucous membranes; tinnitus	Assess for signs/symptoms; provide education on expected occurrence of anemia; erythropoiesis-stimulating agents (administration requires careful consideration); blood transfusions
Arthralgia/myalgia Headache	BTKs, TKIs	Joint/muscle discomfort/pain occurs early after treatment initiation	Provide anti-inflammatory drugs and short courses of corticosteroids; non-prescription analgesics; caffeine for headaches
Fatigue	BTKs, Chemotherapy, Chronic leukemia	Generalized weakness, difficulty performing ATLs; insomnia; not feeling rested after sleeping at night; may be self-limited or chronic	Assess and obtain patient report of severity and impact on ATLs; recommend physical activity, eating a well-balanced diet, staying hydrated, limiting stress, resting as needed, prioritizing activities; referral to physical therapist
Infections due to neutropenia	BTKs, Chemotherapy, Chronic leukemia	Fever, chills, myalgia, malaise, nausea, hypotension, hypoxia; sepsis (temperature > 38.5°C, tachycardia, muscle weakness, fatigue, confusion, drop in blood pressure)	Provide education on prevention and early recognition of infection and when to notify HCP; hand washing, adherence to general infection protection recommendations; consider antimicrobial prophylaxis
Skin rash, dermatologic events	BTKs, TKIs	Maculopapular rash, acne-like rash. Dry skin, brittle nails	Supportive care, topical emollients, cortico-steroids; Referral to dermatologist for rash evaluation; Suspend BTK if rash severity grade ≥ 3
Thrombocytopenia/bleeding	BTKs, Chemotherapy, Chronic leukemia	Mucosal/gastrointestinal bleeding; increased bruising, difficulty stopping bleeding; petechiae	Educate patient on safety measures to ↓ bleeding events, educate on S/S of bleeding and when to contact HCP; Avoid taking aspirin or ibuprofen; Evaluate need for anticoagulation and use of antiplatelet agents in patients being considered for BTK treatment, discontinue prior to therapy if possible

ATLs, activities of daily living; BTK, Bruton tyrosine kinase inhibitors; HCP, healthcare professional; S/S, signs and symptoms ; TKI, tyrosine kinase inhibitors
Sources: Dunse 2021; Wilson 2018

Management of Treatment-related Toxicities in Chronic Lymphocytic Leukemia (CLL)

Generally, the adverse events associated with oral targeted therapies (i.e., ibrutinib) are primarily a problem during the first year of therapy (**Table 2**) but are, nevertheless, associated with tolerability and health-related quality of life issues (Dunse 2021).

Off-target effects are somewhat reduced in second generation BTK inhibitors with subsequent higher tolerance. These toxicities can occur more strongly with some BTK inhibitors. For example, in a study of the efficacy and safety of acalabrutinib compared with ibrutinib in patients with resistant/refractory CLL, ibrutinib was associated with a higher incidence of diarrhea than acalabrutinib (Byrd 2021). Patients who are intolerant to one BTK may not experience dose-limiting toxicities with another. Lastly, cardiovascular events, which can be life-threatening, are less common with acalabrutinib than with ibrutinib and incidences of atrial fibrillation and hypertension seem to be higher in real-world settings and with longer follow-up with ibrutinib (Cheung 2020).

Low-grade toxicities of BTKs (i.e., arthralgias, myalgia, headache, diarrhea, rash, fatigue, minor bleeding) are not typically life-threatening but can adversely affect quality of life and lead to drug discontinuation. For this reason, identification and management of adverse events should be performed in a timely manner to prevent drug discontinuation and/or drug non-adherence. More serious and potentially life-threatening toxicities (i.e., cardiovascular events, major bleeding, infection) require immediate intervention (Dunse 2021).

