Chapter 158: Chronic Leukemias

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UPDATE SUMMARY

Update Summary

June 1, 2023

The following updates to this chapter were made:

- Treatment, Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitors: added asciminib and relevant information
- Treatment, Chronic Myeloid Leukemia, Adverse Drug Reactions, and Drug Interactions: added asciminib and relevant information
- Treatment, Chronic Myeloid Leukemia, TKI Resistance and Subsequent Treatment: added asciminib and relevant information
- Treatment, Chronic Lymphocytic Leukemia, Initial Therapy: added zanubrutinib as a treatment option
- Treatment, Chronic Lymphocytic Leukemia, Treatment of Relapsed or Refractory CLL: added zanubrutinib as a treatment option
- Treatment, Chronic Lymphocytic Leukemia, Summary of Treatment Options: clarified treatment options per current guidelines.
- Updated self-assessment Questions 5 and 15

KEY CONCEPTS

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1. Chronic myeloid leukemia (CML) is defined by the presence of the Philadelphia chromosome (Ph), a translocation between chromosomes 9 and 22. The resulting abnormal fusion protein, p210 *BCR-ABL*, phosphorylates tyrosine kinase residues and is constitutively active, resulting in uncontrolled hematopoietic cell proliferation.

2. Without treatment, the disease course of CML is characterized by a progressive increase in white blood cells over a period of years that ultimately transforms into acute leukemia.

3. Allogeneic hematopoietic stem cell transplant (HSCT) is the only known curative treatment option for CML and is reserved for patients with a suitable donor who progress after treatment with tyrosine kinase-based therapy.

4. The commercially available BCR-ABL tyrosine kinase inhibitors, imatinib, dasatinib, nilotinib, bosutinib, and ponatinib, have demonstrated efficacy in the treatment of newly diagnosed CML patients in chronic phase as well as in patients in accelerated phase or blast crisis.

5. CML monitoring requires the assessment of milestones throughout therapy, which includes hematologic, cytogenetic, and most importantly, molecular responses.

6. The management of chronic lymphocytic leukemia (CLL) is highly individualized. It includes observation in patients with early-stage disease and treatment with targeted therapy, chemotherapy, and/or biologic therapy in patients with more advanced disease.

7. Rituximab, obinutuzumab and ofatumumab are monoclonal antibodies indicated for the treatment of CLL.

8. Regimens such as fludarabine, cyclophosphamide, and rituximab are considered first-line therapy for patients with CLL who are younger and have immunoglobulin heavy-chain variable (IGHV) mutation.

9. Novel agents such as ibrutinib, acalabrutinib, zanubrutinib, idelalisib, duvelisib, and venetoclax provide orally administered options for the treatment of CLL. These agents, alone or in combination with anti-CD20 monoclonal antibodies, are now preferred treatment options.

BEYOND THE BOOK

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Chronic Myeloid Leukemia (CML)

Watch the video entitled “What Is Chronic Myelogenous Leukemia?” by the Khan Academy. https://www.youtube.com/watch?v=ST6mSB-RvE0

This 10-minute video provides a brief overview of CML, its signs and symptoms, diagnosis, and a basic treatment overview. This video is useful to enhance student understanding regarding COLLECT and ASSESS steps in the patient care process.

Chronic Lymphocytic Leukemia (CLL)

Watch the video: “Understanding Chronic Lymphocytic Leukemia with Lindsey Roeker, MD.” https://www.youtube.com/watch?v=cgYuEC69QXg

This 11-minute video by the Lymphoma Research Foundation briefly reviews CLL, diagnosis, and treatment options. This video is designed to aid in the student’s patient care process, particularly the COLLECT and ASSESS steps.

INTRODUCTION

Chronic leukemias include chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, and prolymphocytic leukemia. The typical clinical presentation of chronic leukemias is an indolent course, in contrast to patients with acute leukemia who will die of their diseases within weeks to months if not treated. This chapter focuses on the two most common types of chronic leukemia, CML and CLL.

CHRONIC MYELOID LEUKEMIA

CML is a myeloproliferative disease that results from malignant transformation of a subpopulation of pluripotent hematopoietic stem cells.[1,2] Bone marrow hyperplasia and the accumulation of differentiated myeloid cells in the peripheral blood are the initial presenting features of the disease. The terminal stage of CML is characterized by the rapid accumulation of blast cells in the bone marrow and suppression of normal hematopoiesis that ultimately leads to death. CML was the first malignant disease identified with a consistent cytogenetic abnormality, namely the Philadelphia Chromosome (Ph) that contains the BCR-ABL oncogene. This dominant cytogenetic abnormality has allowed CML to become the template for the development of targeted drug therapies.[2]

Epidemiology and Etiology

It is estimated that 8,930 new cases of CML will be diagnosed in the United States in 2022.[3,4]The median age at diagnosis is 67 years.[5] The development of CML is not associated with hereditary, familial, geographic, ethnic, or economic status. An increased risk of CML has been noted with ionizing radiation exposure and in atomic bomb survivors from Hiroshima and Nagasaki.[2]

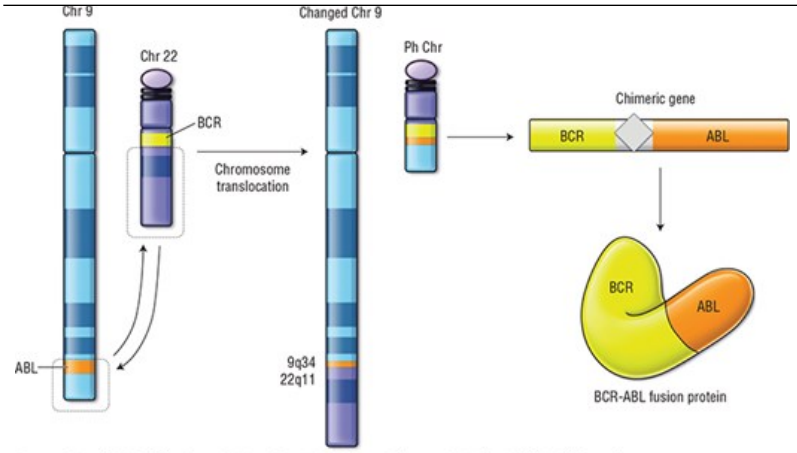
Pathophysiology

CML was first described in 1845, but extensive research into the genetic and molecular characteristics of the disease began with the discovery of the Ph in 1960 by Nowell and Hungerford.[6] Research in the 1980s identified the molecular changes that occur as a result of the Ph when an oncogenic protein was identified and associated with the pathophysiology of CML.[1,6] Ph is the first karyotypic abnormality specifically implicated in the pathogenesis of cancer, and its discovery has resulted in extensive research into the molecular biology of CML. This chromosomal abnormality is characteristic of CML and is present in about 95% of patients with the disease.[1]

1 Ph, identified as a shortened long arm of chromosome 22, is found in granulocyte and erythrocyte progenitors, macrophages, megakaryocytes, and lymphocytes. The Ph is the consequence of breaks in chromosomes 9 and 22, resulting in a transposition that relocates the 3′ end of *ABL* (Abelson proto-oncogene) from its normal site on chromosome 9 at band 34 to the 5′ end of *BCR* (breakpoint cluster region) on chromosome 22 at band 11 (symbolized as *t*[9;22][q34;q11]).[1,7] This results in the formation of the hybrid *BCR-ABL* fusion gene (Fig. 158-1). Through this chromosomal translocation, the *ABL* proto-oncogene escapes normal genetic controls and is activated into a functional oncogene, directing the transcription of messenger ribonucleic acid (mRNA). The mRNA is translated into a 210-kDa protein—p210 BCR-ABL—that is constitutively (ie, constantly) activated compared to the 145-kDa protein translated by the normal *ABL* gene.[1,7]

FIGURE 158-1

Specific chromosomal translocation that results in the Philadelphia chromosome. The fusion of these DNA sequences allows the generation of a constitutively activated fusion protein. *(Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2019.)*



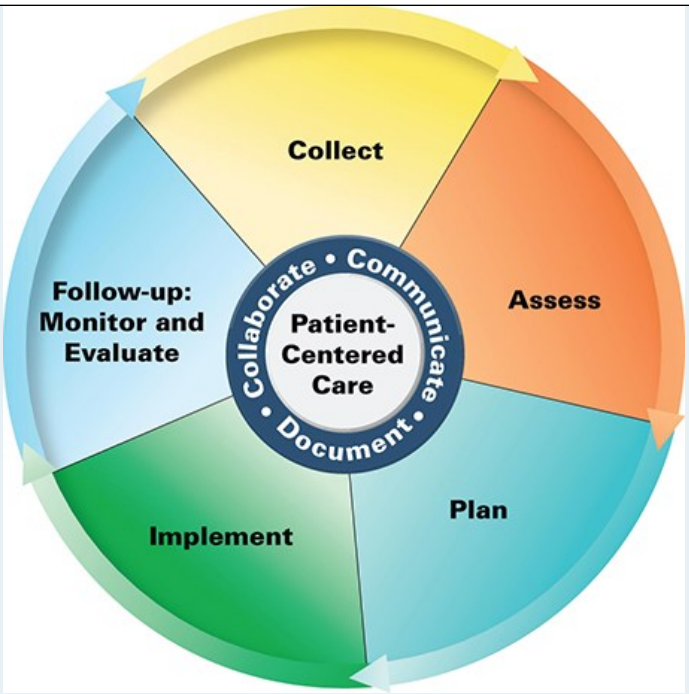
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

CML is considered a clonal disease because it begins with the malignant transformation of a single cell. The progeny from this transformed primitive hematopoietic stem cell results in a proliferative advantage over normal hematopoietic cells that displaces normal hematopoiesis. The Ph is found in both myeloid and lymphoid cells, which suggests that the transformed cell of CML is a pluripotent stem cell.[2] Disrupted maturation leads to a number of circulating granulocytes that may be many times higher than normal. In the advanced stages of CML, cytopenias may occur in association with fibrotic changes in the bone marrow.

The *BCR-ABL* fusion gene encodes for a constitutively active tyrosine kinase that is involved in both the increased proliferation of the CML clone and a reduction in apoptosis.[8] Characterization of the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase has provided a target for inhibition of tyrosine kinase activity. The first Food and Drug Administration (FDA)-approved tyrosine kinase inhibitor (TKI), imatinib mesylate (Gleevec®), was indicated for patients in chronic phase who had failed interferon alfa (IFN-α) or for those with advanced disease. Imatinib received additional FDA approval in 2002 for first-line treatment in newly diagnosed CML. Second-generation TKIs with a higher binding affinity and selectivity for BCR-ABL kinase are now approved as both first-line agents and salvage therapy for patients with resistance or intolerance to imatinib. Asciminib,a first-in-class specifically targeting the ABL myristoyl pocket (STAMP) inhibitor that prevents the kinase activity of BCR-ABL1 via allosteric binding, was approved in 2021.

Patient Care Process

Patient Care Process for Chronic Myeloid Leukemia (CML)



Collect

- Patient characteristics (eg, age, sex)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current medications including acid-suppressing agents, herbal products, dietary supplements, and inhibitors/inducers of CYP3A4
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including Complete Blood Counts (CBC) with differential, comprehensive metabolic panel, liver function tests, and uric acid
  - Objective confirmation of CML via bone marrow biopsy with chromosomal and molecular analysis

Assess

- Bone marrow biopsy morphology, cytogenetics, molecular mRNA transcripts
- CBC and presence of active bleeding due to potential thrombocytopenia
- Presence of VTE provoking factors (eg, recent surgery, plaster casting of lower extremity, indwelling catheter)
- Ability/willingness to obtain laboratory monitoring tests (eg, CBC, CMP, BCR-ABL assessments)
- Comorbidities (eg, diabetes, chronic kidney disease, pulmonary arterial hypertension)
- Emotional status (eg, presence of anxiety, depression)

Plan

- Drug therapy regimen including tyrosine kinase inhibitor dose, route, frequency, and duration (see Tables 158-3 and 158-4)

- Monitoring parameters including efficacy (eg, cytogenetic response, BCR-ABL mRNA PCR) and safety (eg, sign and symptoms of bleeding, anemia, fluid retention, ECG); frequency and timing of follow-up
- Patient education (eg, goals of treatment, drug-specific information, oral medication adherence, drug-drug interactions)

Implement

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence to oral therapy

Follow-up: Monitor and Evaluate

- Routinely monitor for assessment of hematologic, cytogenetic, and molecular milestones
- Presence of adverse drug reactions
- Patient adherence to treatment plan using multiple sources of information
- Addition of any new medications, including over-the-counter agents and/or herbal supplements

**Collaborate with patient, caregivers, and other healthcare professionals.*

Clinical Presentation

The diagnosis of CML is often made incidentally during a routine examination or when a complete blood count is obtained for unrelated reasons, as patients are often asymptomatic upon presentation. The differential diagnosis of CML includes infection, myeloproliferative disorders (ie, polycythemia vera, essential thrombocythemia, myelofibrosis), and chronic myelomonocytic leukemia. Initial laboratory workup includes complete blood count with differential and complete metabolic panel. A bone marrow aspiration and biopsy are required to confirm the diagnosis of CML.[7] Bone marrow is markedly hypercellular (75%-90%) with increased erythropoiesis and normal megakaryocytes.[5,7] Karyotyping (ie, cytogenetic analysis) is required for a diagnosis. The bone marrow aspiration is analyzed with fluorescence in situ hybridization (FISH) to determine the presence of the Ph chromosome. Quantitative reverse-transcription polymerase chain reaction (RT-PCR) is also performed to assess the baseline *BCR-ABL* transcript levels in the blood and monitored with the International Scale (IS). In the IS, the standardized baseline, defined as the mean expression of *BCR-ABL1* transcripts observed from previous study patients, is set to 100%. Levels measured by individual laboratories may need to be converted to the IS by a conversion factor.

