



EDUCATIONAL OBJECTIVE: Readers will be familiar with the presentations of and treatments for chronic myelogenous leukemia and chronic lymphocytic leukemia

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Your patient has chronic leukemia: Now what?

ABSTRACT

Although still in their infancy, biologic therapies for hematologic cancers are making rapid strides, diminishing the role of chemotherapy and offering long-term remission. More patients are surviving cancer and therefore are increasingly being seen by primary care physicians, who must be aware of complications of standard and newer treatments and how to manage them.

KEY POINTS

Chronic myelogenous leukemia (CML) can now be functionally cured with tyrosine kinase inhibitors, which interfere with the product of the oncogene causing the disease.

Patients diagnosed with CML should begin therapy immediately even if they have no symptoms.

Tyrosine kinase inhibitors have side effects that increase cardiovascular risk.

Chronic lymphocytic leukemia (CLL) is an immunologic disease involving clonal proliferation of B cells. Chemotherapy for CLL should begin only when symptoms or indicators of impaired marrow function reach a certain threshold.

New treatments for CLL increase the risk of atrial fibrillation and autoimmunity.

Experimental B-cell-targeted therapies have demonstrated encouraging results even when chemotherapy fails in CLL and other B-cell cancers.

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THE ADVENT of targeted therapies has dramatically changed the management of chronic leukemia. Chemotherapy—highly toxic, non-specific drugs that can be dangerous to patients and providers and result in only modest success—is gradually being replaced by biologic targeting of malignancy. Scientists are rapidly identifying extracellular and intracellular targets on tumor cells and are developing and testing promising new therapies aimed at these targets. Survival of cancer patients has become so common that clinicians outside the specialties of hematology and oncology are now caring for them.

This article describes new biologic therapies for chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL), along with the diagnosis of these diseases and management of survivors in the primary care setting.

■ CHRONIC MYELOGENOUS LEUKEMIA

A seemingly healthy person needs laboratory blood work, perhaps for an insurance physical examination or for a preoperative workup. Or a patient comes to the emergency department with a sore throat and routine blood tests are ordered. Their laboratory values:

- White blood cell count $250 \times 10^9/L$ (reference range 3–11)
- Neutrophils 70% (40%–70%)
- Blasts 1% (0)
- Metacytes and myelocytes 5% (0)
- Bands 5% (0)
- Lymphocytes 10% (22%–40%)
- Monocytes 5% (0–7%)
- Basophils 3% (0–1%)
- Eosinophils 1% (0–4%)
- Hemoglobin 12.1 g/dL (11.5–15.5 in women, 13.0–17.0 in men)
- Platelet count $525 \times 10^9/L$ (150–400).

TABLE 1

Phases of chronic myelogenous leukemia

Characteristic	Chronic	Accelerated	Blastic
Blasts (%)	1–15	≥ 15	≥ 30
Basophils (%)	Increased	≥ 20	Any number
Platelets	Increased or normal	Increased or decreased	Decreased
Bone marrow	Myeloid hyperplasia		
Duration	4–6 years	Up to 1 year	3–6 months

Based on information in references 3 and 4.

Leukocytosis and a ‘left shift’

Although this scenario often raises concern for acute leukemia, a careful look shows evidence of a chronic myeloproliferative disorder instead. Specifically, this patient’s laboratory values show a “left shift”—an increase in immature neutrophils, ie, blasts, myelocytes, and bands.

This picture is characteristic of CML, an uncommon leukemia with about 4,500 new cases annually in the United States. Patients can present at any age, but the disease occurs more often in older people, with a median age of 66.¹

The presentation is usually subtle: about half of cases are detected by routine laboratory testing, which typically reveals a left-shifted leukocytosis with basophilia and a few blasts. Mild anemia is common. The platelet count is elevated in 30% to 50% of patients at diagnosis. Bone marrow aspirate shows significant myeloid hyperplasia without dysplasia, and sometimes shows mild fibrosis.