Table 2. Management of Toxicities of Treatments for Chronic Lymphocytic Leukemia

Drug/Route	Most Common Toxicities	Nursing Management
Bruton Tyrosine Kinase (BTK) Inhibitors		
Toxicities common to all BTK inhibitors		
	Infections (viral, fungal) due to neutropenia	Increased risk of viral infections and reactivation; Provide education on prevention and early recognition of infection and when to notify HCP; hand washing, adherence to general infection protection recommendations; consider virus prophylaxis; yearly flu vaccination advisable (inactivated vaccines only); monitor for fungal and opportunistic infections (see **Table 1**)
	Thrombocytopenia/bleeding risk	(see **Table 1**)
	Cardiovascular: hypertension, atrial fibrillation (less frequent with acalabrutinib)	Detailed baseline clinical evaluation for cardiovascular comorbidities, review of concomitant medications; Monitor closely for drug interactions including palpitations/chest pain/atrial fibrillation while on treatment; Monitor BP: development of new/worsened hypertension associated with major adverse cardiac events (i.e., arrhythmias, myocardial infarction, stroke, congestive heart failure, cardiovascular death)
	Hepatic impairment	Avoid BTKs in patients with severe liver impairment; reduce BTK dose for mild/moderate impairment; monitor liver enzymes
	Diarrhea: increased frequency of bowel movements, loose/watery/soft stools, abdominal cramps, dehydration, weight loss	Provide patient with education on the frequency/timing of diarrhea and what measures to take if it occurs: ↑ intake of non-caffeinated, non-carbonated, non-alcoholic clear fluids, smaller/frequent meals (low-fiber, high-calorie); take anti-diarrheal medications (i.e., loperamide), alert HCP if diarrhea becomes worse; consider suspending BTK treatment and re-evaluate symptoms
Ibrutinib Oral	Drug coadministration considerations	Avoid coadministration with strong CYP3A inhibitors, strong CYP3A inducers, warfarin and other vitamin K antagonists; co-administer with caution with drugs that prolong PR interval; reduce dose with moderate CYP3A inhibitors, voriconazole; avoid grapefruit, Seville oranges, fish oil, flaxseed, vitamin E preparations
Acalabrutinib Oral	Drug coadministration considerations	Avoid coadministration with strong CYP3A inhibitors, strong CYP3A inducers, proton pump inhibitors, stagger dosing with H2-receptor antagonists and antacids (drug-drug interactions may vary with new formulations of acalabrutinib)
	Headache	(see **Table 1**)

Table 2. Management of Toxicities of Treatments for Chronic Lymphocytic Leukemia

Drug/Route	Most Common Toxicities	Nursing Management
BCL Inhibitors		
Venetoclax Oral	Neutropenia	Administer growth factors (G-CSF, GM-CSF) for grade 4 neutropenia; possibly reduce dose
	Tumor lysis syndrome	Preventative measures: ↑ fluids, monitor electrolytes; Monitor for S/S (↑ potassium, ↑ uric acid, ↑ phosphorous, ↑ LDH, ↓ calcium, nausea, vomiting, shortness of breath, irregular heartbeat, lethargy, joint pain); allopurinol or rasburicase administration; provide patient education on occurrence, risks, management
PI3K Inhibitor		
Idelalisib Oral	Hepatotoxicity	Avoid in patients with severe liver impairment; monitor liver enzymes
	Colitis, diarrhea	Take loperamide following HCP directions; Drink fluids, eat/drink often in small amounts, avoid high fiber foods; Contact HCP if diarrhea does not improve in 24 hours or lasts longer than 36 hours despite medication
Chemotherapy Agents		
Chlorambucil (alkylating agent) Oral	Infections due to neutropenia	Monitor closely for development of infectious complications; monitor for fungal and opportunistic infections; educate patient on signs/symptoms of infection, wash hands frequently, contact HCP if temperature > 38°C; consider virus prophylaxis; yearly flu vaccination advisable (inactivated vaccines only)
	Thrombocytopenia/bleeding	(see **Table 1**)
Cyclophosphamide (alkylating agent) Oral, Intravenous	Hemorrhagic cystitis	Educate on S/S of bladder infection, recommend frequent urination; encourage high intake of fluids
	Alopecia	Educate patient on occurrence; use gentle shampoo, gentle brushing, use head covering to protect against sunburn, apply mineral oil to scalp to reduce itching
	Anorexia, nausea, vomiting	Advise patient to take antiemetics as prescribed, drink plenty of fluids
Fludarabine (antimetabolite) Intravenous	Infections due to neutropenia	(see above; see **Table 1**)
	Thrombocytopenia/bleeding risk	(see **Table 1**)
Monoclonal antibodies		
Obinutuzumab (Anti CD20 monoclonal antibody) Intravenous	Infections due to neutropenia	(see above; see **Table 1**) Reduction in B-cell immunity, reduced efficacy of vaccinations
	Thrombocytopenia/bleeding risk	(see **Table 1**)
Rituximab (monoclonal antibody) Intravenous	Allergic reactions (with infusion)	Administer pre-medications with antihistamine and antipyretic effects; Monitor for S/S of allergic reaction including flushing, rash, hives, itching, dizziness, swelling, breathing problems
	Tumor lysis syndrome	(see above)
	Infections due to neutropenia	(see above; see **Table 1**)
	Thrombocytopenia/bleeding risk	(see **Table 1**)