Historically, the three clinical phases of CML were chronic phase (CP), accelerated phase (AP), and blast crisis (BC) (Table 158-1).[5,7] Newer classification systems now classify CML into two clinical phases: chronic phase and advanced phase (AP).[7] Although many patients in CP-CML are asymptomatic, signs and symptoms may include fatigue, sweating, bone pain, weight loss, abdominal discomfort, and early satiety secondary to splenomegaly.[9] Leukocytosis is the hallmark of CP, and the white blood cell count can be as high as 1,000,000 cells/mm^3 (1,000 × 10^9/L), placing patients at risk for complications of leukostasis. Symptoms secondary to leukostasis include acute abdominal pain resulting from splenic infarctions, priapism, retinal hemorrhage, cerebrovascular accidents, confusion, hyperuricemia, and gouty arthritis.

TABLE 158-1

Criteria for Different Phases of Chronic Myeloid Leukemia

Chronic Phase	Accelerated Phase	Blast Crisis
<10% blasts in peripheral blood or bone marrow	• 10%-19% blasts in peripheral blood or bone marrow • Platelets <100,000 cells/mm^3 (100×10^9/L) unrelated to therapy or >1,000,000 cells/mm^3 ($1,000 \times 10^9$/L) unresponsive to therapy • Persistent or increasing white blood cells >10,000 cells/mm^3 (10×10^9/L), unresponsive to therapy • 20% or more basophils in the peripheral blood • Any new clonal chromosomal abnormalities in Ph+ cells that occur during therapy	• >20% blasts in peripheral blood or bone marrow • Large clusters of blasts on bone marrow biopsy • Presence of extramedullary infiltrates
	Additional findings • Cytogenetic evolution • Progressive splenomegaly, unresponsive to therapy	

Data from References 7,10, and 11.

AP is characterized by a loss of efficacy of drug therapy and the progressive arrest of myeloid maturation. The most commonly observed cytogenetic changes with disease progression are an additional Ph chromosome, trisomy 8, trisomy 19, and isochromosome 17q.[9,11]

BC is the terminal stage of the disease and clinically resembles acute leukemia, in which the leukemic clone overwhelmingly dominates the bone marrow at the expense of normal hematopoiesis. The WHO classification defines BC CML as the presence of one or more of the following: greater than 20% blasts in the peripheral blood or bone marrow, extramedullary disease, or large clusters of blasts in the bone marrow.[7,12] Patients can present occasionally with BC without an apparent AP. One-third of patients present with BC of lymphoid lineage, while two-thirds present with BC of myeloid lineage or undifferentiated phenotype. The transformation to BC CML is the consequence of several factors in addition to *BCR-ABL*, such as the activation of the oncogene signaling pathways and loss of tumor suppressors such as p53.

CLINICAL PRESENTATION: Chronic Myeloid Leukemia

General

- 90% of patients are diagnosed in CP
- 50% are asymptomatic in CP and often diagnosed following abnormal complete blood count

Signs and Symptoms

- Fatigue
- Left upper quadrant pain
- Abdominal pain or distension
- Weight loss
- Night sweats

Physical Examination

- Splenomegaly
- Hepatomegaly

Laboratory Tests

Peripheral blood

- Leukocytosis
- Thrombocytosis
- Basophilia
- Low or undetectable leukocyte alkaline phosphatase
- Elevated uric acid and lactate dehydrogenase

Molecular testing

- Presence of *BCR-ABL* by RT-PCR

Bone marrow

- Hypercellular
- Fully mature myeloid cells
- Increased megakaryocytes
- <10% blasts in CP

Cytogenetics

- Presence of Ph
- Additional abnormalities may occur

Data from References 5 and 7.

Prognosis

Several models have been proposed to estimate prognosis in patients with CML, but the model developed by Sokal et al. is the historical standard.[13] The Sokal algorithm uses spleen size, percentage of circulating blasts, platelet count, and age as prognostic factors for patients in CP. However, this scoring system was developed before the advent of TKI therapy and may have limited predictive value in the current treatment landscape. The median overall survival for patients diagnosed with CP, AP, and BC CML was reported to be 47 months, 12 to 24 months, and 3 to 6 months, respectively, in the era before TKIs were introduced.[14]

The European Treatment and Outcome Study (EUTOS) Long Term Survival (ELTS) score is gaining popularity since it is based on data from patients with CML treated with TKIs.[7,15] Factors such as age, spleen size, platelet count, and percentage of circulating blasts are used to stratify patients into low, intermediate, or high risk of disease progression.

Treatment: Chronic Myeloid Leukemia

Desired Outcomes

Without effective treatment, CML disease progression leads inexorably to a fatal outcome within 5 years. The introduction of TKI therapy has dramatically altered the clinical course of CML, as patients can now expect to maintain disease control for many years.[5] The survival of patients who are newly diagnosed with CML in CP is now nearly equivalent to that of the general population, with the risk of death from other comorbid conditions greater than from CML.[5,7,16]

The overriding treatment goals for CML include the eradication of the leukemic clone from the bone marrow and maintenance of CP with minimal toxicity from treatment.[5,7] The only proven therapy to eradicate the malignant clone from the bone marrow is allogeneic hematopoietic stem cell transplantation (HSCT). Both immunotherapy with IFN-α and TKI-based therapies have demonstrated the ability to extend CP beyond the expected period of several years, with TKIs now being the preferred treatment option.[5,7]

Clinical response in CML is measured by hematologic, cytogenetic, and molecular indices, all of which have standardized criteria.[1,5,17] *Hematologic response* is defined as the normalization of peripheral blood counts and is the earliest type of response observed in CML patients. *Cytogenetic responses* are based on the percentage of cells positive for Ph in a bone marrow biopsy. A *complete cytogenetic response* is defined as the elimination of Ph from all cells in the marrow sample and a *major cytogenetic response* is defined as ≤35% Ph-positive cells. Patients who have a major or complete cytogenetic response have improved survival compared to those who fail to achieve a cytogenetic response.

More sensitive and less invasive tests to monitor disease status are now used because most patients on BCR-ABL TKIs achieve a complete cytogenetic response.[5] *Molecular responses* are determined by RT-PCR (based on IS), which are several logs more sensitive than methods used to measure cytogenetic responses. An early molecular response is the observation of ≤10% *BCR-ABL* (IS) at 3 and 6 months. A *major molecular response* is a ≥3 log reduction in *BCR-ABL* mRNA from the baseline or a BCR-ABL (IS) of <0.1%. A *complete molecular response* is the absence of *BCR-ABL* transcripts by RT-PCR. Clinicians should interpret RT-PCR assays carefully because they have varying sensitivities and may show a complete molecular remission even when low levels of *BCR-ABL* transcripts are present.[18] Quantitative RT-PCR should be performed before initiating therapy and throughout therapy to monitor residual disease. Peripheral blood can often be used for this analysis because bone marrow and peripheral blood *BCR-ABL* mRNA levels are correlated.

Hematopoietic Stem Cell Transplantation

3 The advent of TKI therapy has resulted in fewer transplants for patients with CML. Allogeneic HSCT remains the only proven therapy to cure patients with CML, with many patients alive and disease-free decades after transplant. Patients undergoing allogeneic HSCT from a human leukocyte antigen (HLA)-matched sibling donor have 5-year survival rates ranging from 60% to 80% and long-term survival of about 50%.[18] In most long-term survivors, the *BCR-ABL* translocation is absent in all diagnostic tests including RT-PCR. Prognostic risk factors associated with survival outcomes include age, phase of disease, and disease duration.[5,7] Increased age is associated with a poorer prognosis, with higher transplant-related mortality in patients older than age 50 years. Patients with CP who receive allogeneic HSCT have better outcomes than those in AP or BC at the time of transplant. The time from diagnosis to transplantation also affects outcomes. Patients who undergo matched-sibling allogeneic HSCT within the first year of diagnosis have a better 5-year survival rate than those who undergo transplantation more than 1 year after their diagnosis (70%-80% vs 50%-60%).[18] However, these data were reported prior to the use of imatinib as first-line therapy for CML.

The major limitation for the application of HSCT is that fewer than 30% of transplant-eligible patients will have an HLA-matched sibling donor. The most practical approach is to use an HLA-matched unrelated donor, if an HLA-matched sibling donor is not available. Matched unrelated donor HSCT has an overall 5-year survival reported to be 40% to 70%, which approaches overall survival data results reported for matched-sibling donor HSCT.[18] Imatinib use before transplantation does not appear to adversely affect transplant-related mortality.[19]

Treatment options in patients who relapse after HSCT are limited. Graft-versus-leukemia (GVL) effect, TKIs, omacetaxine, IFN-α, and a clinical trial are reasonable options.[7] The infusion of donor lymphocytes functions as a form of adoptive immunotherapy that can induce a GVL effect. In relapsed CML, donor lymphocytes induce durable responses and these responses strongly correlate with the development of graft-versus-host disease (GVHD).[7,20]

Conventional Chemotherapy

At present, conventional cytotoxic chemotherapy is only used in CML to reduce and temporarily control high peripheral white blood cell (WBC) counts. The agent most often used for cytoreduction is hydroxyurea (Hydrea®).[21] Hydroxyurea rapidly lowers high circulating WBCs in CML by inhibiting ribonucleotide reductase, which inhibits DNA synthesis, eliminating cells in the S phase of the cell cycle, and synchronizing cells in the G_1 or pre-DNA synthesis phase. Hydroxyurea is initiated at 40 to 50 mg/kg/day in divided doses until the WBC count falls to approximately 10,000 cells/mm^3 (10×10^9/L). Hydroxyurea may be discontinued once adequate control of the WBC count is achieved and a TKI has been initiated. Hydroxyurea does not change the natural progression of the disease to BC.

Interferon Alfa

The interferons are a family of glycoproteins involved in many of the functional aspects of the hematopoietic system. Before imatinib was available, IFN-α was the preferred agent in the treatment of CML. The use of IFN-α in the treatment of CP CML was based on reports that 20% to 50% of patients achieved a major cytogenetic response, which led to prolonged survival.[1,22] However, IFN-α use is limited by its toxicity profile, as it is associated with both short-term constitutional toxicities and potentially dose-limiting long-term toxicities.[1,23,24] The most predictable early toxicity is a flu-like syndrome characterized by fever, chills, myalgia, headache, and anorexia. These dose-dependent effects may be a result of IFN-α–induced leukocytosis and the release of inflammatory cytokines. Cardiovascular toxicities (eg, tachycardia, hypotension) are seen in about 15% of patients in the first few weeks. Long-term adverse drug reactions include weight loss, alopecia, neurologic effects (eg, paresthesia, cognitive impairment, and depression), and immune-mediated complications (eg, hemolysis, thrombocytopenia, nephrotic syndrome, systemic lupus erythematosus, and hypothyroidism), which occur in about 5% to 20% of patients. The National Comprehensive Cancer Network (NCCN) guidelines now recommend IFN-α only for CML patients with post-transplant relapse or during pregnancy if the treatment benefit outweighs the risk to the mother and fetus.[7]

Tyrosine Kinase Inhibitors

4 A transformative discovery in cancer therapeutics was the characterization of the adenosine triphosphate binding site on the BCR-ABL tyrosine kinase. This specific receptor established a novel drug discovery platform for molecularly targeted therapy in CML. Numerous TKIs were in development in the 1990s and STI571 (STI stands for *signal transduction inhibitor*), subsequently named imatinib, has high binding affinity for the BCR-ABL tyrosine kinase and emerged as the drug with the best oral bioavailability at that time.[25] Imatinib competitively binds to the adenosine triphosphate (ATP)-binding site on BCR-ABL, which inhibits the phosphorylation of proteins involved with CML clone proliferation. In 2001, imatinib mesylate received FDA approval for patients in CP-CML who had failed IFN-α treatment and in patients with AP- or BC-CML based on phase II studies. In 2002, it received FDA approval for first-line treatment in newly diagnosed CML based on the IRIS phase III trial results.[23] Imatinib inhibits several other tyrosine kinases including BCR-ABL, c-Kit, and platelet-derived growth factor receptor (PDGFR) (Table 158-2).[23]

TABLE 158-2

Cytogenetic and Molecular Response Rate Associated with Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia

Drug (Disease Status)	Daily Dose (mg)	CCyR (%)	MMR	Median Follow-up (months)
Imatinib (CP)	400	82	57%	70
	800	90	NR	30
Imatinib (AP)	600	43	NR	12
	400	11	NR	
Imatinib (BC)	400-800	7.40	NR	—
Dasatinib (CP)	100	83	76%	60
Dasatinib (AP)	140	32	NR	15
Nilotinib (CP)	600	87	77%	36
Nilotinib (AP)	800	16	NR	24
Bosutinib (CP–3rd line)	500	24	15%	28.5
Bosutinib (CP–1st line)	500	79	59%	12
Omacetaxine (CP–2nd line, T315I mutation)	2.5	16	NR	19.1
Ponatinib (CP-resistant/intolerant disease)	45	37	NR	10
Ponatinib (CP-T315I mutation)	45	66	NR	10
Asciminib (CP-resistant/intolerant disease)	80	54	48	24
Asciminib (CP-T315I mutation)	400	41	24	24

AP, accelerated phase; BC, blast crisis; CCyR, complete cytogenetic response; CP, chronic phase; MCyR, major cytogenetic response; MMR, major molecular response; NR, not reported.