Philadelphia chromosome is diagnostic

A definitive diagnosis is made by demonstration of an abnormally short chromosome 22. Described in 1960 by Peter Nowell of the University of Pennsylvania and David Hungerford of the Institute for Cancer Research,² this abnormality, called the Philadelphia chromosome, was the first specific genetic abnormality associated with a human cancer. Later, researchers used banding techniques to find that the Philadelphia chromosome results from a reciprocal translocation of

genetic material between the *BCR* gene on chromosome 22 and the *ABL1* gene on chromosome 9, t(9:22).^{3,4} The resulting chimeric gene, called *BCR-ABL*, codes for an oncogenic protein, a tyrosine kinase with constitutive activity.

The Philadelphia chromosome is present in 95% of patients with CML and can be found in all myeloid cell lineages, including erythrocytes, granulocytes, monocytes, and megakaryocytes as well as some cells of lymphocytic lineage, indicating that malignant transformation to CML takes place at the stem cell level.

The mutation causes several problems: the abnormal tyrosine kinase increases cell proliferation, inhibits apoptosis, and alters adhesion molecules in the stroma of the bone marrow, allowing immature cells to leak into the bloodstream. Most important, the mutation increases genomic instability so that additional mutations are likelier to occur over time, making it inevitable that, without treatment, the disease will progress to a fatal blast crisis within an average of 5 years of diagnosis.

CML has three clinical phases

Untreated, CML progresses through three distinct phases: chronic, accelerated, and blast crisis, defined by abnormalities in the blood smear and bone marrow (Table 1).^{5,6} Most patients (85%) are diagnosed during the chronic phase. The accelerated and blastic phases resemble acute leukemia.

Chronic phase management

Therapies over the years have included arsenic (Fowler solution), splenic radiotherapy, busulfan, hydroxyurea, cytarabine, and interferon. All had some palliative success, but usually did not suppress leukemic progression.⁷

In contrast, patients undergoing allogeneic bone marrow transplant had a 5-year survival rate of 60% to 80% during the chronic phase of CML, 40% to 60% during the accelerated phase, and 10% to 20% during a blast crisis.⁸ Long-term survival confirmed the ability of transplant to cure CML, and bone marrow transplant with matched donors was the standard of care for younger patients until the end of the 20th century.

About half of CML cases are detected by routine laboratory testing

Tyrosine kinase inhibition

A new paradigm in treatment began with the development of imatinib, a tyrosine kinase inhibitor that directly interferes with the product of the chimeric *BCR-ABL* gene.⁹

Patients treated with imatinib during the chronic phase of CML have survival rates similar to those of people without the disease, and they usually do not progress to the accelerated and blast phases. As a result of this success, the number of transplants for CML has fallen precipitously.

Other tyrosine kinase inhibitors (dasatinib, nilotinib) that have since been developed have shown even better results in achieving remission and preventing progression. Improved survival is more difficult to demonstrate because the control groups in studies receive imatinib and have 10-year survival rates of about 90%.¹⁰⁻¹²

With the tyrosine kinase inhibitors, CML can be regarded as functionally cured.¹³ Patients take these drugs for life and usually experience a relapse if they stop. Patients with CML are now more likely to die of a comorbidity than of CML.

Choose therapy by tolerability

Which tyrosine kinase inhibitor to use depends more on the side-effect profile of the drug than on its efficacy. Nilotinib should be avoided in patients with vascular disease, and dasatinib avoided in patients with pulmonary disease. Each drug may be associated with some degree of nausea, diarrhea, cramps, rash, and edema.¹⁰⁻¹²

CML is not an immunosuppressive disease, nor are the drugs used to treat it. Patients with CML have an intact immune system. Therefore, precautions taken for patients with acute leukemia or lymphoid malignancy are not required for patients with CML.

Managing survivors

Since imatinib was introduced in 2000, the US Food and Drug Administration (FDA) has approved approximately 20 tyrosine kinase inhibitors for various cancers. These drugs are improving survival rates so well that patients with cancer are increasingly being seen by their primary care doctors for their medical problems.