BP, blood pressure; ECG, echocardiogram; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; HCP, healthcare professional; LDH, lactate dehydrogenase; S/S, signs/symptoms
Sources: BCCancer 2021; Dunse 2021

Management of Treatment-related Toxicities in Chronic Myeloid Leukemia (CML)

All tyrosine kinase inhibitors (TKIs) approved for the management of CML inhibit a range of kinases other than ABL; the side effects of TKIs are associated with this inhibition. Generally, the most common side effects of TKIs include cytopenias, nausea, diarrhea, fatigue, rash and liver damage (Garcia-Gutierrez 2019), although there are adverse effects that are drug specific (**Table 3**). While these side effects are frequent, most can be managed with dose reductions or transient drug interruption (Garcia-Gutierrez 2019). Some adverse effects, however, can persist leading to a disruption in the patient's quality of life (QoL).

For many of the common treatment toxicities of TKIs, management is first and foremost evaluation of risk prior to beginning therapy, continual monitoring, and interruption of treatment, or discontinuation if severe toxicities occur. All TKIs have toxicities which may cause clinically relevant complications, and these should be considered in conjunction with the patient's underlying health condition. For example, cardiovascular events occurring with TKIs seem to occur at higher rates in patients with cardiovascular risk factors or existing cardiovascular disease (Manouchehri 2020) and, therefore, previous or concomitant arteriovascular disease is a strong contraindication to nilotinib first-line and ponatinib second or third line (Andrews 2019; Jain 2019). Although ponatinib has demonstrated strong efficacy in the presence of several genetic mutations, it is one of the most cardiotoxic of the approved TKIs. Respiratory failure and previous or concomitant pleuro-pulmonary disease are strong contraindications to dasatinib first line (Hochhaus 2020).

Toxicities should not only be identified early, but management should be implemented as soon as possible to prevent poor adherence to treatment. Furthermore, because duration of treatment of CML is prolonged, specialty care for complications of chronic TKI therapy is required for optimal management. At initiation of treatment with TKIs, administering a lower dose then escalating the dose in patients with pre-existing relevant comorbidities or intolerance to previous TKIs in frail patients with lower disease risk may improve compliance and decrease early drug discontinuation (Cortes 2018). Although adverse events commonly occur with TKI treatment, these events are generally tolerable (Claudiani 2022).

Table 3. Management of Toxicities of Treatments for Chronic Myeloid Leukemia

Drug/Route	Most Common Toxicities	Nursing Management
	Tyrosine Kinase Inhibitors (TKIs)	
Toxicities common to all TKIs		
	Cardiovascular	Perform general cardiovascular risk assessment prior to beginning therapy; evaluation for hypertension, hyperlipidemia and diabetes mellitus should be assessed regularly after treatment begin; monitor potassium/magnesium levels; treatment interruption and cardiology consultation if event occurs
	Diarrhea	Occurs during first weeks of therapy; often self-limited; common with bosutinib; administer diphenoxylate/atropine or loperamide; provide management of symptoms; reduce/interrupt dose of TKI if severe. Educate patient that diarrhea is common, provide dietary guidance (avoid spicy/fatty food, caffeine, alcohol, dairy products, raw fruit/vegetables), eat low fiber starchy food, small meals
	Constipation	Maintain a high fluid intake and high fiber diet if medically appropriate; increase physical activity; consider laxatives and stimulants
	Hepatotoxicity (particularly with ponatinib)	Monitor for hyperbilirubinemia, ↑ transaminase; limit/avoid alcohol intake; interrupt/discontinue treatment if severe
	Cytopenia	Usually limited to first weeks/months of treatment; severity ↓ with time Supportive care with G-CSF, temporary support with blood products if severe; adjust dose if needed; monitor blood counts weekly during first weeks of treatment; educate patient/caregiver on prevention and early recognition of infection and bleeding and when to confer with HCP