Table 158-3 summarizes the dosing, food-drug interactions, and drug-drug interactions of imatinib and other TKIs.

TABLE 158-3

Dosing of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia*

Drug	Brand Name	Dose Range	Food-Drug Interactions	Drug-Drug Interactions
Imatinib	Gleevec®	• 400 mg/day (CP) • 600 mg/day (AP/BC)	Take with food and a large glass of water	• CYP3A4 inducers may decrease C_{max} and AUC • CYP3A4 inhibitors may increase C_{max} and AUC

				• Imatinib inhibits CYP3A4 and 2D6 • Package labeling recommendations against using warfarin concurrently
Dasatinib	Sprycel®	• 100 mg/day (CP) • 140 mg/day (AP/BC)	With or without meals; do not crush tablets	• CYP3A4 inhibitors may increase dasatinib levels • CYP3A4 inducers may decrease dasatinib levels • H_2 antagonists/PPIs decrease dasatinib levels
Nilotinib	Tasigna®	• 300 mg BID (CP) • 400 mg BID (AP/BC)	Take with water; avoid food 2 hours prior to a dose or 1 hour after	• Avoid drugs concurrently known to prolong QT interval • CYP inducers may decrease nilotinib concentrations • CYP inhibitors may increase nilotinib concentrations • H_2 antagonists/PPIs decrease nilotinib levels • Nilotinib is an inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6 • Nilotinib is an inducer of CYP2B6, CYP2C8, and CYP2C9
Bosutinib	Bosulif®	• 400 mg/day (CP) • 500 mg/day (AP/BC or resistance/intolerance to other TKI therapy)	Take with food; PPIs may decrease absorption	• Concurrent use with CYP3A4 or Pgp inhibitors increase bosutinib concentrations • Concurrent use with CYP3A4 inducers reduces bosutinib concentrations
Ponatinib	Iclusig®	45 mg/day (lower dosing may be required as the optimal dose is not defined)	With or without food	• Concurrent use with CYP3A4 or Pgp inhibitors increase ponatinib concentrations • Concurrent use with CYP3A4 inducers reduces ponatinib concentrations
Asciminib	Scemblix®	• 80 mg/day or 40 mg BID (CP) • 200 mg BID (CP with T315I mutation)	Avoid food 2 hours prior to a dose or 1 hour after	• Concurrent use with CYP3A4 inhibitors increases asciminib concentrations • Avoid co-administration with itraconazole oral solution containing hydroxypropyl-β-cyclodextrin • Asciminib is an inhibitor of CYP3A4, CYP2C9 and Pgp

AP, accelerated phase; AUC, area under the curve; BC, blast crisis; BID, twice daily; C_{max}, maximum concentration; CP, chronic phase; CYP, cytochrome P450; Pgp, P-glycoprotein; PPI, proton pump inhibitor.

Information obtained from each agent's prescribing information.

Tables 158-3 and 158-4 summarize drug-drug interactions, adverse drug reactions, and monitoring of BCR-ABL TKIs.

TABLE 158-4

Monitoring of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia*

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Imatinib	Common: • Myelosuppression • Fluid retention (pleural/pericardial effusion, ascites, periorbital, and peripheral edema) • Nausea/vomiting • Rash • Fatigue • Hepatotoxicity • Hypothyroidism • Myalgias Rare but serious: • Congestive heart failure/left ventricular dysfunction • Hemorrhage • Bullous dermatologic reactions	• CBC for myelosuppression • CMP for hepatotoxicity • Consider baseline echocardiogram if preexisting cardiac dysfunction or risk factors for cardiac dysfunction, repeat if experiencing symptoms of cardiac dysfunction • Thyroid-stimulating hormone	Nausea and vomiting improved when administered with food
Dasatinib	Common: • Myelosuppression • Myalgia • Fluid retention • Cardiotoxicity • Rash • Gastrointestinal toxicity • Hypophosphatemia • Hepatotoxicity Rare but serious: • Pleural effusion • Pericardial effusion • QT prolongation • Congestive heart failure/left ventricular dysfunction • Pulmonary arterial	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • ECG if risk factors for QTc prolongation • Chest radiograph for signs and symptoms of pleural effusion • Evaluate for signs/symptoms of underlying cardiopulmonary disease for pulmonary arterial hypertension	Gastrointestinal hemorrhage reported to be fatal; severe pleural effusions requiring thoracentesis; fatal myocardial infarction are reported

	hypertension • Hemorrhage		
Nilotinib	Common: • Myelosuppression • Rash • Gastrointestinal toxicity • Peripheral edema • Liver function abnormalities • Elevated serum lipase/amylase • Electrolyte abnormalities (hypophosphatemia, hypokalemia, hypocalcemia, and hyponatremia) Rare but serious: • Tumor lysis syndrome • Cardiotoxicity (QTc prolongation/sudden cardiac death/left ventricular dysfunction)	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • Serum amylase/lipase • Lipid panel • ECG if risk factors for QTc prolongation at baseline, 7 days thereafter and then as clinically indicated	Sudden deaths reported with nilotinib; ventricular repolarization abnormalities may have been contributory
Bosutinib	Common: • Myelosuppression • Gastrointestinal toxicity • Fluid retention • Hepatotoxicity • Hypophosphatemia • Rash Rare but serious: • Embryofetal toxicity	• CBC for myelosuppression • CMP for hypophosphatemia and hepatotoxicity • Serum amylase/lipase • ECG if risk factors for QTc prolongation at baseline, 7 days thereafter and then as clinically indicated	Potential for additive risk of hepatotoxicity when given concurrently with letrozole
Ponatinib	Common: • Myelosuppression • Arthralgia • Headache • Fatigue • Fever • Pancreatitis • Elevated lipase • Hypertension • Gastrointestinal toxicity • Dermatologic toxicity • Electrolyte abnormalities • Fluid retention	• CBC for myelosuppression • Serum lipase • CMP for hepatotoxicity, at baseline for tumor lysis syndrome • Blood pressure as clinically indicated • Ocular exam at baseline and then as clinically indicated	Deaths reported from hepatotoxicity, thrombosis including myocardial infarction and hemorrhag

	Rare but serious: • Arterial thrombosis • Hepatotoxicity • Cardiotoxicity (arrhythmia/congestive heart failure) • Embryofetal toxicity • Hemorrhage • Tumor lysis syndrome • Impaired wound healing/GI perforation • Ocular toxicity		
Asciminib	Common: • Upper respiratory tract infections • Musculosketal pain • Fatigue • Nausea • Rash • Diarrhea Rare but serious: • Pancreatic toxicity • Cardiovascular toxicity • Embryofetal toxicity	• CBC for myelosuppression • Serum amylase/lipase • Blood pressure	

CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; GI, gastrointestinal.

Information obtained from each agent's prescribing information.

Myelosuppression is one of the most common adverse drug reactions observed during therapy with imatinib.[26] Moderate-to-severe myelosuppression occurs in about 5% to 10% of patients with CP-CML and 50% to 60% of patients in AP or BC. Myelosuppression typically occurs within the first 4 weeks of therapy and is more common in patients with advanced disease (ie, high blastic involvement of the bone marrow), those receiving higher doses and those with low hemoglobin. When imatinib is initiated, patients should have complete blood counts drawn every 1 to 2 weeks to assess for myelosuppression until they have stabilized.[27] Appropriate initial management of myelosuppression is to interrupt imatinib treatment rather than dose reduce because dose reductions below 300 mg daily do not fully inhibit BCR-ABL and may lead to the emergence of imatinib resistance.[5,7]

Many other non-hematologic toxicities associated with imatinib have been reported (Table 158-4).[5,7,27] Drug rash frequently occurs but is usually mild and can be managed with antihistamines or topical steroids. Hepatotoxicity can occur with imatinib, and the drug should be withheld if liver function tests exceed five times the upper limits of normal. It is recommended that patients on imatinib limit their use of acetaminophen to 1,300 mg daily.[7] Other medications that are known to be hepatotoxic should be used with caution while patients are treated with imatinib.

Dasatinib can cause edema and pleural effusions, which can be managed by drug holiday, diuretics, thoracentesis, and/or short courses of steroids.[5,7,27,28] Dasatinib may also be associated with an increased risk of bleeding due to its effects on PDGFR.[29] A rare adverse drug reaction of dasatinib is pulmonary arterial hypertension (PAH), which warrants permanent discontinuation.[7,28] Nilotinib can be associated with indirect bilirubin elevations in 10% to 15% of patients.[5,7,27,28] Nilotinib may prolong the QTc interval (Black Box Warning), and patients should have an

electrocardiogram at baseline, at 7 days following initiation of therapy, and periodically thereafter. Nilotinib has also been associated with "metabolic syndrome," consisting of hyperglycemia, hypercholesterolemia and hypertriglyceridemia; careful attention should be given to eliminate or reduce risk factors for these conditions. Bosutinib is associated with gastrointestinal adverse drug reactions such as diarrhea, nausea and vomiting, and abdominal discomfort.[5,7,27] These gastrointestinal effects are typically self-limiting and can be managed with over-the-counter medications. Ponatinib can cause hepatotoxicity (including reports of liver failure), vascular occlusion, and heart failure, with some events occurring within 1 week of starting therapy.[5,7,28,30] The ponatinib manufacturer recommends specific dose modifications for myelosuppression, hepatotoxicity, and elevated lipase; monitoring for cardiovascular effects should also be routinely performed.

Similar to imatinib, advanced-generation TKIs are metabolized by cytochrome P450 (CYP) 3A4.[31] Clinicians need to be aware of possible drug interactions with inducers and inhibitors of the CYP3A4 pathway such as phenytoin, azole antifungals, or macrolide antibiotics (Table 158-3).[7,27] Drug interactions with BCR-ABL can not only affect toxicity but efficacy outcomes as well. It is recommended to re-evaluate drug-drug and, if applicable, drug-food interactions in patients do not reach their disease response goal.