Some problems have emerged that are

consequences of this successful therapy. Angiogenesis inhibitors such as bevacizumab affect vascular endothelial growth factors, which injure endothelial cells. These effects may result in high blood pressure and arterial occlusive disease. Algorithms have been proposed for managing cardiovascular complications for patients taking tyrosine kinase inhibitors.¹⁴ Further, cardiovascular risk factors such as hyperlipidemia, diabetes, and obesity must be aggressively managed in patients taking tyrosine kinase inhibitors.

Vascular effects, rashes, and drug interactions may best be managed by primary care physicians, cardiologists, and nephrologists, who deal with such problems regularly.

■ CHRONIC LYMPHOCYTIC LEUKEMIA

A patient undergoes routine laboratory blood work in the emergency department or clinic, with these results:

- White blood cell count $250 \times 10^9/L$
- Neutrophils 1%
- Lymphocytes 99%
- Hemoglobin 12.1 g/dL
- Platelet count $160 \times 10^9/L$.

Like patients with CML, those with CLL usually present with no symptoms. The complete blood cell count reveals numerous white blood cells and lymphocytosis. Patients may have painless lymphadenopathy, anemia, and thrombocytopenia, but they do not typically have fever, sweats, or weight loss.

The disease is characterized by clonal proliferation and accumulation of mature-appearing neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. The peripheral blood smear shows “smudge cells,” indicating fragile lymphocytes.

The median age at diagnosis is about 70, with fewer than 15% of newly diagnosed patients under age 50.

CLL is the most common leukemia in the Western world, accounting for about 30% of cases of leukemia in adults. It is rare in Asians, probably because of genetic differences.

Monoclonal B-cell lymphocytosis precedes CLL

Monoclonal B-cell lymphocytosis is related to CLL and always precedes it. It is a common

CML can be functionally cured with tyrosine kinase inhibitors

TABLE 2

Staging of chronic lymphocytic leukemia

Stage	Simplified 3-stage system	Clinical features	Median survival (years)
0	Low risk	Lymphocytosis in blood and marrow only	> 10
I	Intermediate risk	Lymphadenopathy	7
II		Splenomegaly with or without hepatomegaly	
III	High risk	Anemia	1.5–4
IV		Thrombocytopenia	

Based on information in reference 19.

Systemic infection is the cause of death for most patients with CLL

condition, detectable in up to 5% of older adults. The differential count shows a less severe lymphocytosis than in CLL.

Because monoclonal B-cell lymphocytosis does not always convert to leukemia, it is important for insurance coverage purposes not to diagnose it as a leukemia. Treatment-free survival of patients diagnosed with monoclonal B-cell lymphocytosis is 87% at 5 years.^{15,16}

Diagnosing CLL

Lymphocytosis can indicate other low-grade lymphoproliferative diseases and malignancies, so further evaluation is critical. To diagnose CLL, the B-cell count by flow cytometry (not the absolute lymphocyte count from the complete blood cell count) must be at least $5 \times 10^9/L$. Below that threshold, monoclonal B-cell lymphocytosis is diagnosed unless lymphadenopathy is present, indicating small lymphocytic lymphoma. Unlike in benign lymphoproliferations, CLL lymphocytes coexpress the B-cell marker CD19 and the T-cell marker CD5.¹⁷ Bone marrow examination is rarely needed for the diagnosis of CLL.

Two types of CLL can be defined, depending on whether the B cells carry V genes that are mutated or unmutated. B cells expressing ZAP-70 and CD38 tend to carry the unmutated gene, which is associated with a worse prognosis.¹⁸ Regardless of which type a patient has, treatments and the indications for treatment are the same.