Table 3. Management of Toxicities of Treatments for Chronic Myeloid Leukemia

Drug/Route	Most Common Toxicities	Nursing Management
	Cutaneous problems (peripheral edema, maculo-papular erythematous rash, skin eruptions, pigment changes)	Appear during first 3-4 weeks of treatment, severity is dose-dependent and self-limiting; more common in older patients; treat with antihistamines, topical/ systemic treatments
	Arthralgias, myalgias, muscle cramps, headaches	Common with imatinib, nilotinib; Monitor serum electrolytes; Symptom management (non-prescription analgesics, massage, warmth, caffeine)
	Tumor lysis syndrome	Preventative measures: ↑ fluids, monitor electrolytes; Monitor for S/S (↑ potassium, ↑ uric acid, ↑ phosphorous, ↑ LDH, ↓ calcium, nausea, vomiting, shortness of breath, irregular heartbeat, lethargy, joint pain); administer allopurinol or rasburicase
Imatinib[1] Oral	Acute renal failure (rare)	Often reversible, renal replacement therapy may be necessary; monitor for tumor lysis syndrome and manage accordingly
Bosutinib[2] (Bosulif) Oral	↑ serum lipase	Monitor for S/S of pancreatitis; provide patient education
	Nausea/vomiting	Take agent with food, take at a different time of day if symptoms occur; eat small meals and snacks; eat mild foods (bananas, rice, applesauce, toast); take antiemetics if needed
Dasatinib[2] Oral	Pleural effusion	Higher risk in older age, twice daily dosing, previous/concomitant cardiac disease or autoimmune disorders, hypertension, hypercholesterolemia, advanced phase disease. Observe for dry cough, fatigue, chest pain and dyspnea; Management can include dose interruption, diuretics, low-dose steroids
	Dysfunctional platelets	Monitor for bleeding disproportionate to platelet count
Nilotinib[2] (Tasigna) Oral	↑ serum lipase	Monitor for signs/symptoms of pancreatitis
	Prolongation of QR interval	Regularly monitor with EKG; interrupt treatment if evidence of event
	Hyperglycemia	Strict glucose monitoring in patients with DM
	Hypercholesterolemia	Monitor serum lipids at baseline and during treatment
Ponatinib[3] Oral	Arterial occlusion events (peripheral)	Thorough pre-treatment examination for severity of risk; monitor cardiac function while on treatment; reduced dose in patients with low resistance/intolerance or ↑ cardiovascular risk; control hypertension, hyperlipidemia, diabetes; recommend smoking cessation
Asciminib Oral	Asciminib Oral	Asciminib Oral

[1]first generation TKI; [2]second generation; [3]third generation; DM, diabetes mellitus; EKG, electrocardiogram; G-CSF, granulocyte-colony growth stimulating factors; GM-CSF, granulocyte macrophage-colony stimulating growth factor; HCP, healthcare professional; S/S, signs/symptoms
Sources: Shah 2022; Awan 2020; Hochhaus 2020; Cortes 2018; Steegmann 2016

Additional information

TKIs can have interactions with other medications, certain foods, vitamins, supplements and herbal alternative therapies. Various clinically relevant drug interactions with TKIs have been identified. Most interactions concern altered bioavailability due to altered stomach pH, metabolism by cytochrome P450 isoenzymes, and prolongation of the QTc interval. Patients must discuss concomitant medications (prescribed and over-the-counter) with healthcare professionals prior to initiation of treatment (Van Leeuwen 2014).

Women of childbearing potential receiving any of the TKIs should use effective contraception during treatment due to documented teratogenicity, and to avoid breast feeding (Steegmann 2016).

Long-term Follow-up

Secondary malignancies, such as CML, myelodysplastic syndromes (MDS), melanoma, gastrointestinal cancer, and other cancer types, can develop following treatment with fludarabine, cyclophosphamide or rituximab for CLL. Patients at higher risk of secondary malignancies are those older than 60 years and males. Regular follow-up appointments with an oncologist/hematologist-oncologist and an annual comprehensive skin exam are recommended.