Similar to other chronic medications, adherence should be reinforced in patients taking BCR-ABL TKIs.[5,7,27,32] Potential barriers to adherence, such as cost, adverse drug reactions, and frequency of dosing, should be identified and routinely assessed. An observational study, ADAGIO, evaluated 169 patients receiving imatinib and found that only 67% of patients were adherent. The percent of imatinib not taken was associated with a lower rate of complete cytogenetic response.[33]

Treatment of Chronic Phase

The IRIS study compared imatinib 400 mg orally daily to IFN-α plus low-dose subcutaneous cytarabine in 1,106 patients with newly diagnosed CP-CML.[23] After a median follow-up of 19 months, patients who received imatinib achieved a complete hematologic response of 95%, major cytogenetic response of 85%, and complete cytogenetic response of 76%. Six percent of patients had progressed to AP or BC, and only four patients discontinued imatinib because of an adverse drug reaction. After 5 years of follow-up, only 3% of patients randomized to receive IFN-α remained on this agent compared to 69% of patients in the imatinib arm.[34] The estimated 10-year overall survival of the 553 patients originally randomized to receive imatinib is 83.3%, with 47% alive and still on initial imatinib treatment. At 10 years, the estimated event-free survival was 79.6%.[35]

Higher doses of imatinib have been evaluated in clinical trials. The German CML IV study randomized 1,551 patients with CP-CML to 400 mg or 800 mg of imatinib daily in a phase III trial.[36,37] Patients who received 800 mg daily were significantly more likely to achieve a major molecular response at 12 months than patients who received 400 mg daily. However, there was no difference between the treatment groups in progression-free or overall survival at 3 or 10 years. Higher doses of imatinib were associated with higher rates of dose interruption, reduction, and discontinuation. The results of this study and others do not justify the routine use of imatinib 800 mg daily as first-line therapy in patients with CML.[7,36–38]

Dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®) are second-generation TKIs originally used for the treatment of CML in patients who are resistant or intolerant to imatinib therapy; all three drugs are also approved for first-line treatment of CP CML. The encouraging results of phase III trials of these agents make them viable alternatives to imatinib for first-line treatment for newly diagnosed CP-CML.[7]

Dasatinib is an oral BCR-ABL TKI that was FDA-approved in 2006 to treat imatinib-resistant CML. Dasatinib is also a TKI of the SRC family, c-KIT, EPHA2, and PDGFR.[29] Preclinical data show that dasatinib is approximately 300 times more potent than imatinib and inhibits the growth of imatinib-resistant clones, except for the T315I mutation. Dasatinib has been evaluated as first-line therapy in the phase III DASISION trial, which included 519 patients with CP-CML.[39] Patients were randomized to dasatinib 100 mg once daily or imatinib 400 mg once daily. A greater percentage of patients achieved a complete cytogenetic response at 12 months with dasatinib compared to imatinib (83% vs 72%). The rate of complete cytogenetic response at 5 years was higher with dasatinib as compared to imatinib (83% vs 78%).[40] The rate of major molecular response was significantly higher in the dasatinib group (76% vs 64%). Five-year progression-free and overall survival were similar in the two groups. A trial evaluating different dosing strategies of dasatinib showed that 100 mg once daily was as efficacious as dasatinib 70 mg twice daily, 50 mg twice daily or 140 mg once daily but with decreased adverse drug reactions such as pleural effusions.[41] The standard dose of dasatinib for patients with CP-CML is now accepted to be 100 mg daily.

Nilotinib has 20 to 30 times the inhibitory activity of the BCR-ABL tyrosine kinase than imatinib, with activity against c-Kit and PDGFR (but not SRC

kinases) due to a modification of the methylpiperazinyl structure of imatinib.[29] Nilotinib has inhibitory activity against imatinib-resistant mutants, with the exception of T315I. For first-line treatment of CP-CML, results of the phase III randomized ENESTnd trial comparing nilotinib at two doses (300 or 400 mg twice daily) to imatinib 400 mg once daily in 846 patients has been published.[42] The primary end point of the trial was major molecular response. In the final 5-year analysis, both nilotinib arms had a significantly higher major molecular response rate at 12 months (77% for nilotinib 300 and 400 mg twice daily) as compared to imatinib (60%).[43] The nilotinib arms also had significantly improved time-to-progression to AP or BC, as compared to the imatinib arm. The number of patients who discontinued treatment was similar in the three treatment arms.

Bosutinib has 15 to 100 times the inhibitory activity of the BCR-ABL tyrosine kinase as imatinib, with activity against SRC kinases but minimal activity against c-Kit and PDGFR.[29] Bosutinib has demonstrated clinical activity against many BCR-ABL kinase domain mutations that are resistant to imatinib, dasatinib, and nilotinib, with T315I as the notable exception. The phase III BELA trial of bosutinib 500 mg daily compared to imatinib 400 mg daily in CP-CML did not meet its primary endpoint of complete cytogenetic response at 12 months, likely as a result of a premature discontinuation rate in the bosutinib arm due to gastrointestinal toxicities.[44] A second phase III trial entitled BFORE compared bosutinib at a lower dose of 400 mg daily to imatinib 400 mg daily in 536 CP-CML patients.[45] Patients who received bosutinib had significantly higher rates of both major molecular response and complete cytogenetic response at 12 months compared to patients receiving imatinib. However, more patients in the bosutinib arm had dose interruptions, reductions, or discontinuation of therapy due to adverse drug reactions.

Ponatinib is considered a third-generation TKI, as it contains a novel triple-bond linkage in its chemical structure that avoids the steric hindrance caused by the bulky isoleucine residue at position 315 in T315I BCR-ABL binding site cleft, providing clinical activity against this resistance phenotype. However, off-target inhibition of vascular endothelial growth factor receptor (VEGFR), PDGFR, SRC, c-Kit, and other receptors may occur.[29] The EPIC trial was a phase III randomized trial comparing ponatinib to imatinib in patients with newly diagnosed CP-CML.[46] The study was terminated in October 2013 after events of arterial thrombosis were reported. The FDA subsequently released a Drug Safety Communication reporting an increased risk of life-threatening blood clots and narrowing of vessels within the extremities in patients who received ponatinib.[47] This agent also carries a Black Box Warning for vascular occlusion, heart failure, and hepatotoxicity.

Now, imatinib, dasatinib, nilotinib, and bosutinib are all recommended for patients with CP-CML who are at low risk of progression according to the ELTS model.[7] In patients with intermediate or high risk of progression, recommended first-line treatment includes dasatinib, nilotinib, and bosutinib. Imatinib may also be used in this setting, although it is not preferred. There are no head-to-head comparisons of dasatinib, nilotinib, and bosutinib, and therefore the clinician should personalize the selection of first-line therapy in CP-CML.[5,7,27] Factors such as comorbidities, potential toxicities, drug-drug interactions, dosing schedule, cost, and patient and physician preference should all be considered. Due to the risk of serious toxicities, ponatinib is generally reserved for patients with a documented T315I mutation or for patients in whom no other TKI therapy is indicated.[5,7]

Monitoring for Response

5 Careful monitoring is necessary to guide clinician decision making for modification of therapy. Recommendations for monitoring include baseline molecular and cytogenetic assessment. Patients with CP-CML who have an optimal response have a complete hematologic response within 3 months, partial cytogenetic response within 6 months, complete cytogenetic response within 12 months and major molecular response within 18 months of starting treatment.[5,7] *BCR-ABL* transcripts should be evaluated by RT-PCR every 3 months and bone marrow cytogenetics performed at 3 months if RT-PCR is unavailable or 12 months if neither complete cytogenetic response nor major molecular response is achieved. Bone marrow cytogenetics are repeated at 18 months if the patient is not in major molecular response or did not have a complete cytogenetic response at 12 months. The loss of hematologic or cytogenetic responses or clonal evolution at any time should be considered a treatment failure warranting a change in therapy. *BCR-ABL* kinase domain mutation analysis is performed for patients who have an inadequate initial response at 3, 6, 12, or 18 months, have any sign of loss of response or demonstrate disease progression to AP or BC.

Although most patients attain a complete cytogenetic response on TKIs, very few patients achieve a complete molecular response. In a study of patients enrolled in the IRIS study, Hughes et al. reported that less than 5% of patients on imatinib have undetectable levels of *BCR-ABL* when analyzed by RT-PCR.[48] Recent data suggest that the level of residual disease is predictive of progression-free survival.[49] Cytogenetic and molecular responses secondary to imatinib are associated with event-free survival and risk of progression to AP or BC.[34] Patients who do not achieve a hematologic response by 3 months, cytogenetic response by 6 months or major cytogenetic response by 12 months fare significantly worse as compared to

responders. In addition, a complete cytogenetic response and at least a 3-log reduction in *BCR-ABL* levels via RT-PCR correlated with a 100% survival without disease progression at 18 months. The risk of disease progression according to the Sokal scoring system predicted the rates of disease progression to be 3%, 8%, and 17% in low-risk, intermediate-risk, and high-risk patients, respectively.

Discontinuation of TKIs

The treatment of CML requires long-term therapy that can have significant adverse drug reactions and financial consequences. Discontinuation of TKI therapy with close monitoring has recently emerged as a possibility in carefully selected patients.[5,7] Candidates for discontinuation include those who achieve and maintain a major molecular response, or what is referred to as a deep molecular response (>4 log decrease in *BCR-ABL* RT-PCR or <0.01% *BCR-ABL* [IS] detection), for at least 3 years. Other criteria include no history of AP or BC, access to reliable response monitoring, and a thorough discussion of the risks and benefits of discontinuing therapy with the patient.

Studies of TKI discontinuation show that about 40% of patients who have achieved a deep molecular response remain in treatment-free remission (TFR) after stopping treatment.[50–52] Most patients who do relapse after stopping TKI do so within the first 6 months after cessation of treatment, and a molecular response is regained in almost all patients when the same TKI is promptly resumed.

An unexpected phenomenon of TKI discontinuation is "TKI withdrawal syndrome."[5,7,53] Pruritis and musculoskeletal pain requiring treatment are seen in up to 30% of patients. However, this phenomenon is reversible, and symptoms often rapidly disappear if TKI therapy is reinitiated.

Careful patient selection for discontinuation of TKI therapy, followed by close monitoring of *BCR-ABL* transcripts and restarting therapy if *BCR-ABL* levels rise may become standard management in the future.

TKI Resistance and Subsequent Treatment

Up to 25% of patients with CP-CML will develop intolerance or resistance to first-line BCR-ABL TKI therapy.[54] Dasatinib, nilotinib, and bosutinib have all demonstrated efficacy in imatinib-intolerant and resistant patients.[54,55] Patients who cannot tolerate or do not respond to imatinib in the first-line setting should be treated with dasatinib, nilotinib, or bosutinib.[5,7] Patients who do not respond to a second-generation TKI in the first-line setting should receive an alternate second-generation TKI. There are not enough data at this time to recommend one second-generation TKI over another in second-line therapy. Mutational analysis may be helpful in this setting, as well as consideration of concurrent disease states, prior therapy, and expected adverse drug reactions. A recent study compared asciminib to bosutinib in patients with CP-CML who were previously treated with two or more TKIs. At 24 weeks, the rate of major molecular response was 25.5% in the asciminib arm compared to 13.2% in the bosutinib arm.[56] The rate of major molecular response at 96 weeks was 37.6% with asciminib compared to 15.8% with bosutinib.[57] After a median follow-up of 2.3 years, asciminib sustained superior efficacy as well as improved safety and tolerability than bosutinib. Subsequently, asciminib is recommended in patients with CP-CML who are resistant or intolerant to at least two prior TKIs.[7]

The most prominent mechanism of TKI resistance is the presence of point mutations in one or more areas of the ABL kinase. More than 100 different mutations have been discovered thus far. Many of these mutations can cause a conformational change in the ATP binding site, which greatly decreases the ability of the TKI to bind and inhibit kinase activity.[58] Imatinib binds to BCR-ABL by establishing a series of hydrogen bonds with side chains of amino acids within the kinase domain. Mutations that alter this surface can decrease the affinity of imatinib for BCR-ABL, potentially preventing binding entirely.[59] The T315I mutation, known as the "gatekeeper mutation," occurs directly within the imatinib binding site and completely disrupts imatinib binding.[60–62] This mutation occurs in up to 20% of patients and is important because it confers resistance not only to imatinib but also to all second-generation BCR-ABL kinase inhibitors.

The PACE trial evaluated the use of ponatinib in 449 patients with resistance or intolerance to prior TKI therapy or with the T315I mutation.[62,63] Complete cytogenetic response rate at 12 months and major molecular response rate were 66% and 56%, respectively, in patients with CP-CML and the T315I mutation. Ponatinib is now recommended in patients with the T315I mutation or in patients who have failed 2 or more TKIs.[5,7]

Omacetaxine mepesuccinate (Synribo®) was approved by the FDA in October 2012 for the treatment of CP- or AP-CML with resistance or intolerance to two or more TKIs. Omacetaxine is a first-in-class cephalotaxine ester that inhibits protein synthesis independent of direct BCR-ABL binding.[64] It is a

semisynthetic form of homoharringtonine derived from the *Cephalotaxus harrintonia* alkaloid. Efficacy with omacetaxine has been demonstrated in two patient groups: CP- or AP-CML resistant to two or more TKIs and patients previously treated with imatinib harboring the T315I mutation. A phase II trial of omacetaxine was conducted in 62 CP-CML patients with a history of the T315I mutation.[65] Complete hematologic response was achieved in 77%, complete cytogenetic response in 16%, and major molecular response in 17% of evaluable patients.

Treatment of Accelerated Phase/Blast Crisis

The goal of therapy in AP or BC is to return the patient to CP.[66] All of the BCR-ABL TKIs can induce responses in AP- and BC-CML, but response rates are lower as compared with those in CP-CML.