Increasing immune dysfunction

CLL is staged according to effects on lymph tissue and hematopoiesis. The Rai system for clinical staging of CLL has been used since 1975 with little alteration (Table 2).¹⁹

CLL is often an indolent lymphoproliferative malignancy and does not always progress to a fatal end stage. Therefore, treatment may be deferred, with a watch-and-wait approach until symptoms develop or the disease progresses. Approximately half of patients never require treatment.²⁰ Progression involves increasing bone marrow impairment with greater susceptibility to infection (due to intrinsic features of CLL and its therapy) and hypogammaglobulinemia in advanced disease.^{21,22} Systemic infection is the cause of death for most patients.

Because CLL is a disease of the immune system, the development of autoantibodies is a cardinal feature. Autoimmune complications are almost exclusively limited to blood and can include hemolytic anemia, pure red cell aplasia, immune-mediated thrombocytopenia, and granulocytopenia. Other autoimmune diseases, such as rheumatoid arthritis, thyroiditis, and Addison disease, are uncommon.^{23,24}

Other complications may occur in patients who have been treated with chemotherapy, and these are usually fatal. The Richter transformation (to an aggressive lymphoma) occurs in about 15%. Other less common complications include prolymphocytoid transformation and secondary malignancies, particularly carcinomas of the lung and gastrointestinal tract and acute (myeloid) leukemia.²⁵

Survival rates in CLL have improved substantially over the past decades,^{26–28} with significant gains following the introduction of antibiotics and, to a lesser extent, transfusions. Median survival is generally between 6 and 9 years, but many patients live for years without requiring therapy.

Chemotherapy: The mainstay of treatment

When to begin therapy remains one of the most challenging issues of patient management. Unlike in CML, there is no advantage to starting at diagnosis when most patients are asymptomatic.²⁹

In 1996, the National Cancer Institute issued guidelines for starting treatment, which

were updated in 2008 with very little change (Table 3).³⁰ In general, the onset of symptoms and evidence of impaired marrow function, including an abnormal hemoglobin level and platelet count, are indications. The white blood cell count continuously increases during the disease course but is not usually an important factor for initiating treatment.

The therapeutic goal for most patients who require treatment has historically been palliation of symptoms. Therapy must be individualized to a patient's age and clinical status, with a heavier reliance on chemotherapeutic agents for patients who can tolerate it and on immunotherapy for others. General strategies are as follows:

- “Go-Go” patients—young, fit, with few comorbidities, good renal function—are the minority. Recommendation: combination chemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR).
- “Slo-Go” patients are reasonably fit and can tolerate chemotherapy but not FCR. Recommendation: combination therapy with either bendamustine and rituximab or chlorambucil and rituximab (for less fit patients). Recent evidence indicates ibrutinib may be useful for such patients.³¹
- “No-Go” patients are frail with short life expectancy. Recommendation: rituximab or observation (see below)

All CLL treatments are potentially toxic. Chemotherapy damages DNA and often causes blood cell counts to fall. Immunosuppression worsens with almost any treatment, involving a substantial risk of secondary malignancy. Although survival improves with therapy, relapse is universal.

Targeting CLL pathways

The new paradigm for cancer therapy is to identify a cellular pathway that drives oncogenesis or proliferation and interfere with it. The B-cell receptor pathway is enormously complex with numerous complex factors, making it difficult to discern the critical mutation that drives the proliferation of lymphocytes.

Bruton tyrosine kinase (Btk) is one factor that is critical for CLL proliferation. Patients with congenitally mutated or dysfunctional Btk have lymphopenia and agammaglobulin-

TABLE 3

Indications to initiate treatment for chronic lymphocytic leukemia

Constitutional symptoms attributable to the disease
Progressive marrow failure
Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids
Massive or progressive splenomegaly
Massive or progressive lymphadenopathy
Rapid lymphocyte doubling time

Based on information in reference 30.

emia, making it a promising target for patients with B-cell disorders. Other experimental therapies are based on other such identified factors.

In 2014, the FDA approved two drugs for CLL—ibrutinib, a Btk inhibitor, and idelalisib, an inhibitor of phosphoinositide 3-kinase—after they were shown in clinical trials to dramatically improve outcomes in patients with relapsed CLL.^{32,33} Trials with these drugs are ongoing. These drugs also inhibit tyrosine kinase and so have vascular side effects in addition to their own idiosyncratic effects.