Because of the high risk of cardiovascular events in this population, especially in patients treated with ibrutinib, vigilant monitoring for these events should be continued throughout BTK inhibitor treatment (Dunse 2021).

Preventative measures and long-term follow-up of patients with CLL

Patients diagnosed with CLL have an increased risk of infection due to impaired cellular and humoral immune function. For this reason, patients should be informed that their immune response to vaccinations is lower than that of the general population, and that they should adhere to protective measures such as wearing masks and avoiding exposure to persons with infections (**Box 1**).

Box 1. Preventative considerations in patients with CLL

- Avoid live vaccines
- Receive annual influenza vaccine and recombinant zoster vaccine
- 20-valent pneumococcal conjugate vaccine (PCV20) recommended in previously unvaccinated patients or those with prior receipt of 23-valent pneumococcal polysaccharide vaccine, 1 year apart
- Adhere to national recommendations for COVID-19 vaccination and protective measures
- Intravenous immunoglobulin infusions every 6 – 8 weeks may benefit patients with frequent sinus/lung infections with a hypogammaglobulinemia (IgG level < 500 mg/dL)
- Follow age-specific cancer screening guidelines
- Screening or genetic testing in family members is not indicated

Adapted from: Shadman 2023

A compromised immune system can not only predispose the patient to an increased infection risk, but also to an increased risk of secondary cancers, such as skin cancer. Patients with CLL have a higher risk of developing a secondary cancer when compared to the general population (Eichhorst 2020). Therefore, patients should be taught the warnings signs of skin cancer and skin cancer screening should be performed at least on a yearly basis, preferably by a dermatologist. Skin cancer prevention is critical (**Box 2**).

Box 2. Skin cancer prevention and monitoring

Prevention recommendations:

- Apply a sunscreen if outdoors during the day. Make sunscreen application part of a regular skincare routine
- Reapply sunscreen after two hours, swimming or excessive sweating
- Use a broad-spectrum sunscreen (a product that contains both UVA and UVB protection with a mineral ingredient such as zinc or titanium) with at least SPF 30, preferably SPF 50
- Wear a wide-brimmed hat, long-sleeved tops and long pants when spending significant time outdoors
- Sun protection is important even if it is cloudy or when in the shade

What to observe by self-monitoring of existing moles or spots on skin:

- Asymmetry: Does the mole or spot have an irregular shape?
- Border: Is the border irregular or jagged?
- Color: Is the color of the mole or spot uneven?
- Diameter: Is the mole or spot larger than the size of a pea?
- Evolving: Has the mole or spot changed during the past few weeks or months?

Adapted from: CLL Society 2022

Supportive Care

Communication with patients and families

Supportive care of the patient with chronic leukemia involves not only addressing problems related to their cancer and its treatment, but also acknowledging and supporting their psycho-social well-being. The communication of clear, evidence-based information on treatment choices, outcomes and possible long-term consequences of treatment is an essential component of supporting the patient with chronic leukemia.

Wherever possible, patients should be directed to remain independent. Activities directed at self-efficacy include:

- Encouraging the patient/caregiver to leverage support networks by providing a current list of sources of support
- Educating patients and guiding them to utilize knowledge and skills to minimize stressors and decrease symptom burden
- Providing patients with a list of support groups
- Providing education relevant to patient needs at each point in the course of their disease and its treatment including information on self-monitoring for disease progression and disease- and treatment-related side effects and when to contact a healthcare professional
- Referring patients to trusted information sources
- Establishing a trust-based relationship that underscores shared decision-making (Makoul 2006)

Medication Adherence

Despite the significant efficacy of oral novel drugs used in treating chronic leukemias, large numbers of patients discontinue treatment due to adverse events, a situation frequently occurring in real-world practice settings. With oral agents, the burden for appropriate administration and monitoring is shifted from healthcare professionals to the patient. Furthermore, instead of a short block of intravenous therapy, patients receive oral therapy for longer periods of time, even indefinitely. This necessitates developing procedures to address the safe prescribing and distribution of medications as well as education, monitoring and follow-up of patients (**Box 3**).