In a combined analysis of two phase II studies for CP- and AP-CML with resistance or intolerance to ≥2 TKIs, omacetaxine was administered at 1.25 mg/m^2 subcutaneously twice daily for 14 consecutive days every 28 days then for 7 days every 28 days as maintenance.[67] Of the 41 patients in AP, 14% achieved or maintained a major hematologic response for a median of 4.7 months. The median overall survival of these patients was 14.3 months.

Traditional therapy for BC-CML is cytotoxic chemotherapy in treatment regimens similar to acute leukemia induction.[5,7,66] Etoposide (VP-16), cytarabine (Ara-C), and carboplatin (VAC-regimen) has demonstrated efficacy in patients with BC-CML with a median overall survival of 7 months.[68] The BCR-ABL TKIs have demonstrated modest activity in BC-CML and they may be added to cytotoxic chemotherapy to improve outcomes. Clinical guidelines recommend induction chemotherapy for acute leukemia based on the type of BP-CML, lymphoid or myeloid, along with a BCR-ABL TKI.[5,7] A BCR-ABL TKI can also be used alone in those with myeloid BP-CML or with a steroid in those with lymphoid BP-CML. Evaluation for allogeneic HSCT should be performed in all patients in BP-CML.[5,7,66] Please refer to the HSCT section above for more information regarding the indications and timing of this approach.

Summary of Treatment Options

The current standard of care is for patients with newly diagnosed CP-CML to receive a BCR-ABL TKI.[5,7] Low-risk patients may receive imatinib, dasatinib, nilotinib, or bosutinib based on comorbid conditions, expected adverse drug reactions, and patient or physician preference. Patients with intermediate- or high-risk disease should receive dasatinib, nilotinib, or bosutinib in the front-line setting. The goal of disease monitoring in CML is to differentiate patients who have optimally responded to an initial course of TKI therapy from those at high risk for treatment failure. With imatinib, nilotinib, dasatinib, and bosutinib as appropriate options for initial therapy for newly diagnosed CP-CML, and ponatinib and omacetaxine approved for salvage therapy, clinicians have many treatment options before allogeneic HSCT is warranted. Future research opportunities will focus on how to select second-, third-, and fourth-line therapies and whether combination therapy provides additional long-term benefits.

CHRONIC LYMPHOCYTIC LEUKEMIA

Epidemiology and Etiology

CLL is a lymphoproliferative disorder characterized by the accumulation of functionally incompetent clonal B lymphocytes.[69,70] CLL is the most common form of leukemia in the United States but is rare in other countries, such as Japan and China.[71] It is estimated that 20,160 new cases of CLL will be diagnosed in the United States in 2022.[4] Occasional family clusters of CLL have been recognized, and first-degree relatives of patients with CLL are at three times the risk of developing a lymphoid malignancy as compared with the general population. Male sex, white race, family history, and advanced age are known risk factors for the disease. CLL is a disease of older adults, with a median age of 71 years, although 20% to 30% of CLL occurs in patients who are younger than 55 years of age.[69,70]

Pathophysiology

CLL cells are comprised of a neoplastic clone of CD5$^+$ cells, which express low levels of surface-membrane immunoglobulin M (IgM) and immunoglobulin D (IgD) compared to normal peripheral blood B cells.[69,70] Normal CD5$^+$ B lymphocytes are present in the lymph nodes and blood. Neoplastic CD5$^+$ cells accumulate in the lymph nodes and spleen because of the loss of apoptosis by either the overexpression of an oncogene, such as *BCL-1* or *2*, or loss of a tumor suppressor gene, such as *RB1*.[69] The BCL-2 protein is a major regulator of apoptosis or programmed cell death.

A monoclonal population of B cells with a similar surface antigen phenotype as CLL cells has been recently identified in patients up to several years before diagnosis of the disease.[70] This phenomenon, termed monoclonal B-cell lymphocytosis (MBL), appears to predict whether a patient is at risk for developing CLL over time.

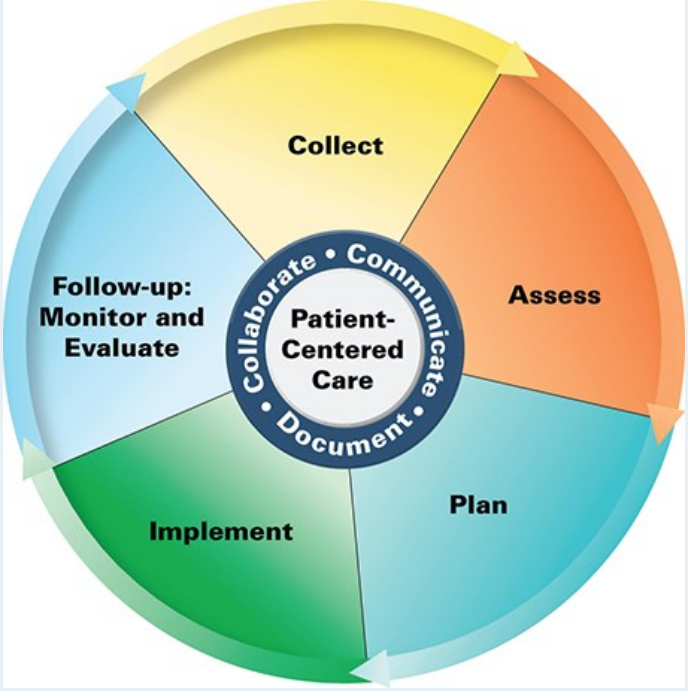
Although CLL lacks a common genetic target as observed in CML, B-cell-receptor signaling is a driver for CLL tumor survival.[69,70] Bruton's tyrosine kinase (BTK), a member of the Tec family of kinases, is essential for the activation of several constitutively active pathways for CLL cell survival. Phosphatidylinositol 3-Kinase (PI3K)-δ is a lipid kinase that plays a critical role in normal B-cell development, function, and transducing signals from receptors. The PI3Kδ signaling pathway is hyperactive in CLL and other B-cell cancers.

Cytogenetic abnormalities correlate with disease progression in CLL.[70] About 80% of patients with CLL have a karyotypic abnormality. The chromosomes that are most frequently involved include chromosomes 11, 12, 13, and 17.[70,72] Additional cytogenetic abnormalities may be acquired during therapy, particularly with deletions of chromosome 17, which have an adverse effect on survival.

About 4% to 10% of patients with CLL will undergo transformation of their disease to an aggressive lymphoma, most commonly non-Hodgkin lymphoma (diffuse large B-cell), which is termed as *Richter's syndrome*.[69,71,73] Richter's syndrome may be triggered by accumulation of additional cytogenetic abnormalities in the malignant clone of lymphocytes or by viral infections, such as Epstein-Barr virus.[73] Patients with Richter's syndrome will typically have a rapidly advancing disease course that mimics diffuse large B-cell non-Hodgkin lymphoma, but a small percentage of patients diagnosed with Richter's syndrome will transform into a Hodgkin lymphoma instead of a non-Hodgkin lymphoma.[71]

Patient Care Process

Patient Care Process for Chronic Lymphocytic Leukemia (CLL)



Collect

- Patient characteristics (eg, age, sex)
- Medical history (personal and family), including personal history of infections

- Social history (eg, tobacco, alcohol, chemical exposure)
- Current medications (eg, complementary or alternative medicines, inducers or inhibitors of CYP3A4, QT prolonging medications, warfarin, over-the-counter medications including aspirin/NSAID use)
- Objective data:
  - Vital signs: height, weight, blood pressure, heart rate, respiratory rate, oxygen status
  - Laboratory data: CBC with differential, CMP
  - Flow cytometry (chromosomal and molecular markers of CLL) and bone marrow analysis if performed
  - Imaging studies (PET or CT scan, if performed)

Assess

- Performance status (ie, to determine if the patient is fit enough to receive chemotherapy)
- Comorbidities
- Cytogenetic and molecular markers of CLL (eg, high-risk disease with del(17p) or *TP53* mutation)
- Immunoglobulin heavy-chain variable (IGHV) mutation status
- Infection risk (eg, IgG <500 mg/dL [5 g/L] or absolute neutrophil count <500 cells/mm^3 [0.5 × 10^9/L])
- Symptoms of disease
- Patient and family's goals of care

Plan

- Observation (also known as "watch and wait") versus treatment
- Drug therapy based on high-risk CLL features, patient age, comorbidities, and schedule and route of therapy
- Monitoring parameters of efficacy (ie, disease response criteria) and safety (eg, myelosuppression, nausea, vomiting)
- Patient education (eg, goals of treatment, drug-specific education, medication adherence, food-drug and drug-drug interactions)

Implement

- Educate patient on all aspects of the treatment plan
- Patient compliance (intravenous vs oral)

Follow-up: Monitor and Evaluation of Response

- Evaluate efficacy using disease response criteria
- Assess safety and adverse drug reactions of treatment regimen
- Assess adherence to treatment plan (eg, patient-initiated delays vs toxicity-related delays)

**Collaborate with patient, caregivers, and other healthcare professionals.*

Clinical Presentation

CLINICAL PRESENTATION: Chronic Lymphocytic Leukemia

Constitutional Symptoms

- Fever, fatigue, weight loss

Physical Examination

- Lymphadenopathy (87%)
- Splenomegaly (54%)
- Hepatomegaly (14%)

Laboratory Tests

Peripheral blood

- Lymphocytosis
- Coombs-positive autoimmune hemolytic anemia
- Hyper- or hypogammaglobulinemia
- Monoclonal gammopathy
- Anemia
- Thrombocytopenia

Bone marrow

- Hypercellular
- Increased mature lymphocytes
- Increased megakaryocytes

Molecular markers

- Cytogenetics (11q, del(13p), del (17p))
- IGHV status
- CD38+ status
- ZAP-70 status

Staging and Prognosis

Survival times for patients with CLL are widely variable, with some patients succumbing to the disease within 3 years and others living into a second decade from the time of diagnosis.[69,74]

The Rai and the Binet staging systems are commonly used in CLL, with the Rai being favored in the United States and the Binet in Europe.[70,74] The Rai

staging system has been combined into a risk classification scheme: low risk (stage 0), intermediate risk (stages I and II), and high risk (stages III and IV) with median survivals of greater than 10, 7, and 2 to 4 years, respectively.[75] While historically useful, the Rai and Binet staging systems are not predictive for individual patients because they do not include immunohistochemistry, cytogenetic, or molecular markers or abnormalities.

Immunoglobulin heavy-chain variable (IGHV) gene mutation status is an important predictor of survival outcomes.[69,76] Unmutated IGHV (≤2% mutated) is an independent indicator of poor prognosis and significantly decreased survival compared to mutated IGHV, regardless of the patient's disease stage.

Biomarkers, such as CD38 expression and ζ-associated protein 70 (ZAP-70) expression, have been explored as prognostic factors for CLL.[70,74] CD38 is a cell-surface antigen that is associated with early progression, shorter overall survival, and a poor response to fludarabine. ZAP-70 is an intracellular protein with tyrosine kinase activity. Once considered as simply a surrogate marker for unmutated IGHV, elevated ZAP-70 expression appears to predict for rapid CLL disease progression and independently correlates with prognosis.

Cytogenetic changes can be biomarkers of response to therapy. Specific chromosomal abnormalities and their associated survival are listed in Table 158-5. Deletion of the short arm of chromosome 17 (del[17p]), which corresponds to p53 silencing, is associated with the shortest survival times. Mutations in the p53 gene (ie, *TP53*) can also occur separately from del(17p) and are associated with uncontrolled cell proliferation and shorter overall survival.[70,74]

TABLE 158-5

Prognosis Associated with Cytogenetic Changes in CLL

Chromosomal Abnormality	Median Overall Survival (months)
del(13)	133
del(12)	114
del(11q)	79
del(17p)	32

Data from References 74,76.

Treatment: Chronic Lymphocytic Leukemia

Desired Outcomes

The primary goals of treatment for CLL are to achieve and maintain a prolonged remission with minimal treatment-related toxicity.[70,74] The management of patients with CLL is highly personalized, with some patients receiving therapy on diagnosis, while other patients, particularly with early-stage disease, are managed expectantly. Indications for initiating treatment include disease-related symptoms (fatigue, night sweats, weight loss, and fever), threatened end-organ function, bulky disease, doubling of lymphocyte doubling time in less than 6 months, progressive anemia, and platelet count less than 100,000/mm^3 (100×10^9/L) or steroid-refractory autoimmune cytopenias.[71] Consideration of initial treatment options is based on several factors, including patient age and comorbid conditions, disease stage, and high-risk prognostic factors, such as del(17p) or *TP53* mutation.

Most patients diagnosed with stage 0 CLL do not require treatment and can be managed with observation.[70] In patients with stage I disease, treatment is controversial. A consistent survival benefit from early therapy has not been reported in asymptomatic patients.[74] In stages II through IV disease, treatment is required, with the goal of achieving a partial or complete remission.