Ibrutinib has anticoagulant effects and should be stopped before surgery. It also can cause or exacerbate atrial fibrillation, making management of CLL difficult. It is associated with hypogammaglobulinemia, often requiring ongoing immunoglobulin replacement.

Idelalisib tends to cause systemic autoimmune phenomena such as pneumonitis and colitis.

Using T cells as therapy

It has long been observed that patients who undergo bone marrow transplant for leukemia have lower relapse rates if the transplant is allogeneic rather than from a twin. Further, if T cells are removed from the donor graft, graft-vs-host disease may be prevented but the risk of relapses increases. Finally, the presence of graft-vs-host disease tends to reduce the risk of relapse.³⁴ Therefore, T cells clearly are key ingredients for success in the setting of bone marrow transplant. In fact, merely providing

Unlike CML, CLL is a disease of the immune system

T cells for a relapse after allogeneic transplant can induce remission. However, because donor T cells are not targeted, acute and chronic graft-vs-host disease often can ensue.

‘Designer’ monoclonal antibodies

The B lymphocyte has multiple potential targets for new therapies for CLL as well as other cancers involving B cells. CD20 was identified on the surface of B cells in 1988 and is the target protein of the monoclonal antibody drug rituximab. Monoclonal antibodies can be modified to target other surface antigens, to link radioisotopes to deliver radiation therapy, and to deliver drugs that would otherwise be too toxic to be given systemically.³⁵ Monoclonal antibodies can also be modified to enhance function.

Antibodies alone, however, must often rely on the host T cells for cytotoxicity and they are often compromised by either the underlying disease or treatment. Adapting the targeting function of antibodies to enhance or genetically alter T cells to recognize cancer-specific antigens is now being explored for leukemias.³⁶

In 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory acute lymphoblastic leukemia. This biopharmaceutical agent recruits T cells with one antibody-like moiety and targets the CD19 receptor of B cells with another. Given as a single intravenous treatment without chemotherapy, it has an almost 50% response rate, and those who respond tend to stay in remission. Other similar drugs are being developed, and using them earlier in treatment and for other B-cell leukemias is being explored.

New B-cell targeted therapy with CAR-Ts

Newer treatments are being developed based on chimeric antigen receptor T (CAR-T) cells. These engineered T cells express an anti-CD19 moiety that targets B cells, but also activate upon binding to them.³⁷ CAR-T technology is being refined and shows great promise

for cancer treatment.

Multiple clinical trials are currently under way in which the investigators collect autologous T cells by leukopheresis from a patient with a relapsed or refractory B-cell malignancy, transduce the T cells with retroviral vectors into anti-CD19 CAR-T cells, and then reinfuse them into the patient following modest chemotherapy.³⁸

Study results from a small number of patients with relapsing or refractory CLL showed that some patients achieved long-term, progression-free survival.³⁹ The most success with this therapy, however, has been in acute lymphoblastic leukemia.⁴⁰ Possibly, this treatment could be applied to other lymphoid malignancies that also express CD19.

More advances

CAR-T cell therapy has drawbacks. The cells attack only the target antigen, which currently limits their use mostly to hematologic malignancies. In addition, autologous T cells are not robust. Also, the use of allogeneic T cells is restricted by their major histocompatibility complex, and the cells will be rejected by the recipient if not matched.

An attempt to overcome some of these drawbacks is to develop T cells redirected for universal cytokine killing. CAR-T cells are modified with a gene that causes them to excrete interleukin 12, which attracts macrophages and natural killer cells to the environment to better fight the tumor.⁴¹

Other modifications include editing out certain genes including the major histocompatibility complex, which avoids the problem of rejection. Another modification is to insert a “suicide gene” that allows the engineered T cells to be killed with an antidote if they do not work as planned.

Such gene-editing techniques hold great promise for curing cancers without chemotherapy in the not so distant future. ■

**CAR-T
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