Poor adherence has been consistently identified as a driver of increased health care burden and costs. In addition to increased healthcare utilization and costs, treatment interruptions and non-adherence may lead to undesirable clinical outcomes; hence, adherence is critical to successful cancer outcomes. In one study, non-adherence to imatinib was associated with poorer response: patients with suboptimal treatment response missed significantly more imatinib doses (23%) than did those with optimal response (7%) (Noens 2009). But in comparison to other types of cancer, patients with CML had the highest mean number of 30-day supply equivalent prescriptions and the lowest rates of discontinuation across multiple cancers and therapies (Doshi 2021). In this study, however, discontinuance of the initial drug prescription for CML treatment might also have meant that the patient was switched to another oral agent, i.e., a newer generation of oral therapy, due to disease progression and/or toxicity. Short treatment interruptions or dose reductions, when necessary, do not necessarily negatively impact disease control or other outcomes (Shah 2022).

Barriers to adherence include low health literacy, limited patient knowledge, complex administration instructions, challenging adverse effects, high out-of-pocket costs, inadequate social support and complex medication regimens (Schneider 2014; Given 2011; Jin 2008). In one study, factors associated with contributing to poor adherence were older age (≥ 65 years of age) and poor adherence was associated with requiring treatment at an emergency department. Conversely, patients who were adherent had lower outpatient utilization and inpatient/emergency utilization (Dashputre 2020).

Nonadherence is often a result of symptom burden and thus interventions aimed at improving symptom reporting may be more useful than those aimed at improving nonadherence (Mackler 2019). Results of a randomized trial indicate that coaching that provides tailored information on knowledge strategies, behavioral skills and affective support provided by an advanced practice nurse can be beneficial in self-report of superior adherence (Schneider 2014).

By contrast, discontinuation of TKI was associated with improvements in patient-report outcomes such as a meaningful improvement in fatigue, depression, diarrhea, sleep disturbance and pain interference (Atallah 2021).

Box 3. Interventions to prevent and manage nonadherence to oral anticancer agents
Establish model in which reporting and management of symptoms is a part of routine care and continue at regular intervals; face-to-face contact may be beneficial in supporting adherence
Education provided to patients/families should be consistent across the oncology care team and should include information on the importance of medication adherence
Provide patient and caregiver with information, evaluate patient's social support network, personal and cultural beliefs and language barriers before providing education
Assessment of patient knowledge, confidence to manage adverse effects and need for follow-up should occur during educational sessions
Schedule follow-up in clinic 7-14 days after start of agent to reiterate instructions and information on oncolytic agents, and to assess adherence and toxicity
Provide patient/caregiver with clinical contact information and translator details if necessary
Launch early and aggressive toxicity management to help improve adherence and persistence to effective medications
Consider switching to an alternate agent if evidence of intolerance and if toxicities are not manageable with adequate supportive care measures
Include patients and caregivers in treatment decision-making, individualize treatment, actively listen to what patient is saying
Ask patients about adherence to oral anticancer therapies in a nonjudgmental fashion, with particular emphasis on barriers to adherence, such as cost and experienced side effects. Encourage use of pill boxes/medication cassettes and/or electronic timers to enhance routine taking of medications
If the patient does not exhibit known adverse drug reactions commonly associated with a specific oral agent (i.e., neutropenia), assess the patient's adherence to treatment
Communication within the oncology team and with the patient's primary care physician should be ongoing
Adapted from: Mackler 2019; Kim 2018

Survivorship

The diagnosis of chronic leukemia, especially CLL, may be a shock for patients as they were previously feeling well, and the disease is discovered during a routine medical check. Patients may experience a second shock when told that no treatment is necessary and instead a wait/active surveillance management strategy will be used. This

information is especially confusing to patients: *a diagnosis of cancer but no treatment.*

Patients experience many changes in their state of health and must adapt correspondingly. For example, an abnormal functioning immune system predisposes the patient to certain risks over time. Vaccines or other medications or treatments may be indicated to prevent or control infection. These include intravenous immunoglobulin (IVIG), antiviral medications (i.e., acyclovir or valacyclovir).