Response definition varies based on the sites of involvement: resolution of lymphadenopathy and organomegaly, reduction of blood or marrow

lymphocytes, and restoration of normal hematopoiesis.[70,74] An emerging goal of therapy is minimal residual disease (MRD), but this endpoint has only been recently introduced in CLL.[70] The clinical relevance of this assessment is currently undefined, as there is controversy as to whether this is a realistic treatment goal in patients with many comorbid conditions.

Cytotoxic Chemotherapy

Alkylating Agents

Historically, orally administered alkylating agents such as chlorambucil, given either alone or with corticosteroids, were used as the primary treatment for CLL.[77] Chlorambucil has been used in older, symptomatic patients as initial treatment for CLL, but its use is based on a small number of studies with no demonstrable survival advantage. Common dosing schedules for chlorambucil are intermittent pulse dosing of 15 to 40 mg/m^2 orally every 28 days or daily doses of 4 to 8 mg/m^2/day.[74] The dose of chlorambucil is often titrated to circumvent myelosuppression.

Bendamustine is an alkylating agent with a purine-derivative benzimidazole ring in its chemical structure that yields a compound that is non–cross-resistant with other alkylating agents. Bendamustine induces cell death via single- and double-stranded cross-links.[78] It is usually combined with an anti-CD20 monoclonal antibody, most often rituximab (eg, BR regimen). The use of bendamustine in the treatment of CLL is declining due to the availability of more targeted agents.[74]

Purine Analogs

Purine analogs, including fludarabine, 2-chlorodeoxyadenosine (cladribine) and 2-deoxycoformycin (pentostatin), are highly active in CLL, and fludarabine is the most widely studied.[70,76,77] Fludarabine is particularly useful in younger patients who can tolerate immunosuppressive chemotherapy. Although it was initially studied as a single agent in the treatment of CLL, fludarabine is now exclusively used in combination with other cytotoxic chemotherapy and/or immunotherapy. The most widely studied combination is fludarabine, cyclophosphamide and biologic therapy with rituximab (discussed below) in the FCR regimen.

Biologic Therapy

Monoclonal antibodies are a mainstay in the treatment of CLL. Rituximab is a chimeric monoclonal antibody that targets CD20 antigens expressed on B lymphocytes. Rituximab received FDA approval for the treatment of CD20-positive CLL in 2010. CLL cells have less prominent CD20 expression on their surface as compared to non-Hodgkin lymphoma, which may explain the lower clinical response in this setting. Rituximab as a single agent has moderate activity in CLL, with a 58% overall response rate reported with 9% complete responses.[70,74] Subsequent studies have used higher rituximab doses (up to 500 mg/m^2 per cycle) when given in combination with other agents. There are currently several biosimilar products of intravenous rituximab that are FDA-approved for use in the CLL population. Rituximab-arrx (approved in 2020), rituximab-pvvr (approved in 2019), and rituximab-abbs (approved in 2018) can all be substituted for rituximab. The decision regarding the specific product is usually based on the hospital or infusion center's formulary and the patient's insurance.

The FDA recently approved subcutaneous rituximab and hyaluronidase (1,600 mg/26,800 units) in combination with fludarabine and cyclophosphamide for the treatment of CLL. Subcutaneous administration of rituximab greatly reduces the time patients spend in an infusion center during their therapy by decreasing rituximab infusion from several hours to 15 minutes. Because of the large volume of rituximab, hyaluronidase is a component of the viscous, subcutaneous solution.[79] The hyaluronidase breaks down collagen, increasing the subcutaneous space for rituximab solution and facilitating absorption. Due to concerns over reactions, the intravenous formulation is given for the first treatment or cycle, and then the subcutaneous version is given with cycle 2 and beyond as long as the patient does not have an infusion-related reaction to intravenous rituximab.

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that does not induce translocation of CD20 monoclonal antibody complexes or complement-dependent cytotoxicity, but rather stimulates direct cell death via actin reorganization and homotypic adhesion.[80] Obinutuzumab, in combination with chlorambucil, was initially FDA approved in 2013 for patients with previously untreated CLL. Obinutuzumab is now combined with oral targeted therapies, such as acalabrutinib and venetoclax, in the frontline setting depending on the patient's del(17p) status.[74]

Targeted Therapy

The advent of oral targeted agents and anti-CD20 biologic therapy has made the use of traditional cytotoxic chemotherapy nearly obsolete in the treatment of CLL.[70] The availability of Bruton's tyrosine kinase inhibitors (BTKi), BCL-2 inhibitors and PI3K inhibitors, has transformed CLL treatment over the past decade.

Bruton's tyrosine kinase (BTK) plays a key role in B cell survival, proliferation, adhesion, and cell migration. The introduction of BTKi has radically changed the treatment landscape of CLL. BTK is primarily expressed in B cells, but not plasma cells or T cells, making it an ideal target in CLL.[69] Ibrutinib is an orally administered compound that covalently binds to the cysteine-481 amino acid of the BTK enzyme and inhibits signaling of ERK, NF-κB, and cytosine phosphate-guanine–mediated tumor cell proliferation and migration.[70] Ibrutinib was FDA-approved in 2014 for the treatment of CLL after at least 1 prior therapy and in 2016 for patients who are treatment-naïve. Acalabrutinib is an irreversible second-generation BTKi with greater occupancy and improved selectivity compared to ibrutinib.[81] Zanubrutinib is a second-generation BTKi designed to minimize off-target kinase inhibition while achieving maximal exposure; it is more selective than ibrutinib for BTK and has less off-target activity against EGFR, TEC, and other kinases.[82]

Venetoclax is an orally administered selective BCL-2 inhibitor.[83,84] BCL-2 is an antiapoptotic protein that regulates the intrinsic apoptosis pathway. BCL-2 is overexpressed in CLL cells resulting in lymphocyte accumulation. BCL-2 inhibition with venetoclax results in apoptosis. Venetoclax was FDA-approved in 2016 based on a phase I/IIb trial of venetoclax in 116 patients with relapsed CLL.

Idelalisib is a small-molecule inhibitor of PI3Kδ and interferes with the PI3Kδ-AKT signaling pathway leading to increased apoptosis.[70] Duvelisib is a dual small-molecule inhibitor of both PI3Kδ and PI3Kγ.[85] While PI3Kδ is involved in the survival and proliferation of B-cells, PI3Kγ is a mediator in the migration and differentiation of T-cells and macrophages. Inhibition of both the delta and gamma kinases blocks malignant B-cell survival and proliferation and disrupts the malignant microenvironment.

Tables 158-6 and 158-7 summarize dosing, drug interactions, adverse drug reactions, and monitoring of oral targeted agents used to treat CLL.

TABLE 158-6

Oral Targeted Agents in Chronic Lymphocytic Leukemia*

Drug	Brand Name	Dosing	Food-Drug Interactions	Drug-Drug Interactions
Acalabrutinib	Calquence®	• 100 mg orally twice daily • Avoid with severe hepatic impairment	• Avoid taking with proton pump inhibitors • Take 2 hours prior to taking an H_2-receptor antagonist • Separate from antacids by at least 2 hours • Avoid grapefruit, Seville oranges, star fruit, and pomegranate	• Substrate of CYP 3A4 to an active metabolite (ACP-5862), 50% less potent than the parent compound • Strong CYP 3A4 inhibitors increase C_{max} by 3.9-fold and AUC by 5.1-fold • Strong CYP 3A4 inducers decrease C_{max} by 68% and AUC by 77% • Weak inhibitor of CYP 3A4/5, 2C8, and 2C9 • Weak inducer of CYP1A2, 2B6, and 3A4
Duvelisib	Copiktra®	25 mg orally twice daily	None	• Substrate of CYP 3A4, P-gp, and BCRP • Strong CYP 3A4 inhibitors increase C_{max} 1.7-fold and AUC 4-fold • Strong CYP 3A4 inducers decrease C_{max} by 66% and AUC by 82% • Moderate inhibitor of CYP 3A4

Ibrutinib	Imbruvica®	• 420 mg/day • 140 mg/day with mild hepatic impairment • 70 mg/day with moderate hepatic impairment	Avoid grapefruit, Seville oranges, and pomegranate	• Strong CYP 3A4 inhibitors increase C_{max} 6.7-fold to 29-fold and AUC 5.7-fold to 24-fold • Strong CYP 3A4 inducers decrease C_{max} >13-fold and AUC >10-fold • Minor substrate of CYP2D6
Idelalisib	Zydelig®	• 150 mg twice daily • Moderate or severe hepatic impairment, reduce dose to 150 mg daily	None	• Idelalisib is a CYP 3A4, 2C8, 2C19, UGT1A1, and P-gp inhibitor • Strong CYP 3A4 inducers decrease C_{max} by 58% and AUC by 75% • Strong CYP 3A4 inhibitors increase AUC 1.8-fold (no change in C_{max})
Venetoclax	Venclexa®	• Week 1: 20 mg once daily • Week 2: 50 mg once daily • Week 3: 100 mg once daily • Week 4: 200 mg once daily • Week 5: 400 mg once daily	• Take with a meal and water • Avoid grapefruit, Seville oranges, star fruit, and pomegranate	• Substrate of CYP 3A4, P-gp, and BRCP • Inhibits CYP 2C8, 2C9, UGT1A1, P-gp, BCRP, and OATP1B1 • Concomitant strong 3A4 inhibitors, reduce dose to 100 mg • Concomitant moderate 3A4 inhibitors, reduce dose to 200 mg
Zanubrutinib	Brukinsa®	• 320 mg daily or 160 mg twice daily • 80 mg twice daily for severe hepatic impairment	Can be taken with or without food	• Primarily metabolized by CYP 3A4 • Concomitant strong or moderate CYP 3A4 inhibitors, reduce dose to 80 mg twice daily • Avoid concomitant use with strong CYP 3A4 inducers • Weak inhibitor of CYP 3A4 and CYP 2C19

AUC, area under the curve; C_{max}, maximum concentration; CYP, cytochrome P450; Pgp, P-glycoprotein; UGT, uridine 5'-diphospho-glucuronosyltransferase; BRCP, breast cancer resistance protein; OATP, organic-anion-transporting polypeptide.

Information obtained from each agent's prescribing information.

TABLE 158-7

Monitoring of Oral Targeted Agents in Chronic Lymphocytic Leukemia*

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Acalabrutinib	Common • Dermatologic toxicity • Diarrhea • Myalgias • Headaches • Fatigue	• CBC for myelosuppression • CMP for renal function and liver function • ECG at baseline if cardiac risk factors	• Acalabrutinib increases the risk of bleeding; therapy may be held from 3 to 7 days prior to and after surgery • Upon initiation, transient increase in lymphocyte count (not progression) • Headaches can usually be managed with

	• Infections • Myelosuppression Rare but Serious • Atrial fibrillation and flutter Hemorrhage		acetaminophen and caffeine combination products
Duvelisib	Common • Edema • Skin rash • Fatigue • Dizziness • Electrolyte abnormalities (hypophosphatemia, hyponatremia, hyperkalemia, hypocalcemia) • Colitis • Diarrhea • Hepatotoxicity • Myelosuppression Rare but serious • Pneumonitis • PJP • Cytomegalovirus disease	• CBC for myelosuppression • CMP for liver function • Signs and symptoms of CMV reactivation or PJP • Signs and symptoms of diarrhea/colitis, intestinal perforation • Signs and symptoms of pneumonitis	PJP prophylaxis needed
Ibrutinib	Common • Edema • Hypertension • Fatigue • Dizziness • Dermatologic toxicity • Myalgias and arthralgias • Fever • Myelosuppression • Renal toxicity Rare but Serious • Hemorrhage • Cardiovascular effects: atrial fibrillation, atrial flutter, ventricular tachyarrhythmias • Nonmelanoma skin carcinoma	• CBC for myelosuppression • CMP for renal function and liver function • ECG at baseline if cardiac risk factors	• Ibrutinib increases bleeding risk; hold 3-7 days prior to and after procedures • If anticoagulation is necessary, avoid warfarin • Upon initiation, transient increase in lymphocyte count (not progression)
Idelalisib	Common • Myelosuppression • Hepatotoxicity • Diarrhea/Colitis • Fatigue • Edema	• CBC for myelosuppression • CMP for renal function and liver function • Signs and symptoms of diarrhea/colitis, intestinal perforation	• Upon initiation, transient increase in lymphocyte count (not progression) • PJP prophylaxis needed

	Rare but serious • Dermatologic toxicity • Gastrointestinal perforation • PJP • Pneumonitis	• Signs and symptoms of pneumonitis • CMV reactivation	
Venetoclax	Common • Myelosuppression • Tumor lysis syndrome • Edema • Dermatologic toxicity • Fatigue • Dizziness • Electrolyte abnormalities (hypocalcemia, hyperkalemia, hypophosphatemia, hyponatremia) • Diarrhea • Nausea • Hepatotoxicity • Myalgias, arthralgias	• CBC for myelosuppression • CMP and uric acid for tumor lysis syndrome, renal toxicity, hepatoxicity	Risk for tumor lysis is based on patient's disease burden and rate of dose escalation
Zanubrutinib	Common • Myelosuppression • Upper respiratory tract infection • Rash • Bruising • Diarrhea Rare but Serious • Atrial fibrillation and flutter • Hemorrhage	• CBC for myelosuppression • CMP for renal function and liver function • ECG at baseline if cardiac risk factors	• Zanubrutinib may increase the risk of bleeding; therapy may be held from 3-7 days prior to and after surgery • Upon initiation, transient increase in lymphocyte count (not progression)

CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; PJP, *Pneumocystis jiroveci* pneumonia.