Because it is not clear if long-lasting remissions observed in some patients after treatment with novel therapies, chemoimmunotherapy or allogeneic stem cell transplant are equivalent to a functional cure, life-long observation and follow-up is recommended (Hochhaus 2017). Therefore, in asymptomatic patients, follow-up should take place every 3 to 12 months by a hematologist-oncologist and include a blood cell count and the palpation of lymph nodes, liver and spleen.

Patients and caregivers should be educated on the importance of follow-up care and encouraged to attend appointments and to keep copies of medical records to provide to healthcare professionals unfamiliar with their case. Other documentation they should gather and have on hand includes:

- A record of cancer diagnosis, summary of previous treatments (e.g., drug names, dosages, dates of administration, response to treatment, etc.)
- List of all healthcare providers
- Diagnosis summary with specifics such as subtype and/or genetic markers
- List of experienced side effects and their management
- Updated and current list of all vaccinations received.

Screening and monitoring for skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung and other types of cancer should be performed at regular intervals.

Patients and caregivers should be encouraged to seek medical and psychosocial support for fatigue, depression and other long-term effects.

Patients may experience a lack of control over their cancer. For some patients, setting priorities, gathering information, being involved in their care, establishing routines and a daily schedule, and putting their lives in order may be ways to gain control over their situation. Practices that may be helpful for patients living with chronic leukemia:

- Stay informed: encourage patients to regularly seek answers to questions they might have and to ask about services available
- Understand and accept that they may not have complete control over their cancer
- Acknowledge fears but learn how to let them go to avoid wasting time and energy needlessly worrying
- Express feelings of fear or uncertainty with a trusted friend or counselor: although talking about feelings may be difficult, most patients feel better after expressing their fears and concerns
- Learn to enjoy the present instead of thinking of an uncertain future or a difficult past, even for a few minutes each day
- Make time for activities that are important
- Work toward a positive attitude, which can create a better feeling about life even if a cure is out of reach. Learn to pay attention to feelings, even negative feelings
- Use energy to focus on what can be done now to stay as healthy as possible. Such as making healthy food choices, daily exercise
- Find ways (and time) to relax (American Cancer Society 2019)

Resources

Resources for Patients	
CLL Society (English)	Patient Education ToolKit: Resources to Support Patients with CLL/SLL Available at: CLL/SLL Patient Education Toolkit - CLL Society
CLL Advocates Network	The mission of CLLAN is to improve chronic lymphocytic leukaemia patient outcomes. Home - CLL Advocates Network.
CML Advocates Network	An international organization connecting 128 patient organizations, across the globe in 93 countries. Home - CML Advocates Network
American Cancer Society -- CML (English)	Educational information on diagnosis, risk factors, treatment, after treatment. Available at: Chronic Myeloid Leukemia (CML) (cancer.org)
American Cancer Society -- CLL (English)	Educational information on diagnosis, risk factors, treatment, after treatment. Available at: Chronic Lymphocytic Leukemia (CLL) (cancer.org)
Leukemia & Lymphoma Society	Information, resources and support for patient and caregivers, research funding Available at: Leukemia & Lymphoma Society | Blood Cancer Leaders | LLS
Leukemia Patient Advocates Foundation (LePAF)	Patient-led non-profit foundation based in Switzerland acting as a legal platform for self-sustained patient advocacy initiatives. Its mission is to improve the lives and survival of patients affected by leukemia and other hematological malignancies. The Leukemia Patient Advocates Foundation - LePAF
Resources for Healthcare Professionals	
The European Leukemia Net (English)	Integration of leading leukemia trail groups, their interdisciplinary partner groups and industry. Available at: Home (leukemia-net.org)