**Information obtained from each agent's prescribing information.*

BTKis have several characteristic adverse drug reactions that require active management and may necessitate pharmacologic treatment.[86] Diarrhea occurs early and often in patients who receive ibrutinib and acalabrutinib, but is usually self-limiting and can be managed with supportive care.[69,74] A common toxicity unique to BTKi is redistribution lymphocytosis secondary to tumor cell mobilization to the peripheral blood.[69] Patient adherence to therapy should be stressed, as this lymphocytosis is *not* an indicator of disease progression and the BTKi should be continued at the standard dose. Resolution of lymphocytosis usually occurs after several weeks.

Minor bleeding or bruising may occur during BTK therapy, and up to 10% of patients may have serious bleeding events.[69] For patients having planned surgical procedures that are considered to be high risk for bleeding, BTKi may be held up to 7 days before and 7 days after the procedure; more minor procedures may warrant holding the BTKi for 3 days before and after the procedure.

BTKis are associated with cardiotoxic adverse effects.[87] Atrial fibrillation (AF) has been noted, most often with ibrutinib but also with acalabrutinib and

zanubrutinib. In a phase III trial of acalabrutinib compared to ibrutinib for the treatment of relapsed CLL, the incidence of AF was significantly lower in the acalabrutinib arm.[88] The mechanism of this adverse drug reaction is poorly understood, but off-target inhibition of cardiac phosphoinositide 3-kinase (PI3K-AKT) has been proposed. The advanced age and comorbid conditions of many patients with CLL make this adverse drug reaction particularly troublesome.[89] If possible, modifiable risk factors for AF such as hypertension, heart failure, obesity, and thyroid function should be identified and treated before the BTKi is started.[74,87] Patients with recurrent AF that is not medically controlled should avoid BTKis; AF that occurs during BTKi therapy should be managed according to current national guidelines.[87,89] The selection of drug therapy for AF during BTKi therapy may be problematic, as drug-drug interactions have been reported between BTKi and amiodarone or non-dihydropyridine calcium channel blockers. Further, the addition of anticoagulation may predispose the patient to bleeding, as noted above. If anticoagulation is necessary, non-warfarin alternatives should be considered since patients taking warfarin were excluded from many BTKi clinical trials.[74,87,89]

BTKis have also been associated with hypertension, with a potential continual rise in risk over time.[90] In retrospective studies, no single anti-hypertensive agent or class of drugs has been associated with the prevention or control of BTKi-related hypertension. The selection of drug therapy should be carefully considered to avoid drug-drug interactions with antihypertensive medications and the patient's current BTKi.[86]

Patients treated with venetoclax can develop tumor lysis syndrome when therapy is initiated.[86] The manufacturer recommends slow dose titration (known as "ramp up") from 20 mg daily to the target dose of 400 mg daily weekly over 5 weeks to minimize the risk of tumor lysis, although faster escalations of dosing may be used in select patient groups. Specific recommendations regarding inpatient versus outpatient initiation, dose escalation, and tumor lysis syndrome prophylaxis are based on disease burden and the patient's clinical status.[74] Drug-drug interactions must also be considered during venetoclax therapy.

Idelalisib, and duvelisib to a lesser extent, has been associated with immune-mediated adverse drug reactions such as colitis, intestinal perforation, elevated liver function tests, and pneumonitis.[69,91] Patients should have complete blood counts and hepatic function monitored before initiation and throughout treatment. Patients receiving idelalisib or duvelisib should receive *Pneumocystis jiroveci* pneumonia prophylaxis and monitoring for CMV reactivation.[74]

Infections are a major cause of morbidity and mortality in patients with CLL, due to both the underlying disease and treatment-related immunosuppression.[69,74,86] Although hypogammaglobulinemia often occurs, intravenous immunoglobulin should only be considered in patients with serum IgG <500 mg/dL (5 g/L) and with recurrent sinopulmonary infections requiring hospitalization or intravenous antibiotics. Prevention of herpes virus infections with acyclovir or an equivalent should be considered, especially if patients are receiving purine analogs, bendamustine or corticosteroids. Hepatitis B reactivation may occur in patients treated with anti-CD20 monoclonal antibodies; screening should be conducted prior to initiation of therapy, and prophylaxis may be required. Finally, vaccination for influenza, pneumococcus and zoster, should be administered as recommended by national guidelines; recombinant forms should be used and live vaccines should be avoided.

Hematopoietic Stem Cell Transplantation

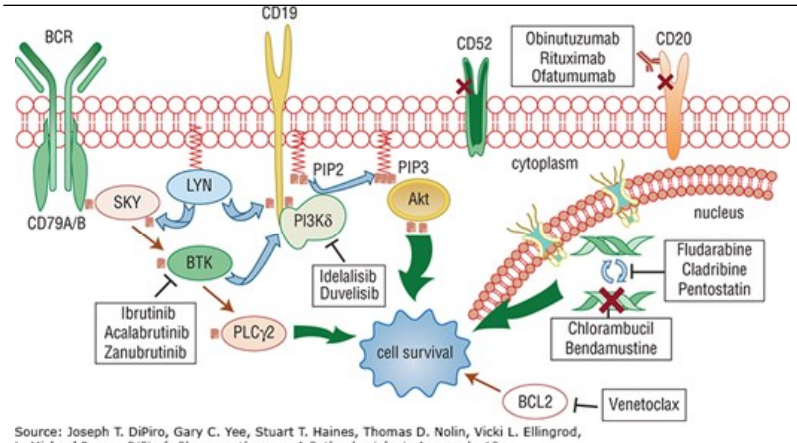
The experience with the use of HSCT in CLL is limited. Although allogeneic HSCT may offer the potential of cure in CLL, the advanced age of most patients, reduced donor availability, and high treatment-related mortality precludes the routine application in the management of this disease.[74] Patients treated with allogeneic HSCT achieve higher remission rates and appear to have longer disease-free survival, but this approach is associated with high treatment-related mortality of about 40%.

Additionally, the new, targeted therapies provide additional options for disease control and overall survival advantages, so the role of allogeneic HSCT is further limited. Older patients who are not candidates for full-intensity allogeneic HSCT may be candidates for non-myeloablative allogeneic HSCT.

Figure 158-2 shows the molecular targets of the various chemotherapy, targeted, and biologic agents used to treat CLL.

FIGURE 158-2

Current treatments and their molecular targets in chronic lymphocytic leukemia. *(Reprinted, with permission, from Manman W, Wang X, Song Z, et al. Targeting PI3Kδ: Emerging Therapy for Chronic Lymphocytic Leukemia and Beyond. Med Res Rev 2015;35:720-752.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Initial Therapy

An evaluation of the patient's fitness for therapy must be conducted before therapy is initiated. Up to 90% of patients with CLL have one or more comorbidities, which may influence the choice of therapy and the patient's treatment goals.[92] There is no standard tool to assess a patient's fitness for therapy at this time. NCCN Guidelines currently base the choice of initial therapy on the presence or absence of deletion 17p or *TP53* mutation.[74]

At present, conventional cytotoxic chemotherapy in CLL is only recommended in younger, fit patients with mutated IGHV. This recommendation is based on the CLL10 study, in which bendamustine and rituximab (BR) was compared to FCR in over 500 previously untreated, fit patients with CLL.[93] The FCR arm showed improved progression-free survival, but overall survival was not different between the treatment groups. A progression-free survival benefit was also seen in those who had mutated IGHV CLL with a median of 42.7 months versus a median of 33.6 months in those without an IGHV mutation. However, the benefit of improved progression-free survival with FCR was not observed in patients older than 65 years of age. Patients who received FCR experienced more grade 3 to 4 neutropenia and infections, as well as an increased risk of secondary myelodysplastic syndromes and leukemias. Therefore, FCR is now only recommended for the first-line treatment of younger, fit patients with IGHV-mutated CLL.[74]

Preferred regimens for initial therapy of younger, fit patients include ibrutinib, acalabrutinib with or without obinutuzumab, zanubrutinib, and venetoclax plus obinutuzumab.[74]

Ibrutinib plus rituximab was compared to FCR in 529 previously untreated patients with CLL who were less than 70 years of age without del(17p).[94] At 45 months, progression-free survival favored ibrutinib and rituximab. Improved progression-free survival was seen across subgroups, but was not observed in patients with mutated IGHV, which strengthens the recommendation for FCR in the first-line treatment of younger, fit patients with IGHV-mutated CLL as discussed above. Although this study examined the use of ibrutinib and rituximab, the true benefit of an anti-CD20 monoclonal antibody in this setting is not clear due to a lack of comparative studies, and therefore ibrutinib alone is recommended in the first-line treatment of CLL.[74,76]

In a three-arm phase III trial that randomized 535 patients with untreated CLL to acalabrutinib plus obinutuzumab, acalabrutinib alone, or chlorambucil plus obinutuzumab.[78] Of note, acalabrutinib was continued until disease progression or unacceptable toxicity while chlorambucil was given for a specific period of time. At a follow-up of 24 months, both of the acalabrutinib-containing treatment arms had significantly longer progression-free survival (87% for acalabrutinib alone and 93% for the acalabrutinib plus obinutuzumab compared to 47% for chlorambucil plus obinutuzumab). Overall survival was not different between the three treatment groups.

A phase III study compared zanubrutinib to bendamustine and rituximab in 590 patients with newly diagnosed CLL.[95] Progression-free survival was significantly improved in patients who received zanubrutinib compred to those who received bendamustine and rituximab, as assessed by an independent review committee.

The combination of venetoclax plus obinutuzumab was approved by the FDA for treatment-naïve patients with CLL. In an open-label, phase III trial comparing venetoclax plus obinutuzumab with chlorambucil plus obinutuzumab, patients treated with venetoclax plus obinutuzumab had a

significant improvement in progression-free survival over chlorambucil plus obinutuzumab after a median follow-up of 28.1 months. No benefit in overall survival has been reported in this trial.[80]

The combination of obinutuzumab plus chlorambucil is also a recommended regimen in the first-line treatment of patients with CLL.[71] The CLL11 study was a phase III trial that randomized 781 patients with untreated CLL and coexisting conditions to one of three treatment groups: single-agent chlorambucil, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil.[93] Median progression-free survival was longer with obinutuzumab plus chlorambucil as compared to the other treatment arms. Overall survival also favored obinutuzumab plus chlorambucil as compared to rituximab plus chlorambucil. However, this regimen has fallen out of favor because of the data showing better progression-free survival outcomes with acalabrutinib and obinutuzumab.[71]

Preferred regimens for the first-line treatment of patients with del(17p) or TP53 mutation include acalabrutinib with or without obinutuzumab, zanubrutinibor venetoclax plus obinutuzumab, regardless of patient age or comorbidities.[74]

Treatment of Relapsed or Refractory CLL

Despite impressive results with the use of new agents in the first-line treatment of CLL, the disease remains incurable and nearly all patients will relapse. Selection of therapy for relapsed disease depends on age, performance status, previous therapy, and response and duration of previous therapy.[70,74] Recommended treatment regimens in this setting include BTKis, venetoclax plus rituximab, and PI3K inhibitors.

Patients who did not receive ibrutinib in the first-line setting may be considered for this agent at relapse. In a phase III trial, ibrutinib was compared to ofatumumab in patients with relapsed or refractory CLL with a primary endpoint of progression-free survival.[96] At 4 years of follow-up, the median progression-free survival was still not reached in patients who had received ibrutinib as compared to 8 months with ofatumumab, and 3-year overall survival continued to favor ibrutinib (59% vs 3%).[97] Patient-reported outcomes were significantly greater in patients who received ibrutinib. Acalabrutinib was compared to ibrutinib in patients with previously treated CLL with del(17p) or del (11q) in the phase III ELEVATE-RR trial.[88] Acalabrutinib was determined to be non-inferior to ibrutinib, with a median progression-free survival of 38.4 months in both arms as assessed by an independent review committee. Zanubrutinib is recommended as second-line or subsequent treatment of CLL in patients who are intolerant or have contraindications to other BTKis.[74] This recommendation is based on a single-arm phase II study of 91 patients with relapsed or refractory CLL. Overall response rate, as assessed by an independent review committee, was 84.6% at a median of 15.1 months.[98]

The combination of venetoclax plus rituximab was compared to bendamustine plus rituximab in 389 patients with relapsed or refractory CLL.[84] Progression-free and overall survival were both significantly higher in the venetoclax plus rituximab arm, and these benefits were maintained across all subgroups. A higher percentage of patients receiving venetoclax plus rituximab also had undetectable MRD at the end of therapy.