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Glossary of Terms

Term	Definition
Allogeneic hematopoietic cell transplantation	A procedure in which stem cells from a genetically matched, but not identical, donor are transfused into the recipient
Autologous stem cell transplantation	A procedure in which stem cells are harvested, stored and later infused into the same person
Biomarker	Any substance, structure or process that can be measured in the body or its products and that influences or predicts the incidence or outcome of a disease. Includes common clinical variables such as age, blood cell counts, spleen size, lymph node involvement and biologic markers such as immune phenotype, molecular features and others
Complete metabolic response	A finding obtained using FDG PET-CT imaging demonstrating the disappearance of metabolic tumor activity in target and non-target lesions, marked by a decrease in tumor standardized uptake value to the level of surrounding normal tissue
Complete molecular response (CMR)	BCR-ABL gene not found using polymerase chain reaction (PCR) test
Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission
Cytochemistry	The biochemistry of cells, especially that of the macromolecules responsible for cell structure and function; also describes a process of identification of the biochemical content of cells
Cytogenetics	The study of the structure of chromosomes (DNA). Used to detect chromosomal abnormalities associated with a disease
Deep molecular response	In CML, a deep molecular response is BCR-ABL levels < 0.01% from baseline and is a prerequisite for discontinuing TKI
Diagnostic biomarker	A biomarker that is useful for the diagnosis of a given disease, most often in combination with other biomarkers
Disease-free survival	A concept used to describe the period after successful treatment during which there are no signs and symptoms of the disease
Event-free survival	The time from randomization to an event which may include disease progression, discontinuation of treatment for any reason, or death
FISH (fluorescence in situ hybridization)	Identifies abnormalities in chromosomes and genetic mutations
Flow cytometry	Provides information about surface markers on blood cells or bone marrow cells, also provides information on evidence of a cancerous clone
Genomic characterization Genetic profiling	A laboratory method used to evaluate genes and the way genes interact with each other and with the environment. Can be useful in identifying genetic predisposition to certain diseases or response to treatment
Genome/Genomics	The study of the complete set of DNA
Hematopoietic stem cells	The stem cells that give rise to other blood cells in a process called hematopoiesis
Hypogammaglobulinemia	Reduced serum immunoglobulin (antibody) levels. Causes: underlying primary/congenital intrinsic immune system defects (e.g., common variable immunodeficiency) or secondary immunodeficient states (e.g., medication-related, hematologic malignancy, protein-losing diseases).
Immunophenotyping	Classification of cancer cells according to the substances (antigens) on their surfaces. Leukemia cells can have different antigens depending on the type of cell in which the leukemia originated and the maturity of the cell

Term	Definition
Lymphoblast	A modified naïve lymphocyte with altered cell morphology. Refers to immature cells, which typically differentiate to form mature lymphocytes. In acute lymphoblastic leukemia (ALL) this term refers to malignant leukemic cells, precursors of the lymphocytes which multiply uncontrollably
Measurable (minimal) residual disease (MRD)	A relevant independent prognostic factor used to guide treatment decisions. MRD refers to the number of cancer cells that remain in a person during and following treatment
Molecular response Major molecular response	Analysis of the number of cells in blood and bone marrow that contain the BCR-ABL gene; measured using a polymerase chain reaction (PCR) test. A molecular response is attained when there is a 1000 times decrease in the BCR-ABL gene cells from baseline (pretreatment) measurement
Myeloblast	A unipotent stem cell which differentiates into the effectors of the granulocyte series; found in the bone marrow
Off-target	Unexpected side effects due to the effects from other targets or the structure of the drug
On-target	Side effects of treatment on normal tissues that occurs when the target that's being inhibited in the tumor is also being inhibited in normal tissue
Oncogene	Arises when normal genes present in the body (protooncogenes) are mutated, causing them to be activated. These genes code for proteins that control cell division.
Oncoprotein	A protein that is coded for by a viral oncogene which has been integrated into the genome of a eukaryotic cell and that is involved in the regulation or synthesis of proteins linked to tumorigenic cell growth
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive; used in clinical trials to measure the efficacy of a treatment
Predictive biomarker	A biomarker that predicts response (or lack of) to a specific therapy
Prognostic biomarker	A biomarker that is informative for the likelihood of a given event (e.g., disease progression) to occur in untreated individuals
Prognostic model	A combination of biomarkers that predict or correlate with the probability of a clinical outcome in cohorts of individuals
Progression-free survival	The time from randomization in a clinical trial to disease progression or death from any cause
Proto-oncogene	A gene involved in normal cell growth. Mutations in a proto-oncogene may cause it to become an oncogene, which can cause the growth of cancer cells
TP53 gene	A regulatory protein that is often mutated in cancer
Treatment-free remission	The ability to maintain a molecular response after stopping therapy
Tumor suppressor gene	A type of gene that makes a protein called a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antigene

Notes

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