Idelalisib and duvelisib may also be considered in the relapsed and refractory settings after treatment with both a BTKi-based regimen and a venetoclax-based regimen.[74] In a randomized phase III trial, patients with relapsed CLL who had comorbidities that precluded them from being treated with standard chemotherapy were randomized to receive rituximab with either placebo or idelalisib.[99] The primary endpoint of progression-free survival was 20.3 months in the idelalisib group as compared to 5.5 months in the rituximab monotherapy group. Patients in the idelalisib group had a higher overall response rate and significantly longer overall survival. In an open-label, phase III clinical trial of previously treated patients, duvelisib showed improved progression-free survival over ofatumumab.[85] The improvement in progression-free survival was also observed in patients with high-risk cytogenetic markers.

For patients with relapsed or refractory disease who have del(17p) or *TP53* mutation, preferred treatment options include ibrutinib (if not previously received), acalabrutinib, zanubrutinib, and venetoclax plus rituximab (all Category 1 recommendations in the NCCN Guidelines).[74] Other recommended regimens include duvelisib, idelalisib plus rituximab, and single-agent venetoclax.

Summary of Treatment Options

CLL is an incurable disease, and the goal of therapy is to achieve and maintain disease remission while minimizing the burden of treatment-related adverse drug reactions.[69,70] Therefore, patients should not be initiated on therapy unless symptomatic. The specific treatment depends on

cytogenetics, age, and comorbidities, andthe presence or absence of deletion 17p or *TP53* mutation.[74]

Historically, FCR has been the preferred initial therapy for symptomatic CLL in younger patients without significant comorbidities, but this regimen is now limited to younger, fit patients with IGHV mutation.[69,70,74] First-line choices for patients without del(17p) include ibrutinib, acalabrutinib with or without obinutuzumab, zanubrutinib, or venetoclax plus obinutuzumab. At relapse, therapy options include alternative regimens used in the first-line setting; idelalisib plus rituximab and duvelisib may be considered in the third-line setting. Patients with del(17p) or *TP53* mutation may receive ibrutinib, acalabrutinib with or without obinutuzumab, zanubrutinib or venetoclax plus obinutuzumab as initial therapy, with alternative regimens employed at relapse.

Careful attention should be paid to the management of adverse drug reactions, and pharmacologic therapy to treat such effects must be carefully chosen to avoid drug-drug interactions (Tables 158-6 and 158-7). Cost must also be considered because many of the oral therapies are given for long periods of time. Patients with CLL are also at risk for opportunistic infections, and prophylactic therapy may be warranted. Future research in CLL will determine the optimum sequence, length, and goals of therapy in CLL, as well as management strategies for long-term adverse drug reactions of such therapies.

ABBREVIATIONS

ABL	Abelson proto-oncogene
ALL	acute lymphoblastic leukemia
AP	accelerated phase
ATP	adenosine triphosphate
BC	blast crisis
BCR	breakpoint cluster region
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CMV	cytomegalovirus
CP	chronic phase
CYP	cytochrome P450
Del(17p)	deletion 17p
ERK	extracellular signal-regulated kinase
FCR	fludarabine, cyclophosphamide, rituximab
FDA	Food and Drug Administration

FISH	fluorescence in situ hybridization
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia (effect)
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
Ig	immunoglobulin M
IGHV	immunoglobulin heavy chain gene
IFN-α	interferon alfa
IRIS	International Randomized study of Interferon vs STI571 trial
IS	international scale
MBL	monoclonal B-cell lymphocytosis
mRNA	messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory drug
PDGFR	platelet-derived growth factor receptor
Ph	Philadelphia chromosome
PI3K	phosphatidylinositol 3-kinase
RT-PCR	reverse-transcription polymerase chain reaction
STI	signal transduction inhibitor
TKI	tyrosine kinase inhibitor
VTE	venous thromboembolism
WBC	white blood cell
WHO	World Health Organization
ZAP-70	ζ-associated protein 70

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SELF-ASSESSMENT QUESTIONS

1. MK is a 60-year-old male with newly diagnosed stage III CLL with deletion 17p and progressive symptoms of thrombocytopenia, anemia, and lymphadenopathy. Which of the following is the most appropriate treatment for MK at this point in his course?

   A. No therapy

   B. Autologous stem cell transplant

   C. Acalabrutinib and obinutuzumab

   D. Imatinib

   E. Rituximab

2. Patients receiving duvelisib for the treatment of CLL require which of the following supportive care measures?

A. Trimethoprim-sulfamethoxazole to prevent *Pneumocystis* pneumonia

B. Prophylactic cranial irradiation to prevent central nervous system involvement

C. Leucovorin rescue to prevent mucositis

D. Aspirin to prevent venous thromboembolism

E. Zoledronic acid to prevent bone lytic lesions

3. Which of the following predicts a more aggressive disease course and shorter remission with standard treatment options for CLL patients?

A. Age less than 65 years

B. Presence of the Philadelphia chromosome (translocation of chromosomes 9 and 22)

C. Presence of the cytogenetic abnormality involving deletion of chromosome 17

D. Having a confirmed sibling matched donor for allogeneic stem cell transplant

E. Presence of the cytogenetic abnormality involving deletion of chromosome 13

4. Which one of the following patients with CML would be the most appropriate candidate for an allogeneic stem cell transplant?

A. A 62-year-old male with newly diagnosed disease, sibling-matched donor available and no prior treatment for CML

B. A 45-year-old female with a sibling match and CML harboring a T315I mutation with disease that has progressed following salvage therapy with ponatinib

C. A 71-year-old female with refractory CML to imatinib and a second-generation tyrosine kinase inhibitor who has no suitable match for transplant

D. A 71-year-old male with refractory CML to front-line nilotinib who has a sibling match

E. A 31-year-old male in chronic phase with molecular response achieved with imatinib

5. JJ is a 69-year-old female with newly diagnosed stage III chronic lymphocytic leukemia (CLL) without del(17p) who is being considered for initial therapy. JJ's medical comorbidities include diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and diabetic neuropathy. Which one of the following treatment options would be the most appropriate first-line treatment for JJ?

A. Cytarabine and daunorubicin

B. Zanubrutinib

C. Bendamustine and rituximab

D. Fludarabine, cyclophosphamide and rituximab

E. Idelalisib and rituximab

6. If a patient being treated for CML has the T315I mutation, which of the following is the most appropriate treatment option?

A. Hydroxyurea

B. Imatinib

C. Ponatinib

D. Interferon alfa

E. Dasatinib

7. The molecular marker in hematopoietic progenitor cells that defines CML is known as which of the following?

A. Philadelphia chromosome (translocation of chromosome 9 and 22)

B. Deletion of chromosome 17

C. Deletion of chromosome 13

D. Inversion of chromosome 16

E. Translocation of chromosome 15 and 17

8. Which one of the following most accurately describes the major toxicities in a patient receiving dasatinib?

A. Myelosuppression, myalgias, pleural effusion

B. SIADH, alopecia, mucositis

C. Seizure, peripheral neuropathy, constipation

D. Thromboembolism, somnolence, neuropathy

E. Nausea/vomiting, neuropathy, hearing loss

9. NH is a 67 year old male with a past medical history of hypothyroidism, hypercholesterolemia, atrial fibrillation, migraine headaches, and seasonal allergies. His medications include levothyroxine, rosuvastatin, warfarin, acetaminophen and cetirizine. He has recently been diagnosed with CLL and will be initiating therapy with acalabrutinib. Which of NH's medications should be changed based on the plan to initiate acalabrutinib?

A. Levothyroxine

B. Rosuvastatin

C. Warfarin

D. Acetaminophen

E. Cetirizine

10. Which of the following is the most appropriate first-line treatment for CML to induce and maintain disease remission with manageable toxicity?

A. Interferon alfa

B. Allogeneic stem cell transplant

C. Imatinib

D. Cytarabine

E. Hydroxyurea

11. MW is a 47 year old male with newly diagnosed chronic phase CML patient who was started on initial therapy with imatinib 400 mg orally daily. At 3 months, MW has not yet achieved a complete hematologic remission. What is the most appropriate course of action for MW at this time?

A. Repeat the bone marrow biopsy for cytogenetic analysis

B. Continue imatinib 400 mg orally daily until 6 months, then assess molecular response

C. Consider a second-generation tyrosine kinase inhibitor such as nilotinib

D. Hold imatinib and monitor molecular response for the next 3 months

E. Discontinue imatinib and start interferon alfa plus cytarabine

12. Which one of the following agents has a black box warning for QTc prolongation?

A. Ponatinib

B. Omacetaxine

C. Nilotinib

D. Imatinib

E. Lenalidomide

13. PS is a 47 year old male with CML who progressed to myeloid blast crisis despite having received three different tyrosine kinase inhibitors over the course of 22 months. What is the most appropriate course of action for further therapy for PS at this time?

A. Re-treat with the tyrosine kinase inhibitor therapy that was used first-line

B. There are no further treatment options for PS

C. Induction/remission therapy with cytarabine and an anthracycline

D. Hydroxyurea

E. Refer for consideration of hospice

14. KH is a 56-year-old female is receiving venetoclax and rituximab for second-line therapy for CLL. Which of the following toxicities associated with venetoclax should be monitored as KH initiates this new regimen?

A. Atrial fibrillation

B. Venous thromboembolism

C. Richter's transformation

D. Tumor lysis syndrome

E. Hemorrhagic cystitis

15. Which of the following treatment settings is most appropriate for the use of idelelisib in CLL?

A. First-line treatment as a single agent in patients with del(17p)

B. In combination with rituximab as third-line treatment

C. Second-line treatment in combination with obinutuzumab

D. In combination with fludarabine in patients with del(17p) as first-line treatment

E. In combination with conditioning chemotherapy for allogeneic stem cell transplant

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** The combination of acalabrutinib and obinituzumab is an NCCN category 1 preferred treatment regimen for patients with deletion 17p regardless of age.
2. **A.** Prophylaxis for *Pneumocystis jiroveci* pneumonia is recommended for patients who receive idelalisib or duvelisib for the treatment of CLL.
3. **C.** Newly diagnosed patients with del(17p) had a median time-to-progression following first-line of only 32 months.
4. **B.** Given that the patient has a T315I, ponatinib is the only TKI to target this DNA mutation. If the patient had disease progression on ponatinib, a hematopoietic cell transplant would be the only treatment option available.
5. **B.** Zanubrutinib is a category 1 recommendation for the treatment of newly diagnosed CLL..
6. **C.** Ponatinib is the only TKI that targets the T315I mutation in CML.
7. **A.** The Philadelphia chromosome is present in 95% of patients with CML and drives the growth of the disease.
8. **A.** Myalgia and myelosuppression may be class-related adverse events of BCR-ABL inhibitors, but pleural effusions can occur in 20% of patients treated with dasatinib.
9. **C.** Patients who were taking warfarin were excluded from many BTKi tria due to concerns of increased bleeding risk. If prolonged anticoagulation is necessary, alternative agents such as enoxaparin or rivaroxaban should be considered.
10. **C.** Imatinib has 10-year survival data with over 80% of patients alive. Chemotherapy and interferon alfa have fallen out of favor in the standard of care. Newer agents such as nilotinib, dasatinib, and bosutinib may also be considered first-line agents.
11. **A.** Since the patient has not achieved the first milestone of hematologic remission, re-assessment of the bone marrow should be done to rule out other factors such as Philadelphia negative disease or a different CML clone. Depending on the results, second-line therapy can be selected and may include options such as dasatinib, nilotinib or bosutinib.
12. **C.** All TKIs can prolong the QTc, but nilotinib has the black box warning.
13. **C.** In the new TKI era, it is uncommon for patients to progress through multiple lines of TKI therapy to blast crisis. However, blast crisis is similar to acute leukemia and requires treatment with traditional chemotherapy agents.
14. **D.** Venetoclax causes rapid lysis of CLL cells resulting in tumor lysis. At initiation, venetoclax dose should be escalated weekly and patients at high risk for tumor lysis syndrome need to be admitted at initiation with dose escalation for monitoring and hydration.
15. **B.** Idelelisib is currently recommended with or without rituximab after treatment with both a BTKi-based regimen an a venetoclax-based regimen.